

The Role of Prescribed Controlled Substance Acquisition As Potential Triggers of Opioid Overdose: A Case-Crossover Study

Allen M. Smith, PharmD, Cheng Peng, MPA, MS, PhD, Austin Porter, MPH, DrPH and Bradley C. Martin, PharmD, PhD

¹Division of Pharmaceutical Evaluation and Policy, University of Arkansas for Medical Sciences, Little Rock, AR, USA, ²Department of Health Policy and Management, University of Arkansas for Medical Sciences College of Medicine, 4301 W. Markham St., Little Rock, AR, 72205, USA, ³Arkansas Department of Health, 4815 W. Markham St., Little Rock, AR, 72205, USA.

BACKGROUND

- Opioid overdoses (OODs) continue to pose a significant public health challenge with over 15,000 fatal OODs that are still attributed to prescription opioids annually.¹
- The role of prescribed opioids and benzodiazepines as risk factors for OOD are well established, however, their role as potential ‘triggers’ of OOD has not been formally investigated.^{2, 3}
- Our team recently discovered a strong temporal association between controlled prescription acquisition and fatal and non-fatal overdose, suggesting that prescribed controlled substances (CS) may trigger or precipitate overdoses in susceptible persons.⁴
 - Approximately 30% of all overdoses were preceded by acquiring a prescribed CS five days prior to an overdose, and over 10% of overdoses involved acquiring a CS prescription the day of or the day prior to OOD.⁴
- To more thoroughly assess the role of prescribed CSs as possible triggers of OOD, the objective of this study was to utilize a case-crossover design to evaluate the temporal relationship between CS acquisition and OOD.

METHODS

Data Source

- This study utilized linked Arkansas statewide data between January 1st, 2014 and December 31st, 2020.
 - Arkansas Prescription Drug Monitoring Program (AR-PDMP)** data were used to assess CS acquisition and fatal and non-fatal OOD were assessed using **linked death certificate, inpatient discharge and emergency department** data describing all deaths and inpatient and ED occurring in AR.
 - Data sources were linked through probabilistic matching using Linkage Wiz software, and patient identifiers were subsequently de-identified for analysis.

Study Subjects

- All persons who experienced an OOD or had ≥ 1 AR PDMP prescription fills between 1 July 2014 and 31 December 2020 that resided in Arkansas were included in the analysis.
 - The first 6 months of data were not included in the analysis so that we can accurately describe CS utilization for at least six months prior to overdose.
 - Persons with in-valid ages (age <0 or age >120) were excluded.

Table 1. Inclusion Criteria

Study group	Inclusion criteria	Study Timeframe
Population at risk	All subjects who had ≥ 1 AR-PDMP fill	July 1, 2014 – Dec 31 st , 2020
Any individual without a PDMP record who:	Experienced ≥ 1 overdose (fatal or non-fatal) involving opioids	July 1, 2014 – Dec 31 st , 2020

AR-PDMP = Arkansas Prescription Drug Monitoring Program

Case-Crossover Study Design

- CS characteristics were described in the 7 days prior to overdose and compared to the CS characteristics in 11 weekly (7 day) control windows prior to OOD.
- Binary CS variables indicating presence or absence of any CS, opioid, benzodiazepine, opioid and benzodiazepine, stimulant, sedative, carisoprodol, and pregabalin were created.
- Additionally, cumulative morphine milliequivalents were calculated for each time window.

Outcome Measure

- Validated ICD10 codes recorded on death certificates were used to identify **fatal OODs**, and validated ICD-9-CM and ICD-10-CM codes in hospital and emergency department discharge abstracts were used to identify nonfatal OODs.⁵

Table 2. ICD-9-CM / ICD-10-CM and ICD10 Codes for Definite Opioid Overdose

Definite OOD	ICD Codes
Nonfatal (Inpatient or ED dataset)	Presence of ICD9-CM diagnosis code ("96500", "96501", "96502", "96509", "E8500", "E8501", "E8502", "E9350", "E9351", "E9352") or ICD10-CM diagnosis code ("T400X1A", "T400X2A", "T400X3A", "T400X4A", "T401X1A", "T401X2A", "T401X3A", "T401X4A", "T402X1A", "T402X2A", "T402X3A", "T402X4A", "T403X1A", "T403X2A", "T403X3A", "T403X4A", "T404X1A", "T404X2A", "T404X3A", "T404X4A", "T40601A", "T40602A", "T40603A", "T40604A", "T40691A", "T40692A", "T40693A", "T40694A") for opioid overdose in inpatient or ED datasets
Fatal (Death dataset)	(Cause of death as drug poisoning ICD10 codes: "X40", "X41", "X42", "X43", "X44" AND One of the multiple causes of death as opioid-related poisoning codes: "T400", "T401", "T402", "T403", "T404", "T406" in the death dataset)

