

Title: Interaction between Benzodiazepines and Prescription Opioids on Incidence of Hard Braking Events in Older Drivers

Running Title: Benzodiazepines and Opioids in Older Drivers

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Key Points:

- About 6% of older adult drivers use benzodiazepines, 6% use prescription opioids, and 1% use both medications.
- The excess risk of hard braking events associated with prescription opioids is 19%.
- There is a positive additive interaction between benzodiazepines and prescription opioids on the incidence of hard braking events.

Why does this matter?

Benzodiazepines are the most commonly used potentially inappropriate medication among older drivers, and concurrent use of benzodiazepines and prescription opioids may affect driving safety through increased incidence of hard braking events.

Abstract

Background: Polypharmacy use among older adults is of increasing concern for driving safety. This study assesses the individual and joint effects of benzodiazepines and prescription opioids on the incidence of hard braking events in older drivers.

Methods: Data for this study came from the Longitudinal Research on Aging Drivers project – a multisite, prospective cohort study of 2990 drivers aged 65-79 years at enrollment (2015-2017). Adjusted incidence rate ratios (aIRRs) and 95% confidence intervals (CIs) of hard braking events (defined as maneuvers with deceleration rates ≥ 0.4 g and commonly known as near-crashes) were estimated through multivariable negative binomial modeling.

Results: Of the 2932 drivers studied, 167 (5.7%) were taking benzodiazepines, 163 (5.6%) prescription opioids, and 23 (0.8%) both drugs at baseline. The incidence rates of hard braking events per 1000 miles driven were 1.14 (95% CI 1.10–1.18) for drivers using neither benzodiazepines nor prescription opioids, 1.25 (95% CI 1.07–1.43) for those using benzodiazepines only, 1.55 (95% CI 1.35–1.76) for those using prescription opioids only, and 1.63 (95% CI 1.11–2.16) for those using both medications. Multivariable modeling revealed that use of prescription opioids was associated with a 19% increased risk of hard braking events (aIRR 1.19, 95% CI 1.03–1.36). There existed a positive interaction between the two drugs on the additive scale but not on the multiplicative scale.

Conclusion: Concurrent use of benzodiazepines and prescription opioids by older drivers appears to affect driving safety through increased incidence of hard braking events.

Keywords: Aging, Benzodiazepines, Driving Safety, Drug Interaction, Opioids

INTRODUCTION

Driving is an instrumental activity of daily living for older adults.¹ As the most preferred mode of personal transportation, driving is essential for maintaining self-identity and independence for many older adults, particularly those living in rural areas.^{1,2} Driving cessation has been linked to accelerated decline in general health and increases in depression, suicide and overall mortality.^{2,3} The number of licensed drivers aged 65 years and older in the United States is projected to increase from 48 million in 2020 to 63 million in 2030.^{4,5} The projected increase in the older adult driver population poses a significant threat to traffic safety as older adult drivers are at substantially increased risk of fatal crash involvement per mile driven compared to drivers aged 30 to 59 years.⁴

Compared with younger drivers, older drivers are more likely to be involved in certain collisions such as intersection and merging crashes due in part to age-related function declines.⁶ Physical, cognitive, and sensory functioning are necessary for safe driving. Deficiencies in physical strength and dexterity, hand-eye coordination, response time, and alertness can impact safe operation of a motor vehicle among older adult drivers.⁷ In addition, health conditions, such as cataracts, sleep disorders, arthritis, and diabetes mellitus, may cause declines in abilities to merge into traffic, switch lanes or enter the highway.^{8,9} Previous studies have shown that increasing functional impairment is associated with an elevated risk of crashes.⁸⁻¹⁰

Polypharmacy, which is defined as the simultaneous use of two or more medications, is prevalent in the older adult population.^{11,12} Over 90% of the participants in the Longitudinal Research on Aging Drivers (LongROAD) project reported taking at least two medications (both prescribed and over-the-counter) and 49% were taking eight or more medications at the time of enrollment.^{13,14} To minimize the potential harm from medications in the older adult population, the

