

# BMJ Open Association of co-prescribing of opioid and benzodiazepine substitutes with incident falls and fractures among older adults: a cohort study

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## ABSTRACT

**Objective** Examine the association between the co-prescribing of opioids, benzodiazepines, gabapentinoids (pregabalin and gabapentin) and selective serotonin reuptake inhibitors/serotonin and norepinephrine reuptake inhibitors (SSRI/SNRIs) in different combinations and the risk of falls and fractures.

**Design** Retrospective cohort study from 2015 to 2018.

**Setting** Medicare enrolment and claims data.

**Participants** Medicare beneficiaries with both chronic pain and anxiety disorders in 2016 with continuous enrolments in Parts A and B from 2015 to 2016 who were prescribed any combination of opioid, benzodiazepine, gabapentinoid and SSRI/SNRI in 2017 for  $\geq 7$  days, as documented in their Medicare Part D coverage.

**Interventions** Any combination of use of seven drug regimens (benzodiazepine +opioid; benzodiazepine +gabapentinoid; benzodiazepine +SSRI/SNRI; opioid +gabapentinoid; opioid +SSRI/SNRI; gabapentinoid +SSRI/SNRI;  $\geq 3$  drug classes).

**Main outcomes** First event of fall and the first event of fracture after the index date, which was the first day of combination drug use that lasted  $\geq 7$  days in 2017.

**Results** A total of 47 964 patients (mean [SD] age, 75.9 [7.1]; 78.0% woman) with diagnoses of both chronic pain and anxiety were studied. The median (Q1–Q3) duration of drug combination use was 26 (14–30) days. After adjusting for demographic characteristics, chronic conditions and history of hospitalisation and fall or fracture, the co-prescribing of  $\geq 3$  drugs (adjusted HR [aHR], 1.38; 95% CI 1.14 to 1.67) and opioid plus gabapentinoid (aHR, 1.18; 95% CI 1.02 to 1.37) were associated with a high fall risk, compared with benzodiazepine plus opioid co-prescribing, findings consistent with the secondary analysis using inverse probability of treatment weighting with propensity scores. The co-prescribing of benzodiazepine plus gabapentinoid (aHR, 0.76; 95% CI 0.59 to 0.98) was associated with lower fracture risk compared with the co-prescribing of benzodiazepine plus opioid, though this finding was not robust.

**Conclusions** Our findings add to comparative toxicity research on different combinations of gabapentinoids and serotonergic agents commonly prescribed with or as substitutes for opioids and benzodiazepines in patients with co-occurring chronic pain and anxiety.

## Strengths and limitations of this study

- This study is a retrospective cohort study with a large sample size of 47 964 Medicare beneficiaries.
- This study evaluates fall and fracture outcomes in patients with both chronic pain and anxiety disorders, two conditions that commonly co-exist in real-world clinical practice.
- Fall and fracture outcomes were compared across subsets of patients who were prescribed seven different drug combinations commonly used to treat chronic pain and anxiety, adding to the limited comparative toxicity research of combinations of opioids, benzodiazepines, gabapentinoids and selective serotonin reuptake inhibitors/serotonin norepinephrine reuptake inhibitors.
- Multivariable models accounting for demographic and clinical characteristics were used to evaluate outcomes, and inverse probability of treatment weighting with propensity score analyses was used to test for robustness of findings.
- One limitation is that the subsets of patients prescribed different drug combinations may differ in regards to their inherent fall risk, thus altering clinicians' decision to prescribe certain medications, that is, confounding by indication.

## INTRODUCTION

The rise in opioid prescribing in the USA over the last two decades has been associated with concomitant increases in the rates of opioid use disorder, overdose and mortality.<sup>1–3</sup> Approximately one-third of opioid overdose deaths involve co-use of benzodiazepines (benzos),<sup>4 5</sup> a class of medication commonly prescribed for anxiety and sleep disorders.<sup>4–6</sup> The co-prescribing of opioids and benzos has steadily risen in recent years,<sup>5 7–9</sup> a reflection in part of the high rate of co-occurrence of pain and anxiety disorders.<sup>10</sup> In a retrospective analysis of claims data from 315 428 commercially insured patients aged 18–64, Sun *et al*<sup>9</sup> reported that 9% used both an opioid and benzo in 2001, increasing to 17% in 2013.



Concurrent opioid and benzodiazepine use increases opioid overdose risk because of their synergistic depression of the central nervous system (CNS) and respiratory function.<sup>11 12</sup> Concurrent opioid and benzodiazepine use is also associated with increased risk of emergency room visit,<sup>9</sup> inpatient admission,<sup>9</sup> falls,<sup>13 14</sup> fractures<sup>13 14</sup> and death due to opioid overdose.<sup>5</sup>

In response, the 2016 Centers for Disease Control and Prevention (CDC) opioid prescribing guideline recommended that clinicians avoid co-prescribing opioids and benzodiazepines 'whenever possible'.<sup>15</sup> The Federal Drug Administration (FDA) has also strongly cautioned against their co-prescribing.<sup>16</sup> These strategies and other government, health system and payer policies have been associated with a decrease in the rate of opioid and benzodiazepine prescribing, separately and concurrently.<sup>17 18</sup> Restrictions on opioid prescribing have paralleled greater interest in the prescribing of the antiepileptic drugs gabapentinoids (GABA), ie, gabapentin and pregabalin as non-opioid analgesics.<sup>19-21</sup> Data from a nationally representative sample of 346177 Americans showed that GABA prescribing has increased from 1.2% in 2002 to 3.9% in 2015.<sup>21</sup> While FDA approved for a limited number of pain conditions, GABAs are widely used off-label to treat chronic pain despite limited evidence of efficacy and safety.<sup>19 21 22</sup> Other off-label use includes prescribing for anxiety disorders.<sup>23 24</sup> The premise for a shift to GABA as a safer alternative to opioids is not supported by evidence, as recent data showed associations of GABA use with dizziness, sedation, falls, fractures and overdose.<sup>19 20 22 25 26</sup>

