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ORIGINAL RESEARCH

Adverse Drug Events Associated with Opioid Treatment for Pain After Motor Vehicle Crash

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Purpose: Thousands of motor vehicle crash (MVC) related deaths and injuries occur among older adults every year in the United States. Injuries from MVC may cause acute or chronic pain resulting in functional decline and disability. Opioid treatment poses risk of adverse drug events (ADEs) including dependency, overdose, respiratory problems, and other complications. Our objective was to evaluate the comparative risks of ADEs associated with three opioid prescribing strategies: 1) greater versus lesser days' supply (≥6 days versus ≤5 days), 2) higher versus lower doses (≥30 MME versus <30 MME), and 3) tramadol versus other opioids over 45 days of follow-up.

Methods: The study utilized Medicare claims linked to New Jersey drivers' licensing and police-reported crashes to emulate three target trials for each pairwise treatment comparison from May 1, 2007–November 16, 2017. The study included Medicare beneficiaries aged >67 years who initiated opioids within 10 days after MVC.

Results: Among 510 beneficiaries, the mean (standard deviation) age was 76.1 (6.6) years, with 59.8% females and 90.4% White race. For the intention-to-treat estimand, risk ratios (RRs) [95% confidence limits (CLs)] were 1.64 (0.64, 4.57), 0.83 (0.45, 1.76), and 0.54 (0.21, 4.01) for days' supply, dose, and tramadol treatment strategies, respectively. There were no significant differences in ADE risk for any of the pairwise treatment comparisons in the intention-to-treat or per-protocol analyses. However, there was a considerable amount of uncertainty surrounding our effect measures.

Conclusion: Physicians must continue to exercise caution while considering prescribing opioids for pain management in older adults.

Keywords: pharmacoepidemiology, prescribing, tramadol, dose, supply

Introduction

There is a high burden of morbidity and mortality resulting from motor-vehicle crash (MVC) among older adults in the United States, with 7,500 deaths and 200,000 crash-related injuries treated at emergency departments in 2020.[1] Injuries sustained during MVC may cause acute or chronic pain, leading to functional decline and disability if left untreated.[2] Despite being recommended as first-line treatment for acute mild to moderate pain relief, non-opioid analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen,[3] may not be the optimal therapy for older adults post-MVC. Older adults are susceptible to adverse drug events (ADEs) resulting from NSAID use due to polypharmacy and medical conditions.[4] Given the limited alternative treatment options, opioids are commonly prescribed to older adults after MVC. In a previous study, our research team found opioids were prescribed to 17% of drivers involved in an MVC, making it among the most frequently prescribed medications after MVC.[5]

Although opioids are a mainstay of treatment for pain after MVC, they pose many significant risks, including sedation, constipation, and acute respiratory failure, among other ADEs.[6–8] The selection of a specific opioid treatment

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strategy therefore requires careful consideration to balance effective pain management with the risk of ADEs in older adults after MVC. The 2016 Centers for Disease Control and Prevention opioid prescribing guidelines highlight the importance of refraining from prescribing opioids whenever possible and prescribing the lowest effective doses for shorter time periods.[9] The decision to choose a particular opioid requires a considerate, patient-focused assessment as their safety and efficacy vary.[10] Tramadol, which works as both a serotonin-norepinephrine reuptake inhibitor and a prodrug that is metabolized into a weaker opioid,[11] is considered safer than stronger opioids like oxycodone and hydrocodone.[12] However, emerging controversial evidence challenging the risk/benefit profile of tramadol underscores the need for further comprehensive assessment.[12,13] There is a dearth of research that investigates the specific treatment strategies most effective in pain management while minimizing the risk of ADEs in older adults.

The objective of this study was to evaluate the comparative risks of three fundamental opioid prescribing strategies defined by days of supply, dose, and tramadol/non-tramadol prescriptions on opioid-related ADEs following MVC among older adults using target trial emulation. By applying the design and analytic principles of a randomized controlled trial to an observational study,[14] we aimed to generate robust estimates of the risks of opioid-related ADEs. Our research seeks to contribute to the optimization of opioid use in acute pain scenarios among older adults, providing a foundation for future clinical practice guidelines that enhance patient safety and pain management in the post-MVC context.

Methods

Data Sources

We used Medicare claims and data from the New Jersey Safety and Health Outcomes (NJ-SHO) Data Warehouse for the years 2007 through 2017. The NJ-SHO Warehouse is an extensive repository of linked data from various NJ statewide administrative sources, including police-reported crashes and driver licensing information. Complete descriptions of the development of the NJ-SHO Warehouse are available in prior work.[15] We linked Medicare fee-for-service enrollment and demographic information, Medicare Provider Analysis and Review (MedPAR) inpatient care data, Medicare claims (Carrier professional service, home health, skilled nursing facility), and Medicare Part D pharmacy claims to data on driver licensing, suspension, and police-reported crash data from the NJ-SHO Warehouse. Additional information about the data and methods used for this study is available in the Brown Digital Repository: https://doi.org/10.26300/gn24-kg23.

Emulation of the Target Trials Using Observational Data

A summary of both the target trial protocol and the emulation can be found in eTable 1 and eFigure 1. Given that all components of the three target trial emulations were identical except for the treatment strategies, we describe a single protocol that is meant to represent all three target trials and one emulation below but differentiate the three target trials in the Treatment Strategies subsection.