American Geriatrics Society established a list of medications that should generally be avoided by adults 65 years and older.¹⁵ The most common types of potentially inappropriate medications used by older drivers are benzodiazepines.¹³ The prevalence of any benzodiazepine use in older adults in the US was 12.9%.¹⁶ Co-prescribing of opioids and benzodiazepines occurred in approximately 1.5 million outpatient visits among older adults in the United States between 2011 and 2013.^{17,18} Opioids and benzodiazepines are both psychoactive drugs that may impact mood, perception, and consciousness.¹⁹ Benzodiazepines are used to treat anxiety and sleep problems, while prescription opioids are used to treat moderate to severe pain. The National Institute on Drug Abuse cautions against the concurrent use of psychoactive drugs owing to the increased risk of overdose, breathing suppression, cognitive function impairment, and mortality. The Centers for Disease Control and Prevention and the American Geriatrics Society advise clinicians to avoid prescribing opioids and benzodiazepines concurrently whenever possible.^{15,20}

A systematic review on psychoactive medications and crash risk in older drivers indicated that the drugs of concern, such as benzodiazepines, are those that can affect a driver's ability to react to external stimuli. Experimental and on-road driving studies have concluded that psychoactive agents have detrimental effects on skills necessary for safe driving.²¹ Benzodiazepines have been found to impair psychomotor functions and driving behaviors in multiple studies.^{22–24} Analyses of fatal 2-vehicle crashes with access to toxicological drug testing results found that the presence of prescription opioids was associated with driver culpability.²⁵ Another study using commercial health insurance data found that use of benzodiazepines was associated with unintentional injuries, including those resulting from motor vehicle crashes.²⁶ The use of lorazepam, one medication within the benzodiazepine class, was associated with an increased risk of motor vehicle crashes of 31–127%. The effects of these two medications on the

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risk of unintentional injuries appear to be synergistic, i.e., the joint effect being higher than the sum of the individual effects.^{24,25} The present study aims to assess the individual and joint effects of benzodiazepines and prescription opioids on hard braking events in older adults using naturalistic driving data. We hypothesize that there is a significant interaction between benzodiazepines and prescription opioids on either the multiplicative or the additive scale.

METHODS

Data Source and Study Sample

Data came from the LongROAD project, a prospective cohort study of older drivers conducted in five sites (Ann Arbor, MI; Baltimore, MD; Cooperstown, NY; Denver, CO; and San Diego, CA) and sponsored by the AAA Foundation for Traffic Safety (Washington, DC).²⁷ The LongROAD project was designed to address major concerns relating to the safety of older drivers, such as the effects of medications and medical conditions on driving behavior and safety. There were 2990 active drivers aged 65–79 years enrolled in the LongROAD project between July 2015 and March 2017 from primary care clinics or healthcare systems. At the time of enrollment, study participants met the following inclusion criteria: (1) being 65–79 years of age; (2) holding a valid driver's license; (3) being fluent in English; (4) driving at least once a week on average; (5) residing in the catchment area of any one of the five study sites for at least 10 months per calendar year; (6) having no plans to move outside of the catchment area within the next 5 years; (7) having access to a motor vehicle of the model year 1996 or newer with an accessible on-board diagnostics II (OBDII) port; and (8) driving the primary vehicle 80% of the time if access to more than one vehicle. Those with significant cognitive impairment or degenerative diseases (e.g., Alzheimer's disease and related dementias) were not eligible for the study. The study design and methods were

described in detail elsewhere.²⁷ During the follow-up, the response rates were 96.6% in the first year, 94.1% in the second year, and 93.9% in the third year. Of the 2990 participants in the LongROAD study, 41 (1.4%) were excluded from this analysis due to missing baseline medication data, and 20 (0.7%) due to unavailable or unreliable driving data. Human subjects research protocols for the LongROAD study were developed collaboratively by the investigators and were reviewed and approved individually by the institutional review boards (IRBs) of the participating institutions. A certificate of confidentiality for the study was obtained from the National Institutes of Health.