While data have shown a shift towards GABA prescribing as a non-opioid analgesic after the 2016 CDC guideline, a similar change in the rate of non-benzodiazepine alternatives (selective serotonin reuptake inhibitors [SSRIs] and serotonin and norepinephrine reuptake inhibitors [SNRIs]) for treating comorbid anxiety in chronic pain patients is not clear. Modern evidence-informed prescribing guidelines strongly recommend SSRIs and SNRIs as first-line anxiolytic agents over benzodiazepines because of their better safety and efficacy profile than benzos.<sup>27-29</sup> SNRIs have an additional FDA indication for neuropathic pain and are commonly used for this purpose.<sup>30 31</sup> Unknown, however, are the differences in toxicity outcomes (eg, falls and fractures, overdose, hospitalisation, death) between opioid/benzo coprescribing and opioid-sparing or benzodiazepine-sparing combinations, such as those that use gabapentinoids or SSRI/SNRIs.

Understanding these differences is especially important for older adults at higher risk of adverse events from the co-use of multiple psychoactive medications. Minimising falls and fractures is a key consideration when prescribing multiple medications for older adults. Comparative safety data can help clinicians choose combinations with the least toxicity to safely treat patients with chronic pain and anxiety disorders, two conditions that commonly co-occur in real-world clinical practice.<sup>10</sup> To address these knowledge gaps, this study aims to examine the association

between seven drug combinations commonly used to treat chronic pain and anxiety disorders and the risk of falls and fractures.

## METHODS

### Data source

This was a retrospective cohort study using enrolment and claims data from a 20% national sample of Medicare beneficiaries enrolled from 2015 to 2018. The data source included the Master Beneficiary Summary File (MBSF), Medicare Provider Analysis and Review (MEDPAR) file, Outpatient Standard Analytic File (OUTSAF), and Carrier and Prescription Drug Event files. The institutional review board of the University of Texas Medical Branch approved this study.

### Study cohort

The cohort selection flowchart is shown in online supplemental table 1. We selected Medicare beneficiaries aged 65 and older who were diagnosed with both chronic pain and anxiety in 2016; continuously enrolled in Parts A and B from 2015 to 2016; used some combination of opioid, benzo, SSRI/SNRI or GABA classes of medication in 2017 for at least 7 days; had 1 month Part D coverage prior to beginning the combination use; no prior combination use in the prior 30 days to initiation of a combination and had complete information in the data files. Chronic pain and anxiety were ascertained using the Chronic Conditions Data Warehouse (CCW) condition categories (online supplemental table 2). These categories are created by including beneficiaries with at least one inpatient diagnosis or two non-drug claims of any type in the 2-year period.<sup>32</sup>

### Measurements

#### Combination drug use

Combination of drug use was created by assessing which of the outpatient prescription drugs each beneficiary was using on each day of 2017. The first combination that was used 7 or more days in 2017 was used as the index combination; the first day of this combination use was the index date. If participants used a combination for  $\geq 7$  days in 2017, they were followed into 2018 for complete prescription duration and outcome data. The index combination was categorised into seven groups: benzo plus opioid (benzo +opioid); benzo plus GABA (benzo +GABA); benzo plus SSRI or SNRI (benzo +SSRI/SNRI); opioid plus GABA (opioid +GABA); opioid plus SSRI or SNRI (opioid +SSRI/SNRI); GABA plus SSRI or SNRI (GABA +SSRI/SNRI) and  $\geq 3$  drugs from the four medication classes. We grouped SSRI/SNRI together as they share mechanisms of action. To ensure that the index combination was an initiation of combination, patients with any of the seven study combinations in the 30 days before the index date were excluded. The list of medications for each drug class is included in online supplemental table 3.

## Fall and fracture

The study outcomes were (1) the first event of falls as any diagnosis and (2) the first event of fracture as a primary diagnosis after the index date. Falls and fractures were assessed using diagnosis codes from the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (online supplemental table 4). Binary indicators were created for each of the outcomes and time to the first event was assessed from the index date. The median and interquartile duration of the initial drug combination was 26 (14–30) days (table 1). Therefore, patients were censored 30 days after the end of their initial drug combination, at loss of Medicare coverage, death or at the end of 6-month follow-up from the drug combination initiation.

## Covariates

Sex, age category, race/ethnicity, Medicaid enrolment, US Census region, original reason for Medicare entitlement, history of fall or fracture, history of hospitalisation and chronic conditions were adjusted for in the analysis. Demographic variables were taken from the MBSF; history of fall, fracture or hospitalisation in the 12 months before the index date were created from MEDPAR, OUTSAF and Carrier files; and chronic conditions were taken from the CCW categories. We selected 19 chronic conditions related to the study outcomes: alcohol use disorders, Alzheimer's disease/dementia, arthritis, asthma, cancer (breast, colorectal, endometrial, lung, leukaemia, lymphoma), chronic kidney diseases (CKD), chronic obstructive pulmonary disease (COPD), depression, diabetes, drug use disorder, epilepsy, hearing impairment, liver disease, migraine/headache, mobility impairment, obesity, osteoporosis, spine injury and vision impairment.