Eligibility Criteria

The target trial would include individuals aged 67 and older, allowing for two years of opioid non-use to be determined (Figure 1). Individuals must have resided in New Jersey and would have experienced a police-reported MVC in the state of New Jersey for which they sought medical care where a Medicare claim was generated. The healthcare encounter may have occurred outside of New Jersey. The first opioid dispensing after the first healthcare encounter at a hospital, emergency department, or outpatient physician clinic within 10 days after the MVC for which a Medicare claim was created would constitute the date of trial enrollment. Individuals must also have been entitled to Medicare due to age at the time of Medicare enrollment and have had continuous enrollment in fee-for-service Medicare Parts A, B, and D for the 24 months prior to the MVC.

Those who received hospice, palliative, or cancer care in the 2 years prior to the MVC would have been ineligible in order to eliminate potential confounding due to differences in opioid use and opioid prescribing patterns. Persons who had opioid fills in either the 24 months before the MVC or between the MVC and the first healthcare encounter post-MVC would have been ineligible in order to ensure an opioid-naïve study population. Individuals would have been enrolled in the target trial starting on May 1, 2007. The last enrollment would have been on November 16, 2017 in order

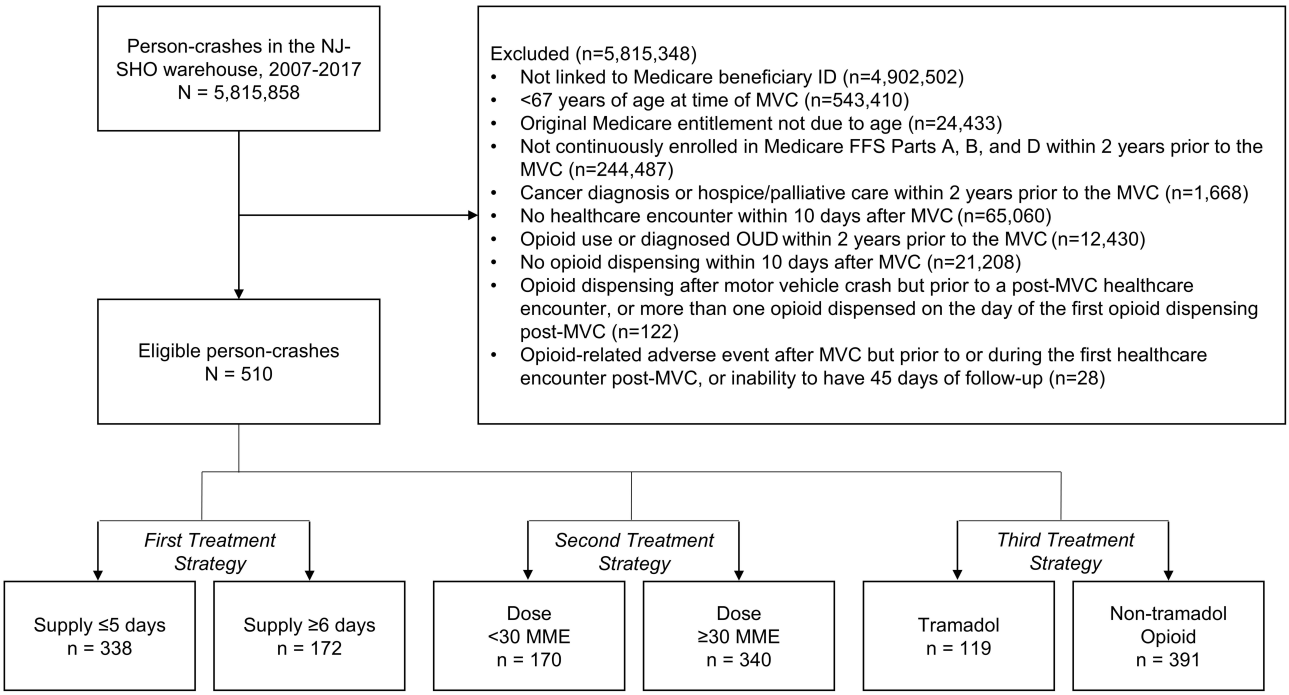

Figure 1 Flow diagram for selection of eligible older adults in the three target trial emulations evaluating the effects of opioid treatment strategies for pain after motor vehicle crash, 2007–2017.

to allow for 45 days of follow-up by the study end date of December 31, 2017. All eligibility criteria for the emulation of the target trial were the same as the target trial but were applied by searching for documentation in the existing NJ-SHO Warehouse and codes in the Medicare claims data.

Treatment Strategies and Assignment Procedures

The treatment strategies of the three target trials would have been as follows: Trial 1: (1a) Initiate any dose of an opioid with a supply of ≥6 days within 10 days of a crash; or (1b) Initiate any dose of an opioid with a supply of ≤5 days within 10 days of a crash; Trial 2: (2a) Initiate an opioid with a daily dose of ≥30 morphine milligram equivalents (MME) within 10 days of a crash; or (2b) Initiate an opioid with a daily dose of <30 MME within 10 days of a crash; Trial 3: (3a) Initiate any dose or days' supply of tramadol within 10 days of a crash; or (3b) Initiate any dose or days' supply of a non-tramadol opioid within 10 days of a crash. The strategies for Trial 1 were chosen based on a 2017 New Jersey law limiting initial opioid prescriptions to 5 days' supply.[16,17] The strategies for Trial 2 were chosen as 30 MME is roughly the median dose of opioid dispensings in this study (data not shown), allowing for similar group sizes. The strategies for Trial 3 were chosen as tramadol has a distinct mechanism of action relative to the other opioids in this study (eBox 1) and there is emerging controversial evidence regarding its risk/benefit profile compared to other opioids.[11–13]

Under all treatment strategies, the decision to discontinue the strategy or initiate any additional therapies other than opioids would have been left to the patient and their healthcare professionals' discretion.