Measures

Benzodiazepines and prescription opioids. Data on benzodiazepines and prescription opioids at baseline were collected through the “brown-bag” review of medications, in which each study participant was asked to bring all current medications (both prescribed and over the counter) and supplements for assessment by the trained research staff following informed consent.²⁷ Annual follow-up assessments were performed through telephone interviews for odd years after baseline and by in-person visits for even years. Data on medication and supplement use were collected from the label on participants’ medication bottles. Medications were classified by pharmacists based on the pharmacologic therapeutic classification system established by the American Society of Health-System Pharmacists in the American Hospital Formulary Service Clinical Drug Information.^{14,28,29}

Covariates. All baseline demographic and health-related variables were collected through questionnaires. Age at baseline was categorized into three levels: 65 to 69 years old, 70 to 74 years old, and 75 to 79 years old. Gender was a binary variable (i.e., male vs. female) while race/ethnicity

was categorized into White non-Hispanic, Black non-Hispanic, or other races. Marital status was grouped into currently married or not married. Highest level of education attained was a four-level categorical variable: high school or less, Associate's degree, Bachelor's degree, and advanced degree. Total household income for the past year was categorized as less than \$50,000, \$50,000 to \$99,999, and \$100,000 or more. Current working status was categorized as yes or no. Urbanicity was classified as urban (core region of a metropolitan statistical area), suburban (noncore region of a metropolitan statistical area), or rural (nonmetropolitan area) according to the Rural Urban Commuting Area values for the zip code of study participant's residence.² All medical conditions, including arthritis, sleep disorder, and diabetes mellitus, were recorded as binary variables (i.e., yes vs.no). Total number of medications was categorized into four levels: 0 to 4, 5 to 8, 9 to 11, and 12 or more.

Hard Braking Events. The outcome measure was hard braking events, defined as maneuvers with longitudinal deceleration rates ≥ 0.4 g. Hard braking events are widely used in naturalistic driving studies as a safety metric.³⁰⁻³⁴ It is also evident that if measured appropriately (e.g., the axes of acceleration and threshold levels), rapid changes in acceleration are correlated with unsafe driving behaviors and crash risk among older drivers.³⁵⁻³⁷ Data on hard braking events were captured for up to 44 months after baseline through the OBDII DataLogger (Danlaw, Inc., Novi, MI, USA), a recording device installed in the study participant's primary vehicle at the time of enrollment.²⁷

Statistical Analysis

Incidence rates of hard braking events per 1000 miles driven were computed according to demographic characteristics, urbanicity, comorbidity, benzodiazepine and prescription opioid use,

and the total number of medication use. Because of over-dispersion in hard braking events, multivariable negative binomial modeling was used to estimate incidence rate ratios (IRRs) and 95% confidence intervals (CIs) of hard braking events with adjustment for confounding variables that may have an impact on the crash risk. Generalized estimating equations with a negative binomial distribution, a log link, and an independent correlation matrix structure were used to address the correlation of medication use and driving data from repeated measurements during the 44-month follow-up.³⁸ The final model adjusted for basic demographic characteristics (i.e., age and gender), along with covariates that remained significant (i.e., marital status and urbanicity). The logarithm of mileage was included as the offset in the negative binomial models. Interaction between benzodiazepines and prescription opioids on hard braking events was assessed on both multiplicative and additive scales. Multiplicative interaction was assessed by including in the multivariable model an interaction term (i.e., the product of the two binary variables indicating use of benzodiazepines and use of prescription opioids), and additive interaction was assessed based on the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (API), and the synergy index (S), as defined below:

$$\begin{aligned} \text{RERI} &= \text{IRR}_{\text{Benzodiazepines+Prescription Opioids}} - \text{IRR}_{\text{Benzodiazepines}} - \text{IRR}_{\text{Prescription Opioids}} + 1 \\ \text{API} &= \text{RERI} / \text{IRR}_{\text{Benzodiazepines+Prescription Opioids}} \\ \text{S} &= \text{RERI} / [(\text{IRR}_{\text{Benzodiazepines}} - 1) + (\text{IRR}_{\text{Prescription Opioids}} - 1)], \end{aligned}$$