## Statistical analysis

Descriptive statistics were generated for each of the covariates with mean and SD for numeric variables and count and per cent for categorical variables across seven drug combination groups. The unadjusted fall or fracture rates for each group were estimated using the Kaplan-Meier method. Cox proportional hazard models were used to assess the effect of drug combination use on each of the outcomes separately adjusted for all variables. In addition, prespecified interactions were assessed in the model adjusted for all variables between drug combination and age, Alzheimer's/dementia status for both outcomes and history of fall/fracture for their correspondent outcome. Proportionality of hazards was tested by adding to the model the logarithm of the time to fall or fracture and assessing its significance. Furthermore, propensity score was generated with a multinomial logit model using average treatment effect estimation that considered all covariates listed in table 1. Backward elimination was used to select variables included in the propensity model, eventually eliminating the comorbidities of asthma and liver disease. Then we used inverse

probability of treatment weighting (IPTW) with propensity scores in Cox proportional hazard models to examine the effect of drug combination on outcomes and limit the effect of confounding by limitation across the study groups. Absolute standardised differences were used to assess balance across treatment groups. Because all variables were balanced following IPTW propensity score, no additional variables were included in the proportional hazards models. Finally, we conducted two sets of sensitivity analyses. First, we excluded patients with cancer diagnoses from our main analyses. Second, to better identify new initiation of drug combination, we repeated our main analyses with a 3-month lookback period, which included patients with part D coverage in the 3 months prior to beginning the combination use and did not have any studied combination in these 3 months. The sensitivity analyses were adjusted for all demographic and clinical characteristics. All analyses were performed with SAS Enterprise V.7.12 at the Centers for Medicare and Medicaid Services Virtual Research Data Center (SAS Institute, Cary, North Carolina).

## Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of our research. The results of our study are not planned to be disseminated directly to study participants, as our data source is deidentified clinical data. However, this report will be available open access to all patient and clinician stakeholders.

## RESULTS

### Baseline characteristics

A total of 47964 Medicare beneficiaries with diagnoses of both chronic pain and anxiety who used any of the seven study drug combinations were included in this study. Table 1 presents the baseline characteristics of these individuals, stratified by the drug combinations. Of the full cohort, 10261 (21.4%) used the combination of benzo +opioid, 9541 (19.9%) used benzo +GABA, 4420 (9.2%) used benzo +SSRI/SNRI, 8625 (18.0%) used opioid +GABA, 6843 (14.3%) used opioid +SSRI/SNRI, 5499 (11.5%) used GABA +SSRI/SNRI and 2775 (5.8%) used any combination of  $\geq 3$  drugs from the four drug classes. Of those who used  $\geq 3$  drug classes, the most common combination was benzo +opioid+SSRI/SNRI (36%), followed by opioid +SSRI/SNRI+GABA (22%), benzo +opioid+GABA (19%), benzo +SSRI/SNRI+GABA (16%) and benzo +opioid+SSRI/SNRI+GABA (7%). The median (Q1–Q3) duration of drug combination use was 26 (14–30) days and mean (SD) was 32.0 (32.3) days. Overall, most individuals were women (78.0%) and white (87.6%), and the mean age was 75.9 (SD, 7.1) years. These characteristics were similar across the seven drug combination groups. A high proportion of the total study cohort had the comorbid chronic conditions of arthritis (78.2%), depression (62.3%), diabetes (37.4%), CKD

**Table 1** Baseline demographic characteristics and comorbid conditions of study participants

	All	Benzo/opioid	GABA +SSRI/ SNRI	3+combo	Benzo+GABA	Benzo+SSRI/ SNRI	Opioid +GABA	Opioid +SSRI/ SNRI
Total	47964	10261	5499	2775	9541	4420	8625	6843
Sex								
Male	10570	2510	1181	580	1762	957	1818	1762
Female	37394	7751	4318	2195	7779	3463	6807	5081
Age (mean, SD)	75.9	7.1	75.6	6.9	76.1	76.2	7.3	75.5
Age category								
65–74	22662	4784	2652	1443	4440	2000	3958	3385
75–84	17993	3824	2103	998	3607	1726	3203	2532
85+	7309	1653	744	334	1494	694	1464	926
Race								
White	42008	8876	4834	2420	8668	3869	7682	5659
Black	2579	728	251	156	211	194	414	625
Hispanic	2168	430	260	125	414	234	328	377
Other	1209	227	154	74	248	123	201	182
Region								
MW	11107	2294	1310	647	2119	977	2191	1569
NE	8204	1506	1037	448	2149	915	1222	927
SO	20784	4650	2269	1256	3899	1839	3759	3112
WE	7869	1811	883	424	1374	689	1453	1235
Original entitlement								
Disabled/ ESRD	13297	3213	1409	958	1927	1056	2483	2251
Old age	34667	7048	4090	1817	7614	3364	6142	4592
Medicaid dual eligibility								
No	35329	7435	4013	1911	7683	3419	6194	4674
Yes	12635	2826	1486	864	1858	1001	2431	2169
Number of days on drug combo								
Mean, SD	32.0	32.3	46.4	36.8	36.9	32.1	27.7	26.7
Median, Q1–Q3	26	14–30	30	15–30	30	17–39	21	22
History of fall	8437	1648	1106	604	1414	630	1832	1203
History of fracture	3537	710	437	270	571	242	785	522
History of hospitalisation	20997	4400	2529	1435	3404	1669	4116	3444