All treatment strategies for the emulation of the target trial were the same as the target trial but were assigned by searching for documentation in the existing NJ-SHO Warehouse and codes in the Medicare claims data. To account for confounding in the emulation, we adjusted for demographics, comorbidity, frailty, prior medication, indication for the healthcare encounter, year of the opioid dispensing, and opioid provider specialty using inverse probability of treatment weights (eTable 2).

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Outcomes, Follow-Up, and Causal Contrasts of Interest

The target trial would have included opioid-related ADEs as the outcome, broadly, opioid use/dependence, respiratory failure or insufficiency, or mental disorder/state resulting from opioid use. Individuals would have been followed from treatment assignment until disenrollment from Medicare (Parts A, B, or D) or enrollment in Medicare Advantage, death, police-reported MVC, or the end of 45 days, whichever occurred first. Police-reported MVC would have been a censoring event as it is another opportunity for the individual to enroll in the study, should the individual meet eligibility criteria for this MVC. A 45-day follow-up period would have been most relevant because opioid use for pain from a major musculoskeletal injury is rarely recommended beyond 45 days and approximately 96% of individuals are observed to discontinue opioid use by 45 days (data not shown). Follow-up would have begun on the day following the opioid dispensing to ensure that outcomes were measured after treatment initiation.

For the emulation, we examined the same outcomes as the target trial, focusing on opioid-related ADEs that were identifiable through codes in the Medicare claims data (eTable 3).[18,19] Treatment assignment and censoring were determined by searching for documentation in the existing NJ-SHO Warehouse and codes in the Medicare claims data. We included the same duration of follow up as the target trial and estimated the observational analogues of the intention-to-treat and per-protocol estimands. The intention-to-treat effect is the effect of initiation of an opioid with ≥6 days' supply vs initiation of an opioid with ≤5 days' supply, initiation of an opioid with ≥30 MME per day vs initiation of an opioid with <30 MME per day, or initiation of tramadol vs initiation of another opioid. The per-protocol effect is the effect of initiation and sustained use of the treatment strategy throughout the entirety of follow-up.

Analysis Plan

We enumerated and defined the covariates in eTable 2 and they broadly encompassed demographics, comorbidity, frailty, prior medication, indication for the healthcare encounter, year of the opioid dispensing, and opioid provider specialty.[20,21] Prior medications and comorbidities were chosen based on their ability to influence MVC and/or for their ability to produce symptoms similar to the opioid-related ADE outcomes in the study.[22] Indication for the healthcare encounter was a categorical variable indicating possible diagnoses of varying severity following an MVC. Covariates were ascertained at one of four times depending on the specific covariate, as detailed in eTable 2: 1) the time of the MVC (demographics), 2) the time of the first healthcare encounter within 10 days post-MVC (indication for the healthcare encounter), 3) the time of the treatment strategy assignment (year of the opioid dispensing, opioid prescriber specialty), or 4) within the two years preceding the first healthcare encounter post-MVC (frailty, comorbidity, prior medication). Our study period covered both the International Classification of Diseases 9th revision (ICD-9) and 10th revision (ICD-10) eras, so we translated all diagnoses and procedures coded with ICD-9-Clinical Modification (CM) and ICD-9-Procedure Coding System (PCS) codes to ICD-10-CM and ICD-10-PCS codes, respectively, to create a homogenous coding scheme that enabled us to use Healthcare Cost and Utilization Project (HCUP) clinical classifications and Chronic Conditions Data Warehouse algorithms.[23–25]

The unit of analysis was person-crash, where each individual may have more than one MVC that meets eligibility criteria and thereby each individual may be in the study population more than once. We fit a pooled logistic regression model conditional on baseline covariates and then estimated the probability of dispensing an opioid of ≥6 days' supply, ≥30 MME, or tramadol, respectively, for each comparison, (ie propensity scores) to construct IPTW to correct for potential confounding due to non-comparable treatment groups.[26,27] We truncated the IPTW at the 1st and 99th percentiles to reduce the impact of extreme weights. We assessed covariate balance using standardized mean differences (SMDs) before and after IPTW (eFigure 2). SMDs <0.10 (in absolute value) were considered adequate balance across each comparison after IPTW.[28,29]

For the per-protocol analysis, we fit a pooled logistic regression model, conditional on baseline covariates, to estimate the probability of remaining uncensored, which we defined as not initiating an additional opioid, and estimated stabilized inverse probability of censoring weights (IPCW) to correct for potential selection bias. We estimated the IPCW for the per-protocol analyses but not the intention-to-treat analyses as there were too few censoring events in the intention-to-treat analysis to reliably estimate the IPCW.