where RERI = 0, API = 0 and S = 1 indicate an absence of interaction while RERI > 0, API > 0, and S > 1 indicate positive additive interaction and RERI < 0, API < 0, and S < 1 indicate negative additive interaction.³⁹⁻⁴² Estimates of additive interaction statistics and 95% confidence intervals were computed using the approach suggested by VanderWeele and Knol.³⁹ Multiplicative interaction implies that the combined effect of two exposures is significantly larger or smaller than the product of the individual effects, and additive interaction implies the combined effect of two

exposures is significantly larger or smaller than the sum of the individual effects. An interaction is positive if the combined effect is larger than the product or the sum of the individual effects, or negative if the combined effect is smaller than the product or the sum of the individual effects. Statistical significance was set at $p < 0.05$. All analyses were performed using SAS[®] OnDemand for Academics Edition (SAS Institute Inc., Cary, NC, USA).

RESULTS

Of the 2929 drivers included in this analysis, age at baseline averaged 71.08 years (standard deviation 4.06 years), 46.8% were male, 85.7% were White, 63.5% were currently married, 41.1% had advanced degrees, 30.2% were employed at the time of enrollment, and 72.8% lived in urban areas. Based on the study participants' baseline self-reported medical checklist and "brown-bag" medication review, 62.6% had arthritis, 24.4% had sleep disorders, 17.9% had diabetes mellitus, and 44.5% were taking nine or more medications (both prescribed and over the counter). Among the drivers included in this study, 5.7% were taking benzodiazepines, 5.6% prescription opioids, and 0.8% both benzodiazepines and prescription opioids at baseline (Table 1).

The follow-up accumulated over 66 million miles of driving data and 76,191 hard braking events, yielding an incidence rate of 1.14 hard braking events per 1000 miles. The incidence rate of hard braking events varied by baseline demographic characteristics, comorbidity, and the total number of medications (Table 2). Elevated incidence rates of hard braking events were found in drivers who were 75 years and older, female, non-white, or currently unmarried, resided in urban areas, had diabetes mellitus, or were taking five or more medications (Table 2). The incidence rates of hard braking events per 1000 miles driven were 1.14 (95% CI 1.10–1.18) for drivers using neither benzodiazepines nor prescription opioids, 1.25 (95% CI 1.07–1.43) for those using

benzodiazepines only, 1.55 (95% CI 1.35–1.76) for those using prescription opioids only, and 1.63 (95% CI 1.11–2.16) for those using both medications (Figure 1).

Relative to drivers using neither benzodiazepines nor prescription opioids, the risk of hard braking events was elevated by 4% (aIRR 1.04, 95% CI 0.87–1.25) for those using benzodiazepines only, 19% (aIRR 1.19, 95% CI 1.03–1.36) for those using prescription opioids only, and 62% (aIRR 1.62, 95% CI 0.77–3.37) for those using both drugs (Supplementary Table S1). There existed a positive interaction between the two drugs on the additive scale but not on the multiplicative scale (Table 3).

DISCUSSION

In this naturalistic driving study, the prevalence of benzodiazepine and prescription opioid use among older drivers were, respectively, 6.5% and 6.4%, which are consistent with other studies of older adults.³³⁻³⁵ Using objectively collected driving data, we were able to assess the individual and joint effects of benzodiazepines and prescription opioids on hard braking events. Prescription opioids were associated with a 19% increased risk of hard braking events. Although use of benzodiazepines alone was not associated with a statistically significant increase in hard braking events, concurrent use of benzodiazepines and prescription opioids conferred a positive interaction effect on hard braking events on the additive scale, increasing the risk by 62%. Previous studies found that the use of prescription opioids by drivers was associated with increased crash culpability.^{25,44,44} Our study indicates that the use of prescription opioids may also affect driving safety among older adults.