Continued

**Table 1** Continued

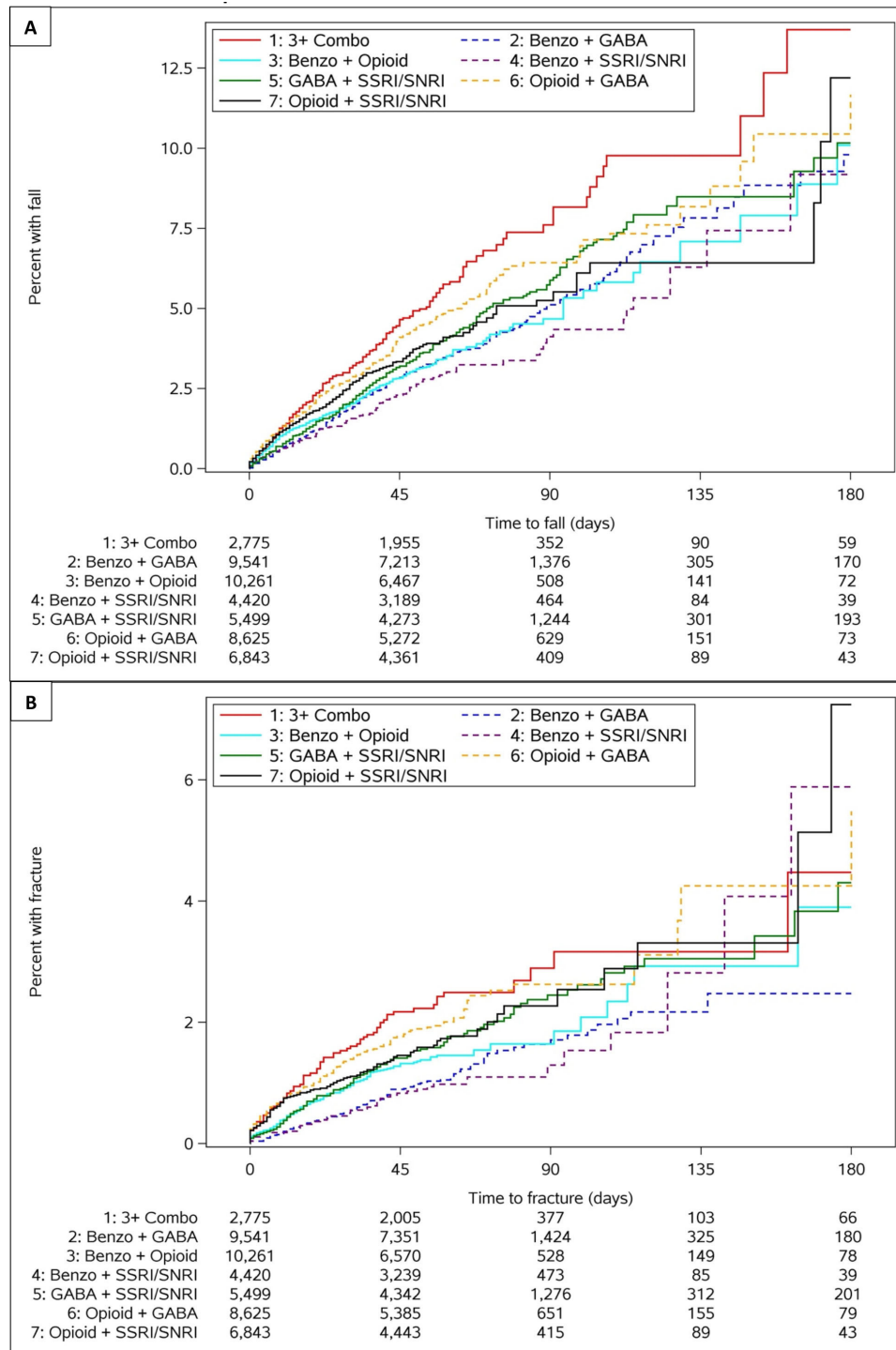
	All	Benzo/opioid	GABA +SSRI/ SNRI	3+combo	Benzo+GABA	Benzo+SSRI/ SNRI	Opioid +GABA	Opioid +SSRI/ SNRI
Chronic conditions								
Alcohol use disorders	2131	417	277	131	365	181	420	340
	4.4%	4.1%	5.0%	4.7%	3.8%	4.1%	4.9%	5.0%
Alzheimer/dementia	10202	1759	1355	665	2008	840	2168	1407
	21.3%	17.1%	24.6%	24.0%	21.0%	19.0%	25.1%	20.6%
Arthritis	37490	8073	4314	2205	6636	3323	7147	5792
	78.2%	78.7%	78.5%	79.5%	69.6%	75.2%	82.9%	84.6%
Asthma	6543	1409	816	408	1168	557	1167	1018
	13.6%	13.7%	14.8%	14.7%	12.2%	12.6%	13.5%	14.9%
Cancer	6917	1511	781	381	1332	700	1230	982
	14.4%	14.7%	14.2%	13.7%	14.0%	15.8%	14.3%	14.4%
CKD	18364	3753	2373	1150	2924	1535	3521	3108
	38.3%	36.6%	43.2%	41.4%	30.6%	34.7%	40.8%	45.4%
COPD	14217	3254	1639	930	2274	1110	2697	2313
	29.6%	31.7%	29.8%	33.5%	23.8%	25.1%	31.3%	33.8%
Depression	29905	4682	4153	2005	6530	2432	6364	3739
	62.3%	45.6%	75.5%	72.3%	68.4%	55.0%	73.8%	54.6%
Diabetes	17962	3460	2537	1088	2949	1601	3293	3034
	37.4%	33.7%	46.1%	39.2%	30.9%	36.2%	38.2%	44.3%
Drug use disorder	5038	1256	478	394	553	325	1044	988
	10.5%	12.2%	8.7%	14.2%	5.8%	7.4%	12.1%	14.4%
Epilepsy	2075	379	281	163	360	191	397	304
	4.3%	3.7%	5.1%	5.9%	3.8%	4.3%	4.6%	4.4%
Hearing impairment	4553	821	592	242	968	416	861	653
	9.5%	8.0%	10.8%	8.7%	10.1%	9.4%	10.0%	9.5%
Hip/Pelvic fracture	1001	196	111	79	174	55	254	132
	2.1%	1.9%	2.0%	2.8%	1.8%	1.2%	2.9%	1.9%
Liver disease	3870	814	473	250	665	344	692	632
	8.1%	7.9%	8.6%	9.0%	7.0%	7.8%	8.0%	9.2%
Migraine/headache	4362	915	532	292	852	464	734	573
	9.1%	8.9%	9.7%	10.5%	8.9%	10.5%	8.5%	8.4%
Mobility impairment	2744	436	453	185	425	218	528	499
	5.7%	4.2%	8.2%	6.7%	4.5%	4.9%	6.1%	7.3%
Obesity	13994	2602	1983	903	2262	1185	2717	2342
	29.2%	25.4%	36.1%	32.5%	23.7%	26.8%	31.5%	34.2%
Osteoporosis	7817	1646	868	443	1487	701	1552	1120
	16.3%	16.0%	15.8%	16.0%	15.6%	15.9%	18.0%	16.4%
Spine injury	1154	247	144	89	160	82	242	190
	2.4%	2.4%	2.6%	3.2%	1.7%	1.9%	2.8%	2.8%
Vision impairment	14508	2929	1772	833	3167	1460	2405	1942
	30.2%	28.5%	32.2%	30.0%	33.2%	33.0%	27.9%	28.4%

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, End-stage renal disease; GABA, gabapentinoids; MW, Midwest; NE, Northeast; SD, standard deviation; SO, South; SSRI, selective serotonin reuptake inhibitors; WE, West.