Finally, we constructed a single weight for each person-crash as the product of their stabilized IPTW and IPCW for the per-protocol analyses and the stabilized IPTW alone for the intention-to-treat analyses. Using the predicted values of marginal structural models, we estimated weighted risks, risk differences (RD), and risk ratios (RR). We constructed 95% confidence limits (CLs) using the non-parametric percentile bootstrap method to account for within-subject correlation in outcomes.[27,30]

Stability Analysis

We conducted a stability analysis in which we separately compared the risk for each treatment strategy using untruncated inverse probability weights to explore the effects of more extreme weights on the risk of an opioid-related adverse event. We also conducted a separate analysis in which we reduced the opioid-washout period from 24 months to 6 months prior to the MVC in order to explore the washout effects on the risk of an opioid-related adverse event.

Software

Data analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Treatment Strategies

There were 913,356 person-crashes with a Medicare beneficiary ID and an MVC in New Jersey during the study period. Of these, 543,410 were <67 years of age and 268,920 individuals did not have the desired Medicare eligibility. About 1,668 had a cancer diagnosis or palliative care. About 98,848 did not have a healthcare encounter within 10 days post-MVC, had an opioid dispensing inconsistent with eligibility requirements, had an outcome prior to treatment initiation, or were unable to have the full 45 days of follow-up prior to the end of the study.

Overall, 510 unique individuals had a dispensing for an opioid analgesic within 10 days after an MVC and met our eligibility criteria. Of the 510 person-crashes, 338 (66.3%) had an opioid days' supply of ≤5 days and 172 (33.7%) had a days' supply of ≥6 days, 170 (33.3%) had an opioid with a daily dose of <30 MME and 340 (66.7%) with a daily dose of ≥30 MME, and 119 (23.3%) had a dispensing for tramadol while 391 (76.7%) had a dispensing for some other opioid.

Patient Characteristics

Table 1 shows the baseline characteristics of the overall cohort and stratified by the three treatment strategies. Briefly, overall, the mean age was 76.12 (sd = 6.60), 59.8% were female, and 90.4% were white. The mean combined comorbidity score was 3.54 (sd = 2.15) and the mean claims-based frailty index was 0.17 (sd = 0.05). One hundred and eight (21.2%) individuals presented with a fracture, 169 (33.1%) with a contusion, dislocation, or sprain, and 233 (45.7%) with another diagnosis at their first healthcare encounter post-MVC. One hundred and forty-two (27.8%) were prescribed their opioid by a practitioner in family or internal medicine, 56 (11.0%) from a nurse practitioner or physician assistant, 113 (22.2%) from a practitioner in emergency medicine, 132 (25.9%) from a practitioner in surgery, 47 (0.9%) from a practitioner in another specialty, and 20 (3.9%) had missing information about their opioid prescriber's specialty. One hundred and seventeen (34.7%) dispensed an additional medication on the same day as their opioid dispensing.

Supply

Briefly, those with a shorter opioid supply (≤5 days vs ≥6 days) were prescribed their opioid less often by a practitioner in family/internal medicine (15.7% vs 51.7%) or a nurse practitioner/physician assistant (9.2% vs 14.5%). These individuals were diagnosed with a contusion, dislocation, or sprain more often (37.9% vs 23.8%) and a fracture less often (19.8% vs 23.8%) at their first healthcare encounter post-MVC.

Dosing

Those with a lower opioid dose (<30 MME/day vs ≥30 MME/day) had a higher mean comorbidity score (3.88 vs 3.37) and a higher mean frailty index (0.18 vs 0.16). These individuals were also prescribed their opioid more often by a practitioner in family/internal medicine (30.6% vs 26.5%), emergency medicine (25.3% vs 20.6%), or surgery (28.8% vs 24.4%).

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Table 1 Characteristics of Older Adults in the Target Trial Emulations Evaluating the Effects of Three Pairs of Opioid Treatment Strategies for Pain on 45-Day Opioid Adverse Event Outcomes After Motor Vehicle Crash (MVC)