Although the study endpoint did not directly measure crash risk, hard braking events have been explored as a potential safety metric in naturalistic driving studies,^{30-34,45} and have been shown to be related to declining abilities and unsafe driving among older drivers.³⁵⁻³⁷ That hard

braking events are much more frequent than crashes allowed us to assess the interaction between benzodiazepines and prescription opioids with adequate study power. Our results indicate that the positive interaction of benzodiazepines and prescription opioids on hard braking events is statistically significant on the additive scale, but not on the multiplicative scale. This finding is consistent with the experimental evidence.⁴⁶ Benzodiazepines act on the gamma amino butyric acid (GABA) receptors in the central nervous system.^{19,47,48} GABA is inhibitory in nature and produces a sedative effect on the brain. When benzodiazepines bind with the GABA receptor, they generate an inhibitory effect throughout the brain, neuromuscular system, and respiratory system. On the other hand, opioids act on the opioid receptor, which produces mainly analgesic and respiratory depressant effects. Our finding of the positive additive interaction between opioids and benzodiazepines is reflective of the different pathways through which the two drugs act on the central nervous system.

Our study highlights the importance of assessing interaction on both the additive and the multiplicative scales. The presence of interaction on the additive but not on the multiplicative scale (positive additive negative multiplicative) ranks very high (second out of eleven) on the interaction continuum, which compares the strength of various types of interactions between two causative exposures.⁴⁹ The positive additive interaction between benzodiazepines and prescription opioids on hard braking events means that the combined risk associated with concurrent use of the two medications is significantly greater than the sum of the individual risks associated with separate use of the two medications. As a result, our study suggests that for older adult drivers taking opioids and benzodiazepines the ability to drive safely may be affected, especially when these medications are used concurrently. Healthcare providers should inform and educate their patients about the potential risks associated with this specific form of polypharmacy use.

While the validity of our study is strengthened by the prospective cohort design and the objectively collected driving and medication data with repeated measurements during the follow up, the results should be interpreted in light of several notable limitations. First, data on medication adherence were not collected and therefore not considered in this study. Moreover, due to the modest number of the study participants taking benzodiazepines and prescription opioids, it was not feasible to include detailed medication information, such as dosage, in the multivariable model. Second, the study sample was not representative of the US older driver population as the participants in the LongROAD project were disproportionately non-Hispanic White, had attained better education on average, and had higher median household income than the general population.²⁷ Finally, the outcome measure we used in this study was a surrogate for vehicular crashes rather than actual crashes. The correspondence between hard braking events and vehicular crashes needs to be further evaluated.⁴⁴⁻⁴⁷

CONCLUSIONS

Our study suggests that concurrent use of benzodiazepines and prescription opioids by older drivers is associated with an excess risk of hard braking events, constituting a positive interaction on the additive scale. Effective interventions to reduce the use of prescription opioids and concurrent use of prescription opioids and benzodiazepines in older adults may help contribute to driving safety and healthy aging.

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Conflict of Interest: The authors have no conflict of interest to disclose.

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Supplementary Table S1. Adjusted incidence rate ratios (aIRRs) and 95% confidence intervals (CIs) of hard braking events from the multivariable negative binomial model according to use of benzodiazepines and prescription opioids, age, gender, marital status, and urbanicity of residence, the Longitudinal Research on Aging Drivers (LongROAD) Study

Table 1. Baseline demographic characteristics and comorbidities of the study sample by benzodiazepines and prescription opioids use status, the Longitudinal Research on Aging Drivers (LongROAD) Study.