(38.3%), vision impairment (30.2%) and obesity (29.2%). Some groups that received different drug combinations differed in demographic characteristics and comorbid conditions. For example, some patient-level differences for those prescribed benzo +GABA versus opioid +SSRI/SNRI were gender (81.5% vs 74.3% female, respectively), Medicaid dual eligibility (19.5% vs 31.7%) and comorbid arthritis (69.6% vs 84.6%).

### Fall and fracture event analysis

The estimated cumulative risks for falls for the seven drug combinations over a 6-month period are presented as incidence curves in **figure 1A** (benzo +opioid: 10.1% at 6 months; benzo +GABA: 9.8%; benzo +SSRI/SNRI: 9.2%; opioid +GABA: 11.7%; opioid +SSRI/SNRI: 12.2%; GABA +SSRI/SNRI: 10.2%;  $\geq 3$  drugs: 13.7%). **Figure 1B**



**Figure 1** Time to the incidence of (A) fall and (B) fracture after initiation of different drug combinations from Kaplan-Meier estimator. SSRI/SNRI, selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor. GABA, gabapentinoid.

presents the curves for fracture (benzo +opioid: 3.9% at 6months; benzo +GABA: 2.5%; benzo +SSRI/SNRI: 5.9%; opioid +GABA: 5.5%; opioid +SSRI/SNRI: 7.2%; GABA +SSRI/SNRI: 4.3%;  $\geq 3$  drugs: 4.5%).

### Fall risk

**Table 2** presents the association between drug combination and fall risk as adjusted HRs from the multivariable model adjusted for demographic characteristics, chronic conditions and history of fall and hospitalisation in the prior year. Regimens with a combination of  $\geq 3$  drugs (aHR, 1.38; 95% CI 1.14 to 1.67) and opioid +GABA (aHR, 1.18; 95% CI 1.02 to 1.37) were associated with a higher risk of falls, compared with use of benzo +opioid. Characteristics that conferred an increased fall risk included older age (75–84: aHR, 1.36; 95% CI 1.22 to 1.52;  $\geq 85$ : aHR, 1.74; 95% CI 1.51 to 2.00) and Medicare entitlement due to age (aHR, 1.14; 95% CI 1.02 to 1.27). History of fall (aHR, 2.48; 95% CI 2.25 to 2.75) and hospitalisation (aHR, 1.20; 95% CI 1.08 to 1.33) in the prior year were associated with a higher fall risk. Multiple comorbid conditions were also associated with increased fall risk: Alzheimer's/dementia (aHR, 1.37; 95% CI 1.24 to 1.52), cancer (aHR, 1.18; 95% CI 1.06 to 1.30), CKD (aHR, 1.20; 95% CI 1.09 to 1.33), COPD (aHR, 1.16; 95% CI 1.04 to 1.29), diabetes (aHR, 1.18; 95% CI 1.02 to 1.35) and history of drug use disorder (aHR, 1.24; 95% CI 1.03 to 1.49).

### Fracture risk

**Table 3** presents the association between drug combination and fracture risk from the multivariable model adjusted for demographic characteristics, chronic conditions and history of fracture and hospitalisation in the prior year. The use of benzo +GABA (aHR, 0.76; 95% CI 0.59 to 0.98) maintained a lower fracture risk compared with benzo +opioid use. Older age (75–84: aHR, 1.23; 95% CI 1.02 to 1.46), history of fracture (aHR, 5.18; 95% CI 4.36 to 6.15) and hospitalisation (aHR, 1.40; 95% CI 1.18 to 1.66) in the prior year were associated with an increased risk of fracture. Comorbid conditions associated with an increased fracture risk were Alzheimer's/dementia (aHR, 1.27; 95% CI 1.08 to 1.51), cancer (aHR, 1.27; 95% CI 1.08 to 1.49), CKD (aHR, 1.32; 95% CI 1.13 to 1.55) and history of drug use disorder (aHR, 1.35; 95% CI 1.03 to 1.77).

### Interactions

Among the tested interactions, only the interaction of drug combination and Alzheimer's/dementia was statistically significant ( $p=0.0023$ ) for the outcome of fall (online supplemental table 5). After stratifying by Alzheimer's/dementia status,  $\geq 3$  drugs (aHR, 1.71; 95% CI 1.22 to 2.39), benzo +GABA (aHR, 1.53; 95% CI 1.16 to 2.02) and opioid +GABA (aHR, 1.41; 95% CI 1.07 to 1.87) were associated with a higher risk of fall in patients with this comorbidity compared with the opioid +benzo combination; in individuals without Alzheimer's dementia,

no combinations were associated with a higher fall risk compared with the benzo +opioid combination.

### IPTW propensity score analysis

IPTW with propensity score was used to limit the impact of confounding by indication across our study groups. Absolute standardised differences were used to assess balance across treatment groups after weighting and are presented in online supplemental table 6. The maximum absolute standardised differences across groups are displayed in **figure 2**, with all values estimated below 0.1. The results from the propensity score model for fall are presented in **table 2**, and the results for fracture are presented in **table 3**. The results from this model were consistent with the multivariable adjusted model for the combination use of  $\geq 3$  drug classes and opioid +GABA for the outcome of fall. Results of benzo +GABA were not significant for predicting a lower risk of fracture, as in the multivariable model.