Characteristics[b]	Overall (n = 510)	Stratified by Supply Strategies[a]		Stratified by Dosing Strategies[a]		Stratified by Tramadol Strategies[a]	
		≤5 days' supply (n = 338)	≥6 days' supply (n = 172)	<30 MME (n = 170)	≥30 MME (n = 340)	Non-tramadol opioid (n = 391)	Tramadol (n = 119)
Demographics, n (%)							
Age at time of MVC, mean (SD)	76.12 (6.60)	75.86 (6.66)	76.63 (6.47)	76.97 (6.89)	75.69 (6.42)	76.11 (6.61)	76.13 (6.59)
Female	305 (59.8)	205 (60.7)	100 (58.1)	105 (61.8)	200 (58.8)	223 (57.0)	82 (68.9)
White Race	461 (90.4)	300 (88.8)	161 (93.6)	155 (91.2)	306 (90.0)	356 (91.0)	105 (88.2)
Calendar Year of Opioid Initiation, n (%)							
2007 – 2010	117 (22.9)	80 (23.7)	37 (21.5)	31 (18.2)	86 (25.3)	105 (26.9)	12 (10.1)
2011 – 2013	134 (26.3)	99 (29.3)	35 (20.3)	49 (28.8)	85 (25.0)	111 (28.4)	23 (19.3)
2014 – 2017	259 (50.8)	159 (47.0)	100 (58.1)	90 (52.9)	169 (49.7)	175 (44.8)	84 (70.6)
Co-Existing Conditions[c], n (%)							
Combined Comorbidity Score, mean (SD)[d]	3.54 (2.15)	3.45 (2.13)	3.72 (2.20)	3.88 (2.14)	3.37 (2.14)	3.53 (2.21)	3.58 (1.96)
Claims-based Frailty Index, mean (SD)[e]	0.17 (0.05)	0.17 (0.05)	0.17 (0.05)	0.18 (0.05)	0.16 (0.05)	0.17 (0.05)	0.17 (0.05)
Asthma	60 (11.8)	44 (13.0)	16 (9.3)	20 (11.8)	40 (11.8)	45 (11.5)	15 (12.6)
Anemia	181 (35.5)	111 (32.8)	70 (40.7)	62 (36.5)	119 (35.0)	133 (34.0)	48 (40.3)
Anxiety	72 (14.1)	49 (14.5)	23 (13.4)	29 (17.1)	43 (12.6)	50 (12.8)	22 (18.5)
Arthritis	243 (47.6)	158 (46.7)	85 (49.4)	78 (45.9)	165 (48.5)	171 (43.7)	72 (60.5)
Atrial fibrillation	77 (15.1)	48 (14.2)	29 (16.9)	31 (18.2)	46 (13.5)	59 (15.1)	18 (15.1)
Cardiomyopathy	32 (6.3)	–[f]	–[f]	12 (7.1)	20 (5.9)	–[f]	–[f]
Chronic kidney disease	111 (21.8)	74 (21.9)	37 (21.5)	43 (25.3)	68 (20.0)	86 (22.0)	25 (21.0)
COPD	101 (19.8)	61 (18.0)	40 (23.3)	40 (23.5)	61 (17.9)	77 (19.7)	24 (20.2)
Coronary atherosclerosis	189 (37.1)	125 (37.0)	64 (37.2)	65 (38.2)	124 (36.5)	147 (37.6)	42 (35.3)
Depression	26 (5.1)	15 (4.4)	11 (6.4)	–[f]	–[f]	–[f]	–[f]

Fracture	150 (29.4)	93 (27.5)	57 (33.1)	51 (30.0)	99 (29.1)	128 (32.7)	22 (18.5)
Heart failure	70 (13.7)	43 (12.7)	27 (15.7)	34 (20.0)	36 (10.6)	53 (13.6)	17 (14.3)
Hyperlipidemia	430 (84.3)	284 (84.0)	146 (84.9)	149 (87.6)	281 (82.6)	328 (83.9)	102 (85.7)
Hypertension	433 (84.9)	284 (84.0)	149 (86.6)	159 (93.5)	274 (80.6)	328 (83.9)	105 (88.2)
Liver Disease	40 (7.8)	28 (8.3)	12 (7.0)	12 (7.1)	28 (8.2)	28 (7.2)	12 (10.1)
Sleep-wake disorder	126 (24.7)	88 (26.0)	38 (22.1)	46 (27.1)	80 (23.5)	100 (25.6)	26 (21.8)
Stroke	53 (10.4)	32 (9.5)	21 (12.2)	21 (12.4)	32 (9.4)	–[f]	–[f]
Prior Medication Use[c], n (%)							
ACE inhibitors and Angiotensin II receptor blocker	270 (52.9)	179 (53.0)	91 (52.9)	97 (57.1)	173 (50.9)	197 (50.4)	73 (61.3)
Antiarrhythmic (except beta-blockers)	61 (12.0)	37 (10.9)	24 (14.0)	22 (12.9)	39 (11.5)	49 (12.5)	12 (10.1)
Anticoagulant	87 (17.1)	55 (16.3)	32 (18.6)	40 (23.5)	47 (13.8)	70 (17.9)	17 (14.3)
Anticonvulsant	72 (14.1)	46 (13.6)	26 (15.1)	22 (12.9)	50 (14.7)	57 (14.6)	15 (12.6)
Antidementia	37 (7.3)	23 (6.8)	14 (8.1)	13 (7.6)	24 (7.1)	–[f]	–[f]
Antidepressant	128 (25.1)	82 (24.3)	46 (26.7)	44 (25.9)	84 (24.7)	94 (24.0)	34 (28.6)
Antiparkinsonian	44 (8.6)	29 (8.6)	15 (8.7)	14 (8.2)	30 (8.8)	–[f]	–[f]
Antiplatelet	90 (17.6)	62 (18.3)	28 (16.3)	31 (18.2)	59 (17.4)	72 (18.4)	18 (15.1)
Antipsychotic	37 (7.3)	26 (7.7)	11 (6.4)	13 (7.6)	24 (7.1)	–[f]	–[f]
Benzodiazepine	87 (17.1)	57 (16.9)	30 (17.4)	35 (20.6)	52 (15.3)	62 (15.9)	25 (21.0)
Beta-blocker	227 (44.5)	148 (43.8)	79 (45.9)	86 (50.6)	141 (41.5)	171 (43.7)	56 (47.1)
Calcium Channel Blocker	178 (34.9)	118 (34.9)	60 (34.9)	65 (38.2)	113 (33.2)	130 (33.2)	48 (40.3)
Corticosteroid (oral)	145 (28.4)	98 (29.0)	47 (27.3)	56 (32.9)	89 (26.2)	107 (27.4)	38 (31.9)
Gabapentinoid	58 (11.4)	39 (11.5)	19 (11.0)	20 (11.8)	38 (11.2)	46 (11.8)	12 (10.1)
Loop diuretic	83 (16.3)	54 (16.0)	29 (16.9)	29 (17.1)	54 (15.9)	65 (16.6)	18 (15.1)
Nitrate and other antianginal	59 (11.6)	41 (12.1)	18 (10.5)	18 (10.6)	41 (12.1)	44 (11.3)	15 (12.6)

(*Continued*)

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Table 1 (Continued).