CM = Clinical Modification; ED = Emergency Department; ICD = International Classification of Diseases; OOD = Opioid Overdose

Time-Varying Covariates

- Covariates included:
 - Prior OOD event.
 - Presence/Absence of other CS acquisitions (ex. Presence of benzodiazepine prescription acquisition(s) when evaluating the association between recent opioid prescription acquisition and OOD).

Analysis

- A graphic analysis of the CS utilization rate by OOD status was conducted among all subjects with ≥ 1 PDMP record(s).
- Among subjects with ≥ 1 PDMP record(s) within 30 days prior to OOD, a graphic analysis of the days between CS acquisition and overdose was conducted.
- Among subjects with ≥ 1 OOD(s), **conditional logistic regression** models were estimated and unadjusted and adjusted odds ratios for each CS characteristic after accounting for other CS and prior overdose events were reported.

Sensitivity Analyses

- Time windows were adjusted to 3-day intervals.
- Potential OOD:** Because definite OODs may be under reported, a series of different OOD case definitions were employed to mitigate under reporting based on naloxone administration in the ED, diagnoses for respiratory depression or use of mechanical ventilation and mentions of opioids in the other causes of death.⁵

RESULTS

- A total of 2,818,135 individuals (45.10% male; 39.94 mean age) were included, of which 28,670 (1.02%) experienced ≥ 1 OOD(s).
- Of those that experienced ≥ 1 OOD(s), 2,812 (24.49%) had an AR-PDMP record in the 0-5 day period prior to OOD and 646 (5.63%) had an AR-PDMP record the day prior to OOD.
- Similar relationships were found in the sensitivity analysis when using a 3-day time window and when using alternative definitions of OOD.

Table 3. Demographics and CS acquisition characteristics for all identified individuals with ≥ 1 AR-PDMP record(s)

Demographic variables	All individuals with at least one AR-PDMP record			
	≥ 1 Definitive OOD(s) n=8,436	≥ 1 Possible OOD(s) n=20,234	No OOD n=2,789,465	P-value
Mean age in years (SD)	45.52 (18.66)	37.92 (20.61)	39.94 (22.75)	<0.001
Sex, n (%)				<0.001
Male	3,534 (41.89)	9,261 (45.77)	1,257,935 (45.10)	
Female	4,478 (53.08)	10,148 (50.15)	1,469,879 (52.69)	
Unreported	424 (5.03)	825 (4.08)	61,651 (2.21)	
AR-PDMP record ≤ 30 days prior to the first OOD, n(%)	5,596 (66.33)	9,504 (46.97)		
AR-PDMP record > 30 days prior to the first OOD, n(%)	2,840 (33.67)	10,730 (53.03)		
Mean RXs by CS type per person-year (SD) ^{a,b}				
Any controlled substance	20.65 (33.75)	12.49 (30.15)	3.41 (8.06)	<0.001
Opioids	13.86 (32.23)	8.69 (29.30)	1.82 (6.38)	<0.001
Benzodiazepines	6.49 (16.10)	4.31 (17.54)	0.95 (4.80)	<0.001
Stimulants	0.68 (4.69)	0.78 (5.78)	0.57 (3.36)	<0.001
Sedatives	1.69 (7.57)	1.06 (6.82)	0.34 (2.63)	<0.001
Muscle Relaxants	1.14 (8.70)	0.51 (7.15)	0.06 (0.94)	<0.001
Pregabalin	0.91 (5.59)	0.51 (5.40)	0.12 (1.82)	<0.001
Other	0.57 (5.41)	0.64 (7.25)	0.30 (3.25)	<0.001

AR-PDMP = Arkansas Prescription Drug Monitoring Program; OOD = Opioid Overdose; SD = Standard Deviation;

^a Prescription utilization over entire study time frame for individuals without OOD, and prescription utilization from study start date until date of OOD for those with OOD