### Sensitivity analyses

Two sets of sensitivity analyses were conducted to test the robustness of findings from the multivariable model. First, excluding patients with cancer from the multivariable analysis showed the combination of  $\geq 3$  drug classes predicting a higher risk of fall and fracture compared with the benzo +opioid combination (online supplemental table 7). Additionally, the combination of benzo +GABA was associated with a lower risk of fracture, consistent with the fully adjusted multivariable model in the main analyses. Second, excluding patients with any drug combination in the prior 3 months to the initiation of a new combination found that the combination of opioid +GABA was associated with a higher risk of fall and fracture compared with the combination of benzo +opioid (online supplemental table 7). Online supplemental table 8 presents the demographic and clinical characteristics of the full study cohorts for our original analyses, of the model excluding patients with cancer, and of the model with the 3-month lookback period.

### DISCUSSION

We examined associations between different combinations of opioid, benzodiazepine, gabapentinoid and SSRI/SNRI classes of medications and the risk of falls and fractures among Medicare beneficiaries with co-existing chronic pain and anxiety disorders. We found that—regardless of medication class—co-prescribing three or more psychotropic medications was associated with increased risk of falls in this population of patients. This finding is consistent with prior research showing an association of psychotropic polypharmacy and greater morbidity in older adults.<sup>33 34</sup> The magnitude of the association between co-prescribing of  $\geq 3$  psychotropics and the risk of falls/fractures is significantly higher in those with Alzheimer's disease and other dementias compared with those without, a finding consistent with research

**Table 2** Association of drug combination with falls

		Model 1*: multivariable analysis	Model 2†: IPTW propensity score analysis
		HR (95% CI)	HR (95% CI)
Drug combination‡	Benzo/opioid	REF	REF
	3+combo	1.38 (1.14 to 1.67)	1.28 (1.05 to 1.57)
	Benzo+GABA	1.05 (0.90 to 1.22)	1.09 (0.92 to 1.30)
	Benzo+SSRI or SNRI	0.85 (0.70 to 1.05)	0.90 (0.72 to 1.11)
	GABA +SSRI or SNRI	1.04 (0.88 to 1.23)	1.07 (0.89 to 1.27)
	Opioid +GABA	1.18 (1.02 to 1.37)	1.17 (1.00§ to 1.37)
	Opioid +SSRI or SNRI	1.09 (0.93 to 1.29)	1.08 (0.91 to 1.29)
Sex	Male	REF	
	Female	0.90 (0.80 to 1.01)	
Age	65–74	REF	
	75–84	1.36 (1.22 to 1.52)	
	85+	1.74 (1.51 to 2.00)	
Race	White	REF	
	Black	1.01 (0.82 to 1.25)	
	Hispanic	0.78 (0.61 to 1.00)	
	Other	1.11 (0.83 to 1.48)	
Region	WE	REF	
	MW	0.97 (0.84 to 1.12)	
	NE	0.85 (0.72 to 0.99)	
	SO	0.89 (0.78 to 1.02)	
Original entitlement	Disabled/ESRD	REF	
	Old age	1.14 (1.02 to 1.27)	
Medicaid dual eligibility	No	REF	
	Yes	1.01 (0.91 to 1.13)	
History of fall		2.48 (2.25 to 2.75)	
History of hospitalisation		1.20 (1.08 to 1.33)	
Chronic conditions (HR is for yes vs no)	Alcohol use disorders	1.20 (0.99 to 1.47)	
	Alzheimer/dementia	1.37 (1.24 to 1.52)	
	Arthritis	1.02 (0.89 to 1.16)	
	Asthma	1.13 (1.00 to 1.27)	
	Cancer	1.18 (1.06 to 1.30)	
	CKD	1.20 (1.09 to 1.33)	
	COPD	1.16 (1.04 to 1.29)	
	Depression	1.07 (0.97 to 1.19)	
	Diabetes	1.18 (1.02 to 1.35)	
	Drug use disorder	1.24 (1.03 to 1.49)	
	Epilepsy	0.93 (0.84 to 1.03)	
	Hearing impairment	1.07 (0.93 to 1.23)	
	Hip/pelvic fracture	0.72 (0.56 to 0.93)	
	Liver disease	1.12 (0.96 to 1.30)	
	Migraine/headache	1.12 (0.96 to 1.30)	
	Mobility impairment	0.87 (0.73 to 1.05)	
	Obesity	0.95 (0.86 to 1.06)	
	Osteoporosis	0.98 (0.87 to 1.11)	
	Spine injury	0.97 (0.87 to 1.10)	
	Vision impairment	1.20 (0.96 to 1.50)	

Continued



Table 2 Continued

	Model 1*: multivariable analysis	Model 2†: IPTW propensity score analysis
	HR (95% CI)	HR (95% CI)

\*The multivariable analysis was adjusted for demographic variables, history of fall, history of hospitalisation and chronic conditions.

†Inverse probability of treatment weighting with propensity score.

‡The p value for the overall drug combination variable is 0.0011 for the fall models.

§The p value for the opioid +GABA combination in the propensity model is 0.0492 and the lower bound is 1.001.