Characteristics[b]	Overall (n = 510)	Stratified by Supply Strategies[a]		Stratified by Dosing Strategies[a]		Stratified by Tramadol Strategies[a]	
		≤5 days' supply (n = 338)	≥6 days' supply (n = 172)	<30 MME (n = 170)	≥30 MME (n = 340)	Non-tramadol opioid (n = 391)	Tramadol (n = 119)
NSAID (oral)	135 (26.5)	85 (25.1)	50 (29.1)	38 (22.4)	97 (28.5)	90 (23.0)	45 (37.8)
Statin	308 (60.4)	210 (62.1)	98 (57.0)	104 (61.2)	204 (60.0)	234 (59.8)	74 (62.2)
Thiazide and thiazide-like diuretic	193 (37.8)	118 (34.9)	75 (43.6)	72 (42.4)	121 (35.6)	143 (36.6)	50 (42.0)
Any medication prescribed the same day as the opioid[g]	177 (34.7)	127 (37.6)	50 (29.1)	65 (38.2)	112 (32.9)	140 (35.8)	37 (31.1)
Opioid Prescriber Specialty, n (%)							
Family/Internal Medicine	142 (27.8)	53 (15.7)	89 (51.7)	52 (30.6)	90 (26.5)	100 (25.6)	42 (35.3)
Nurse Practitioner/Physician Assistant	56 (11.0)	31 (9.2)	25 (14.5)	–[f]	–[f]	–[f]	–[f]
Emergency Medicine	113 (22.2)	81 (24.0)	32 (18.6)	43 (25.3)	70 (20.6)	76 (19.4)	37 (31.1)
Surgery	132 (25.9)	121 (35.8)	11 (6.4)	49 (28.8)	83 (24.4)	111 (28.4)	21 (17.6)
Other	47 (9.2)	–[f]	–[f]	11 (6.5)	36 (10.6)	–[f]	–[f]
Missing	20 (3.9)	–[f]	–[f]	–[f]	–[f]	20 (5.1)	0 (0.0)
Indication for Post-MVC Healthcare Encounter, n (%)							
Fracture	108 (21.2)	67 (19.8)	41 (23.8)	31 (18.2)	77 (22.6)	94 (24.0)	14 (11.8)
Contusion/Dislocation/Sprain	169 (33.1)	128 (37.9)	41 (23.8)	58 (34.1)	111 (32.6)	134 (34.3)	35 (29.4)
Other	233 (45.7)	143 (42.3)	90 (52.3)	81 (47.6)	152 (44.7)	163 (41.7)	70 (58.8)

Notes: [a] Treatment strategies were determined at the time of the first opioid dispensing after the first healthcare encounter post-MVC. [b]All the characteristics were summarized at the person-crash level. [c]Measured over the 2 years before the first healthcare encounter post-motor vehicle crash. [d]Gagne combined comorbidity score has a range from −2 to 20. It predicts short and long-term mortality, with a higher score correlated with a higher risk of mortality. [e]Ranges from 0 to 1 with prefrail 0.15 to <0.25, mildly frail 0.25 to <0.35, moderately frail 0.35 to <0.45, and severely frail ≥0.45. [f]Cells suppressed to comply with the Centers for Medicare & Medicaid Services Cell Size Suppression Policy. [g]Any non-opioid medication for any indication that is dispensed on the same day as the initiation of the opioid treatment strategy.

Abbreviations: SD, standard deviation; COPD, chronic obstructive pulmonary disease; ACE, Angiotensin-Converting Enzyme; NSAID, non-steroidal anti-inflammatory drug; MVC, motor-vehicle crash.

Tramadol

Those person-crashes with a non-tramadol opioid dispensing were more often female (57.0% vs 68.9%) and had arthritis less often (43.7% vs 60.5%). They also took an oral NSAID less often (23.0% vs 37.8%). Individuals who received tramadol were more often prescribed their opioid from a practitioner in surgery (28.4% vs 17.6%) and more often had a fracture (24.0% vs 11.8%) or a contusion/dislocation/sprain (34.3% vs 29.4%). Tramadol was dispensed in later years (2014–2017) more often (70.6%) than in earlier years (2007–2010, 10.1%).

Propensity Scores, IPTW, and Covariate Balance

The propensity scores overlapped sufficiently and the IPTW was appropriately distributed for all treatment strategies (eTables 4, 5 and eFigure 3). Covariates were generally well-balanced after IPTW (eFigure 2), though some covariates had SMDs greater than 0.10 or less than −0.10 for the days' supply and tramadol treatment strategies.