Variables	Total Number of Drivers ^a	Number of Drivers on Benzodiazepines and Opioids (% ^b)								
		Neither		Benzodiazepines Only		Opioids Only		Both		
Age, years										
	65-69	1215	1087	(41.46%)	64	(44.44%)	53	(37.86%)	11	(47.83%)
	70-74	1017	912	(34.78%)	45	(31.25%)	53	(37.86%)	7	(30.43%)
	75-79	697	623	(23.76%)	35	(24.31%)	34	(24.29%)	5	(21.74%)
Gender										
	Male	1372	1262	(48.13%)	48	(33.33%)	56	(40.00%)	6	(26.09%)
	Female	1557	1360	(51.87%)	96	(66.67%)	84	(60.00%)	17	(73.91%)
Race										
	White, Non-Hispanic	2508	2236	(85.41%)	136	(94.44%)	115	(82.14%)	21	(91.30%)
	Black, Non-Hispanic	207	188	(7.18%)	2	(1.39%)	15	(10.71%)	2	(8.70%)
	Other	210	194	(7.41%)	6	(4.17%)	10	(7.14%)	0	(0.00%)
Marital Status										
	Married	1843	1686	(64.92%)	81	(57.04%)	67	(47.86%)	9	(39.13%)
	Not Married	1059	911	(35.08%)	61	(42.96%)	73	(52.14%)	14	(60.87%)
Education										
	High School or Less	325	288	(11.02%)	17	(11.81%)	18	(12.86%)	2	(8.70%)
	Associate’s Degree	711	600	(22.95%)	37	(25.69%)	62	(44.29%)	12	(52.17%)
	Bachelor’s Degree	684	619	(23.68%)	36	(25.00%)	26	(18.57%)	3	(13.04%)
	Advanced Degree	1201	1107	(42.5%)	54	(37.50%)	34	(24.29%)	6	(26.09%)
Total Household Income Past Year										
	<\$50,000	757	638	(25.24%)	45	(33.09%)	64	(47.06%)	10	(43.48%)
	\$50,000–\$99,999	1129	1026	(40.59%)	48	(35.29%)	50	(36.76%)	5	(21.74%)
	≥\$100,000	937	864	(34.18%)	43	(31.62%)	22	(16.16%)	8	(34.78%)
Working Status										
	Yes	884	1803	(68.79%)	107	(74.83%)	117	(83.57%)	16	(69.57%)
	No	2043	818	(31.21%)	36	(25.17%)	23	(16.43%)	7	(30.43%)

Urbanicity										
	Urban	2132	1892	(72.16%)	108	(75.00%)	110	(78.57%)	22	(95.65%)
	Suburban	412	377	(14.38%)	19	(13.19%)	15	(10.71%)	1	(4.35%)
	Rural	385	353	(13.46%)	17	(11.81%)	15	(10.71%)	0	(0.00%)
Arthritis										
	Yes	1832	1030	(39.31%)	41	(28.47%)	21	(15.00%)	3	(13.04%)
	No	1095	1590	(60.69%)	103	(71.53%)	119	(85.00%)	20	(86.96%)
Sleep Disorder										
	Yes	715	2021	(77.14%)	96	(66.67%)	85	(60.71%)	10	(43.48%)
	No	2212	599	(22.86%)	48	(33.33%)	55	(39.29%)	13	(56.52%)
Diabetes Mellitus										
	Yes	523	2158	(82.37%)	124	(86.11%)	103	(73.57%)	18	(81.82%)
	No	2403	462	(17.63%)	20	(13.89%)	37	(26.43%)	4	(18.18%)
Total Number of Medications										
	0-4	859	831	(31.69%)	17	(11.81%)	11	(7.86%)	0	(0.00%)
	5-8	768	721	(27.50%)	29	(20.14%)	15	(10.71%)	3	(13.04%)
	9-11	718	632	(24.10%)	49	(34.03%)	33	(23.57%)	4	(17.39%)
	≥12	584	438	(16.70%)	49	(34.03%)	81	(57.86%)	16	(69.57%)

^aTotals within variables may vary due to missing data.

^bPercentage indicating column percentage within each variable.

Table 2. Incidence rates of hard braking events per 1000 miles by baseline demographic characteristics and comorbidities, the Longitudinal Research on Aging Drivers (LongROAD) Study.