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, End-stage renal disease; GABA, gabapentinoid; IPTW, inverse probability of treatment weighting; MW, Midwest; NE, Northeast; REF, reference group; SNRI, serotonin–norepinephrine reuptake inhibitor; SO, South; SSRI, selective serotonin reuptake inhibitor; WE, West.

showing amplified toxicity of cause of CNS-active medications in persons with dementia disorders.<sup>35</sup>

We also found opioid +GABA co-prescribing was independently associated with a greater risk of falls compared with opioid +benzo co-prescribing, a finding that persisted in the IPTW propensity score analysis. This finding is unexpected, as past research has shown associations of opioid +benzo co-prescribing with high rates of falls, fractures and deaths.<sup>4,5,9–13,36</sup> It is unclear why opioid +GABA demonstrated higher fall risk than opioid +benzo, given that, alone or in combinations, all CNS-active agents (opioid, GABA and benzo) are associated with impaired alertness and motor response, which increase fall and fracture risk.<sup>37–40</sup> One possible explanation is that opioid +GABA users likely have more pain conditions (eg, knee, back or hip pain, peripheral neuropathy) that may affect mobility, balance and strength, thus further elevating the risk of falls, in addition to the fall risks from the CNS depressant effects of opioid +GABA. Yet, the higher fall risk remains significant in our analysis after adjusting for pain conditions, suggesting the possibility of other unmeasured fall-associated factors when opioids and GABA are used in combination. It is possible that the sedating effects of gabapentinoids, particularly in combination with opioids, are being underestimated by clinicians, and that this benzodiazepine-sparing combination is not inherently safer than the combination of opioids and benzodiazepines for the outcome of fall.

Our finding of decreased fracture risk with the benzo +GABA combination from the multivariable model was not robust and was inconsistent with the IPTW propensity score analysis, possibly a reflection of unmeasured variables that may influence likelihood of the complex outcome of fracture. Future research is needed to inform safe and effective combinations of medications in patients regarding fracture risk, possibly in more narrowly selected groups of patients.

For the sensitivity analysis that excludes patients with a combination in the prior 3 months, versus 1 month, as in the main analysis, the results are different compared with the fully adjusted multivariable model: the combination of opioid +GABA predicts a higher risk of both fall and fracture versus the combination of benzo +opioid. In addition to a halving of the sample size, it is possible that, compared with the main analysis' cohort, the demographic and clinical differences in this group of patients may be responsible for the differences in risk of fall and fracture. For example, patients in this group had older

age distributions and lower rates of depression, drug use disorder and obesity. The duration of their combination use was also shorter, and this cohort of patients had a lower proportion of the benzo +opioid and  $\geq 3$  drug combinations.

The absence of significant reduction in the risk of falls/fractures between GABA+SSRI/SNRI and other opioid-sparing or benzodiazepine-sparing combinations versus opioid +benzo co-prescribing was contrary to our expectations. Recent guidelines and federal and state policies urge against the combination of benzodiazepines and opioids. While this combination is now known to confer a high risk for morbidity and overdose mortality, there is not significant research that informs clinician prescribing of alternative combinations to treat comorbid chronic pain and anxiety. Despite the convention that opioid-sparing and benzodiazepine-sparing drug combinations might be safer for patients, emerging research highlights the adverse effects of gabapentinoids, particularly in combination with opioid analgesics. However, it is also important to recognise that both opioids and benzodiazepines, as well as gabapentinoids and SSRI/SNRIs, are important and effective medications in the right clinical contexts. Emerging comparative drug toxicity research should not be used to drive consequential prescribing decisions for patients without carefully weighing the benefits and harms within an individualised patient-centred framework, particularly in those with chronic pain and anxiety disorders. Often, the race to de-prescribe without a circumspect, cautious approach can lead to greater harm for patients.<sup>41,42</sup>

There are several limitations to this study, including its retrospective design and the fact that drug prescriptions do not necessarily indicate their use. This study also did not analyse the association of dose within and across combination drug regimens, but only compared combinations by pharmacologic class. Additionally, confounding by indication is also a limitation of this study, common in observational research of drug effects. While this study seeks to adjust for many clinical factors in the multivariable analysis, and test for robustness using IPTW propensity score analysis, it is possible that the indication for certain combinations was linked to fall or fracture outcomes, rather than outcomes being predicted solely by the combination. Indeed, that many of the statistically significant findings from the multivariable model were insignificant in the IPTW propensity score analysis highlight this point and the underlying challenges untangling adverse effects