Outcomes and Follow-Up Time

There were 28 opioid-related adverse outcome events overall in the intention-to-treat analysis, corresponding to an overall risk of 5.49%. The mean follow-up times did not meaningfully vary across the three treatment groups (eTable 6). The mean follow-up times differed slightly in the per-protocol analysis for the days' supply treatment strategies (38.59 vs 42.46 days) and tramadol strategies (42.62 vs 40.90 days) but not in the dosing treatment strategies (40.47 vs 40.85 days).

Main Treatment Effect Estimates

Table 2 shows the estimated risks, RRs, and RDs for an opioid-related adverse event during 45 days of follow-up for each treatment strategy.

Intention-to-Treat

For the intention-to-treat estimand, the RRs (95% CLs) were 1.64 (0.64, 4.57) for the supply treatment strategies (≤5 vs ≥6 days), 0.83 (0.45, 1.76) for the dosing treatment strategies (<30 vs ≥30 MME), and 0.54 (0.21, 4.01) for the tramadol treatment strategy (non-tramadol opioid vs tramadol). The RDs (95% CLs) were 2.05 (−2.23, 5.51) for the supply treatment strategies, −0.85 (−3.97, 2.63) for the dosing treatment strategies, and −4.79 (−18.90, 4.67) for the tramadol treatment strategies.

Per-Protocol

For the per-protocol estimand, the RRs (95% CLs) were 1.29 (0.64, 4.57) for the supply treatment strategies, 0.83 (0.45, 1.76) for the dosing treatment strategies, and 0.54 (0.21, 4.01) for the tramadol treatment strategies. The RDs (95% CLs) were 0.97 (−3.79, 4.13) for the supply treatment strategies, −0.51 (−4.20, 3.56) for the dosing treatment strategies, and −7.45 (−23.04, 3.52) for the tramadol treatment strategies.

Stability Analysis

The intention-to-treat and per-protocol estimates were generally similar to those of the main analysis when using untruncated IPTW (eTable 7). The estimates when considering an opioid-washout period of 6 months were closer to the null and the 95% CLs were narrower than those of the main analysis (eTable 8).

Discussion

In this observational study emulating three target trials to estimate the effect of 1) greater versus lesser days' supply of opioids, 2) higher versus lower opioid doses, and 3) tramadol versus non-tramadol opioids for managing pain following MVC, there were no notable differences in the risks of ADEs. The results of the stability analyses were similar to those of the primary analyses. However, due to the high degree of uncertainty surrounding the effect measures, we cannot firmly establish that there is indeed no meaningful difference between the treatment strategies.

Our study has multiple notable strengths. To the best of our knowledge, this is the only study to date to estimate the comparative risk of ADEs associated with opioid treatment strategies for managing pain after MVC. It is also unique among studies examining pain treatment strategies of any kind after MVCs in that we employed a target trial emulation approach.

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Table 2 Estimated Effects of Opioid Treatment Strategies for Pain After Motor Vehicle Crash on Opioid-Related Adverse Event[a] Outcomes Over 45 days of Follow-Up

Analysis[b]	Number of Adverse Events		IPW 45-Day Risk, % (95% CLs)[c]		IPW Effect Estimates[c]	
Supply Strategies	**≤5 days (n = 338)**	**≥6 days (n = 172)**	**≤5 days**	**≥6 days**	**Risk difference, ≤5 vs ≥6 days (95% CLs)**	**Risk ratio, ≤5 vs ≥6 days (95% CLs)**
Intention-to-Treat	–[d]	–[d]	5.25 (2.93, 8.00)	3.20 (1.21, 6.70)	2.05 (−2.23, 5.51)	1.64 (0.64, 4.57)
Per-Protocol	–[d]	–[d]	4.31 (1.95, 6.77)	3.34 (1.42, 7.43)	0.97 (−3.79, 4.13)	1.29 (0.43, 4.07)
Dosing Strategies	**<30 MME (n = 170)**	**≥30 MME (n = 340)**	**<30 MME**	**≥30 MME**	**Risk difference, <30 vs ≥30 MME (95% CLs)**	**Risk ratio, <30 vs ≥30 MME (95% CLs)**
Intention-to-Treat	12	16	4.28 (2.38, 7.36)	5.13 (2.80, 8.02)	−0.85 (−3.97, 2.63)	0.83 (0.45, 1.76)
Per-Protocol	–[d]	–[d]	4.27 (1.95, 7.79)	4.78 (3.24, 7.32)	−0.51 (−4.20, 3.56)	0.89 (0.40, 2.28)
Tramadol Strategy	**Non-Tramadol Opioid (n = 391)**	**Tramadol (n = 119)**	**Non-Tramadol Opioid**	**Tramadol**	**Risk difference, Non-Tramadol Opioid vs Tramadol (95% CLs)**	**Risk ratio,Non-Tramadol Opioid vs Tramadol(95% CLs)**
Intention-to-Treat	–[d]	–[d]	5.59 (3.42, 8.06)	10.37 (1.35, 24.27)	−4.79 (−18.90, 4.67)	0.54 (0.21, 4.01)
Per-Protocol	–[d]	–[d]	4.68 (2.39, 7.08)	12.13 (1.60, 27.90)	−7.45 (−23.04, 3.52)	0.39 (0.14, 3.04)

Notes: [a]Broadly, opioid abuse/dependence, drug induced respiratory abnormality/failure, pulmonary insufficiency, shortness of breath, pneumonia, mental disorder/altered mental state, suicide, rhabdomyolysis, mixed acid-base balance disorder, or other adverse effect of an opioid (eTable 3). [b]Analysis done at the person-crash level. [c]All per-protocol estimates were weighted by inverse probability of treatment and censoring weights and intention-to-treat estimates by inverse probability of treatment weights. All weights were truncated at the 1st and 99th percentiles. Confidence limits were estimated using Huber-White robust standard errors. [d]Cells suppressed to comply with the Centers for Medicare & Medicaid Services Cell Size Suppression Policy.