Variables	Miles in Thousands	Number of Hard Braking Events	Incidence Rate/1000 Miles	95% Confidence Interval
Age, years				
65-69	29125	32101	1.10	1.04, 1.16
70-74	22933	27014	1.18	0, 1.24
75-79	13483	17076	1.27	0, 1.35
Gender				
Male	33352	37955	1.14	1.08, 1.19
Female	32189	38236	1.19	1.13, 1.24
Race and Ethnicity				
White, Non-Hispanic	56962	63101	1.11	1.07, 1.15
Black, Non-Hispanic	4481	5908	1.32	0, 1.48
Other	4027	7027	1.74	1.57, 1.92
Marital Status				
Married	43263	46601	1.08	1.03, 1.12
Not Married	21745	28835	1.33	0, 1.40
Education				
High School or Less	6671	7034	1.05	0.94, 1.17
Associate's Degree	16188	20157	1.25	1.16, 1.33
Bachelor's Degree	15192	17964	1.18	1.10, 1.26
Advanced Degree	27328	30878	1.13	1.07, 1.19
Total Household Income Past Year				
<\$50,000	15208	19841	1.30	1.22, 1.39
\$50,000–\$99,999	26857	27892	1.04	0.98, 1.10
≥\$100,000	21308	26057	1.22	1.15, 1.29
Employment Status				
Yes	22234	26109	1.17	1.10, 1.25
No	43258	49962	1.15	1.11, 1.20
Urbanicity				
Urban	43511	60824	1.40	1.35, 1.45
Suburban	11691	8264	0.71	0.63, 0.79
Rural	10338	7103	0.69	0.60, 0.77
Arthritis				
Yes	40024	47910	1.20	1.15, 1.25
No	25498	28268	1.11	1.05, 1.17
Sleep Disorder				
Yes	15841	18715	1.18	1.10, 1.26
No	49681	57463	1.16	1.11, 1.20
Diabetes Mellitus				
Yes	11510	15411	1.34	1.24, 1.44
No	54005	60758	1.13	1.08, 1.17
Total Number of Medications				
0-4	20240	22120	1.09	1.02, 1.16
5-8	17979	20019	1.11	1.04, 1.19

9-11	15378	17620	1.15	1.07, 1.22
≥ 12	11943	16432	1.38	1.28, 1.47

Table 3. Multiplicative and additive interaction statistics and 95% confidence intervals (CIs) between benzodiazepines and prescription opioids on hard braking events, the Longitudinal Research on Aging Drivers (LongROAD) Study.

Statistic	Value ^a	95% CI
Interaction on the multiplicative scale		
Benzodiazepines x Opioids	0.27	(-0.50 1.03)
Interaction on the additive scale		
Relative Excess Risk due to Interaction	0.38	(0.07, 0.83)
Attributable Proportion due to Interaction	0.24	(0.02, 0.46)
Synergy Index	2.66	(1.01, 7.02)

^aEstimates from a multivariable negative binomial model with adjustment for age, gender, marital status, and urbanicity.

Figure 1. Incidence rates and standard errors of hard braking events per 1000 miles driven according to driver use of benzodiazepines and prescription opioids, the Longitudinal Research on Aging Drivers (LongROAD) Study

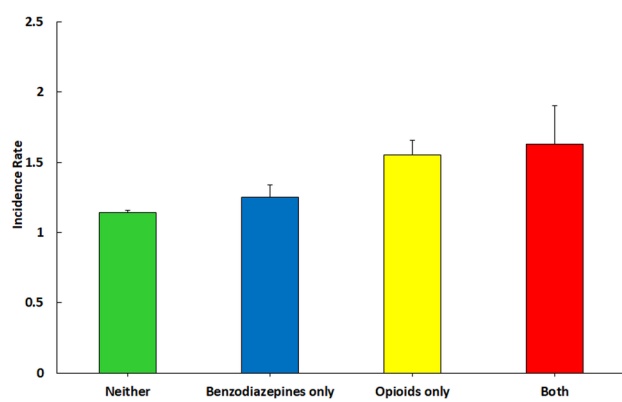


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