**Table 3** Association of drug combination with fracture

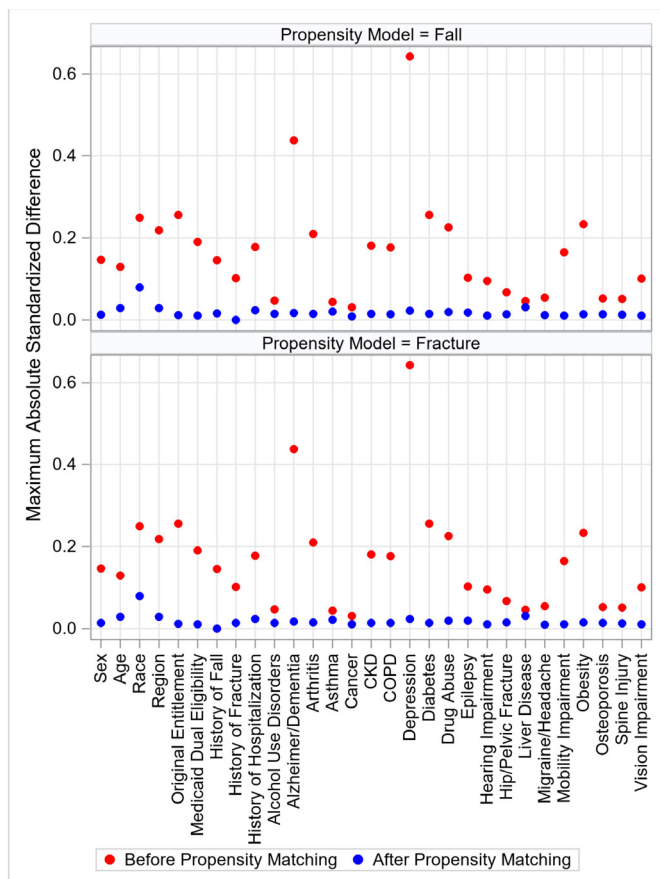
		Model 1*: multivariable analysis	Model 2†: IPTW propensity score analysis
		HR (95% CI)	HR (95% CI)
Drug combination‡	Benzo/opioid	REF	REF
	3+combo	1.30 (0.97 to 1.74)	1.12 (0.82 to 1.53)
	Benzo+GABA	0.76 (0.59 to 0.98)	0.82 (0.62 to 1.09)
	Benzo+SSRI or SNRI	0.73 (0.52 to 1.02)	0.75 (0.53 to 1.06)
	GABA +SSRI or SNRI	1.05 (0.81 to 1.36)	1.09 (0.83 to 1.43)
	Opioid +GABA	1.19 (0.94 to 1.49)	1.15 (0.90 to 1.45)
	Opioid +SSRI or SNRI	1.12 (0.88 to 1.44)	1.17 (0.89 to 1.53)
Sex	Male	REF	
	Female	0.85 (0.70 to 1.02)	
Age	65–74	REF	
	75–84	1.23 (1.03 to 1.46)	
	85+	1.22 (0.98 to 1.53)	
Race	White	REF	
	Black	0.97 (0.67 to 1.40)	
	Hispanic	0.76 (0.50 to 1.15)	
	Other	1.29 (0.84 to 1.99)	
Region	WE	REF	
	MW	0.69 (0.54 to 0.87)	
	NE	0.99 (0.78 to 1.24)	
	SO	0.77 (0.63 to 0.94)	
Original entitlement	Disabled/ESRD	REF	
	Old age	1.06 (0.89 to 1.26)	
Medicaid dual eligibility	No	REF	
	Yes	0.85 (0.72 to 1.01)	
History of fracture		5.18 (4.36 to 6.15)	
History of hospitalisation		1.40 (1.18 to 1.66)	
Chronic conditions (HR is for yes vs no)	Alcohol use disorders	1.03 (0.76 to 1.41)	
	Alzheimer/dementia	1.27 (1.08 to 1.51)	
	Arthritis	0.83 (0.67 to 1.03)	
	Asthma	1.04 (0.86 to 1.26)	
	Cancer	1.27 (1.08 to 1.49)	
	CKD	1.32 (1.13 to 1.55)	
	COPD	1.15 (0.97 to 1.36)	
	Depression	0.90 (0.77 to 1.06)	
	Diabetes	1.01 (0.81 to 1.26)	
	Drug use disorder	1.35 (1.03 to 1.77)	
	Epilepsy	0.92 (0.79 to 1.08)	
	Hearing impairment	1.06 (0.85 to 1.32)	
	Hip/pelvic fracture	0.90 (0.66 to 1.21)	
	Liver disease	1.18 (0.93 to 1.49)	
	Migraine/headache	1.01 (0.79 to 1.30)	
	Mobility impairment	0.97 (0.74 to 1.27)	
	Obesity	0.91 (0.77 to 1.08)	
	Osteoporosis	1.18 (0.99 to 1.40)	
	Spine injury	0.95 (0.79 to 1.15)	
Vision impairment	1.15 (0.87 to 1.53)		

\*The multivariable analysis was adjusted for demographic variables, history of fracture, history of hospitalisation and chronic conditions.

†Inverse probability of treatment weighting with propensity score.

‡The p value for the overall drug combination variable is 0.0008 for the fracture models.

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; GABA, gabapentinoid; IPTW, inverse probability of treatment weighting; MW, Midwest; NE, Northeast; REF, reference group; SNRI, serotonin–norepinephrine reuptake inhibitor; SO, South; SSRI, selective serotonin reuptake inhibitor; WE, West.



**Figure 2** Maximum absolute standardised differences before and after inverse probability of treatment weighting with propensity score for the fall and fracture mode. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease. CKD, chronic kidney disease. COPD, chronic obstructive pulmonary disease.

of drugs that may have different use cases, by approved indication or by real-life use pattern. Prescribers may be modifying their psychotropic prescribing practices to reflect their clinical perceptions of patients' risk of side effects such that high-fall risk patients may be given SSRI/SNRIs instead of benzodiazepines for anxiety, for example. In this vein, this study did not adjust severity in chronic pain or anxiety conditions, a factor that may influence clinician prescribing as well. Claims data may not capture such severity-based adjustment of choice and dosing of medications for pain and anxiety conditions, but this is an area for future quantitative and qualitative study. Finally, uncaptured and unmeasured differences in characteristics across patients being prescribed different drug regimens may explain predisposition to fall or fracture, beyond exposure to combination prescriptions.

In sum, this study found that the prescribing of  $\geq 3$  classes of medications and opioid +GABA co-prescribing were associated with a higher fall risk than opioid +benzo co-prescribing in patients with co-occurring chronic pain and anxiety. Our findings add to the body of research on the comparative toxicity profiles of different combinations of psychoactive medications (GABAs, SSRIs and

SNRIs) commonly used with or as substitutes for opioids or benzodiazepines in patients with chronic pain and anxiety disorders. Our findings may help clinicians weigh benefits and harms when prescribing drug combinations, especially in older patients with chronic pain and comorbid anxiety disorders, conditions that commonly co-occur in clinical practice. More research is required on the compound effects of multiple CNS-active agents on morbidity and mortality in older patients, particularly in the chronic use setting.

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**Contributors** Y-FK and JW had full access to all of the data in this study and take full responsibility for the integrity of the data and accuracy of the data analysis. Concept and design: MAR, Y-FK. Acquisition, analysis or interpretation of the data: RS, MAR, JW, Y-FK. Drafting of the manuscript: RS, MAR, JW, Y-FK. Critical revision of the manuscript for important intellectual content: RS, MAR, JW, Y-FK. Statistical analysis: Y-FK, JW. Obtained funding: MAR, Y-AK. Administrative, technical or material support: Y-FK, JW. Supervision: Y-FK, MAR. Y-FK is responsible for the overall content of this study as the guarantor.

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