^b Rates of prescriptions per person-year in each therapeutic class

Figure 1: Controlled Substance Utilization Rate by Opioid Overdose Status^{a,b}

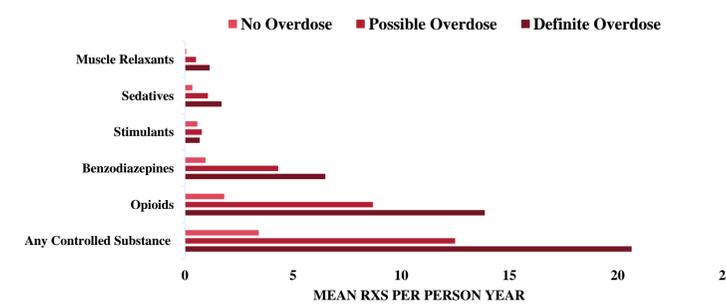
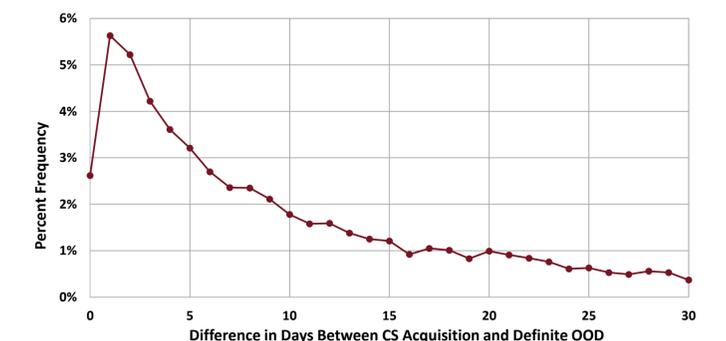


Figure 2: Temporal relationship between controlled substance acquisition and definite opioid overdose



^a Figure only represents data for the first 30 days prior to OOD

CS = Controlled Substance; OOD = Opioid Overdose

Table 4. Conditional logistic regression of controlled substance acquisition and opioid overdose within seven-day windows among Arkansas residents, 2014-2020

Controlled Substance Acquisition Within 7 days of Definite OOD	Unadjusted OR	95% CI	P Value	Adjusted OR	95% CI	P Value
Any Controlled Substance *	1.856	1.764, 1.954	<0.001	1.856	1.764, 1.954	<0.001
Opioid	2.097	1.987, 2.212	<0.001	1.982	1.875, 2.095	<0.001
Benzodiazepine	1.635	1.524, 1.754	<0.001	1.358	1.262, 1.462	<0.001
Opioid + Benzodiazepine	2.378	2.170, 2.605	<0.001	2.302	2.098, 2.526	<0.001
Stimulant	0.853	0.640, 1.136	0.276	0.723	0.541, 0.967	0.029
Sedative	1.222	1.047, 1.427	0.011	1.001	0.855, 1.172	0.988
Muscle Relaxant	2.117	1.747, 2.564	<0.001	1.490	1.224, 1.815	<0.001
Pregabalin	1.213	0.991, 1.485	0.061	0.988	0.805, 1.214	0.911
Other	1.017	0.728, 1.420	0.920	0.918	0.655, 1.286	0.620
7-day cumulative MME (REF: 0 MME)						
0 < MME ≤ 200	1.873	1.705, 2.056	0.407	1.785	1.624, 1.961	0.441
200 < MME ≤ 400	2.203	2.030, 2.390	<0.001	2.081	1.915, 2.261	<0.001
400 < MME ≤ 600	2.246	1.978, 2.549	<0.001	2.109	1.856, 2.398	<0.001
> 600 MME	2.095	1.887, 2.327	0.001	1.970	1.771, 2.190	0.004

CI = Confidence Interval; OOD = Opioid Overdose; OR = Odds Ratio; Ref = Reference Group

^a Odds ratio only adjusted for prior opioid overdose

CONCLUSION

- ✓ The risk of OOD is uncommon among persons acquiring CSs, as only 0.3% of individuals identified in the PDMP experienced a definite OOD over 6.5 years.
- ✓ Acquiring prescribed CSs appears to trigger OOD
 - ✓ Acquiring any prescribed CS or acquiring an opioid or in the 7 days immediately prior to OOD nearly doubles the risk of OOD compared to acquiring these substances in the weeks to months prior to OOD.
 - ✓ More modest increases in risk were observed for acquiring prescribed muscle relaxants and benzodiazepines in the 7 days prior to OOD
 - ✓ The highest risk of OOD was observed for acquiring both opioids and benzodiazepines in the 7 days prior to OOD
 - ✓ For those who experienced an OOD, a high proportion obtained CSs immediately prior to their opioid overdose, with approximately 25% of OODs occurring within 5 days of CS acquisition.

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