Abbreviations: CLs, confidence limits; MME, morphine milligram equivalents; IPW, inverse probability weighted.

By emulating the design and analytical principles of the target trial, we aimed to produce results that would closely mirror those obtained from an actual randomized controlled trial (RCT), considered the gold standard for clinical research.[31–33]

The most closely related study to our own is work by Beaudoin et al examining the effects of opioids versus NSAIDs among individuals aged 18 to 65 years who presented to the ED within 24 hours of an MVC across eight EDs in four states (Florida, Massachusetts, Michigan, and New York) between February 2009 and October 2011.[34] The authors concluded that the 158 individuals prescribed an opioid had no difference in self-reported pain six weeks after the MVC as compared to the 193 individuals prescribed NSAIDs. Participants in both medication groups received a median duration of 3 days of analgesic medications. The duration of use was similarly short in our study. The absence of notable effects in either study may be due to these limited durations of analgesic use that preclude observable effects on outcomes after MVC.

Restriction to new users of opioids and the use of target trial emulation ensured the temporality of covariate assessment before treatment initiation. This prevented selection bias resulting from prevalent-user bias or depletion of susceptibles, ie reduction of treated person-crashes most susceptible to ADEs due to developed tolerance of the opioids early on during follow-up.[35–37] The temporal sequence of covariate assessment before treatment initiation also prevented the adjustment of intermediate variables.[38,39]

Next, prior investigations surrounding opioid use after MVC have primarily focused on patients visiting the ED for treatment of pain.[2,34,40,41] Our study sample was more inclusive compared to past studies and comprised individuals who were dispensed opioids post-MVC following outpatient visits, ED-related or not. Therefore, we were able to infer the risk of ADEs associated with opioids among a diverse group of individuals being treated for pain associated with MVC.

Our study has several potential limitations. First, our sample size and statistical power are limited since individuals must have experienced an MVC, a relatively rare event, to be eligible for our study. The rarity of opioid-related ADEs as an outcome further limited statistical power. The resulting effect estimates were therefore imprecise and compatible with a wide range of possible inferences.

Second, we did not have direct measures of the frequency, severity, or type of pain that individuals might have experienced while using each treatment strategy. The absence of pain measures prevents us from fully understanding any potential benefits of one opioid treatment strategy over another, or how those benefits might have been balanced against the risks of opioid related ADEs.

Third, although we adjusted for the apparent indications for opioid initiation in addition to numerous patient characteristics from various domains such as comorbidities, medication use, healthcare utilization, etc, we were unable to rule out the possibility of residual confounding. One potential source of residual confounding is that opioids may have been prescribed in our study sample to treat pain that did not result from the MVC and that the prevalence of these alternative potential indications may have varied across treatment strategy groups. However, it is unlikely that individuals would have other indications within the 10 days after the MVC, so any possible bias would be very small in magnitude. If residual confounding is present, the direction of the bias is challenging to anticipate for each set of treatment strategies.

Finally, we did not define medication use based on the days of supply available in Part D prescription fill claims. Instead, we considered person-crashes to be using opioids from the date of dispensing through the entire duration of follow-up until the first experience of the outcome, a new dispensing of any opioid, or another censoring event in the per-protocol analysis. Therefore, person-crashes may have stopped using opioids days or weeks before we identified them as having discontinued in our per-protocol analysis. This misclassification could have varied across treatment strategies.

Conclusion

In this study, opioid treatment strategies involving different days of supply, doses, and tramadol for managing pain after MVCs were comparable in their risks of adverse events. Our study has notable strengths in its robust design and analytic approaches to address confounding and selection bias. It comprises a more diverse population receiving care from both ED and non-ED visits compared to prior studies that focused on individuals receiving care through ED visits only. Although there is considerable uncertainty, our results showed no significant differences in risk. Prescribers should therefore continue to judiciously minimize dose and duration when prescribing opioids for MVC-related pain in older adults. Our study can also be a useful guide to researchers who may leverage these methods to further investigate the risks and benefits of opioid treatment after MVC.

Data Sharing Statement

The Medicare claims data are available from the Centers for Medicare and Medicaid Services (CMS). These third-party data are subject to a legally binding data use agreement with CMS and cannot be made publicly available to other researchers. However, researchers can establish their own data use agreement with CMS to obtain access to the raw data through the Research Data Assistance Center (ResDAC), a contractor that provides free assistance to researchers interested in CMS data (https://resdac.org/). Like the CMS data, the New Jersey Safety and Health Outcomes (NJ-SHO) data are subject to a legally binding data use agreement and cannot be made publicly available to other researchers. Researchers interested in using the NJ-SHO data can email njsho@chop.edu.

Ethics Approval and Informed Consent

The Brown University Institutional Review Board approved the study (Protocol# 1903002365). Due to the use of deidentified administrative data, the need for informed consent was waived. The data accessed complied with all relevant data protection and privacy regulations.

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