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ORIGINAL RESEARCH

Incidence of Opioid Overdose Among Patients Using ER/LA Opioid Analgesics Before and After Implementation of the Class-Wide Opioid Risk Evaluation and Mitigation Strategy

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Introduction: The United States (US) Food and Drug Administration (FDA) required a Risk Evaluation and Mitigation Strategy (REMS) for extended-release and long-acting (ER/LA) opioid analgesics on 09 July 2012.

Methods: This study compared the incidence of opioid overdose before (July 2010-June 2012) and after (July 2013-September 2016) the initiation of the Risk Evaluation and Mitigation Strategy (REMS) for extended-release and long-acting (ER/LA) opioid analgesics. We identified patients with ≥1 ER/LA opioid dispensing in either time period in national data from the HealthCore Integrated Research Database^{SM} (HIRD) and in United States (US) Medicaid claims data from four states. We described each population, calculated the incidence rate (IR) of opioid overdose, and assessed crude and propensity score adjusted incidence rate ratios (IRR) comparing the overdose rate after vs before implementation of the REMS.

Results: A total of 121,229 commercially insured and 11,488 Medicaid patients were included in the analysis. Rates of overdose were substantially higher in Medicaid patients than in the commercially insured patients (IR 192.0, 95% confidence interval [CI] 162.60–225.18 versus 102.60, 95% CI 93.0–112.93 in the active period). The IRRs for opioid overdose were 1.01 (95% CI 0.87–1.17) in the commercially insured population and 0.70 (95% CI 0.52–0.93) in Medicaid.

Conclusion: This leveling off of overdose rates among commercially insured patients and decline among Medicaid patients is encouraging, but it is difficult to disentangle the specific impact of the REMS from many other ongoing initiatives with similar goals.

Keywords: opioid, overdose, REMS, Medicaid, claims

Plain Language Summary

The United States Food and Drug Administration mandated a class-wide Risk Evaluation and Mitigation Strategy (REMS) for extended-release (ER)/long-acting (LA) opioids that went into effect in July 2012. This study used administrative data from the HealthCore Integrated Research Database (HIRD) linked to the National Death Index (NDI) and Medicaid plans from four participating states to compare rates of emergency department visits or hospitalizations due to opioid overdose among those patients who were using ER/LA opioids before and after the REMS program went into effect. Overall, opioid overdose rates were stable or decreased in this population. Medicaid patients had more opioid overdoses than privately-insured patients both before and after the REMS. Opioid overdose deaths decreased slightly in privately-insured patients, but could not be assessed in Medicaid. Because many programs are concurrently

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working to reduce opioid harm, alternative approaches are needed to formally assess the relation between the REMS and rates of opioid overdose.

Introduction

Extended-release and long-acting (ER/LA) opioid analgesics are approved by the United States (US) Food and Drug Administration (FDA) for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.[1] Although these medications are an important therapeutic option for many patients, concerns have arisen in recent years about misuse, abuse and the risk of overdose. The Centers for Disease Control and Prevention report that opioid overdose deaths more than tripled between 1999 and 2010, and abuse and misuse account for hundreds of thousands of emergency department (ED) visits each year.[2] Although overall opioid overdose rates continue to climb, rates due to natural and semisynthetic opioids, which include prescription ER/LA opioid analgesics, appear to have plateaued or declined starting in 2011.[2–4] Likewise, increases in the rate of overdose deaths began to slow in 2006.[5] More recently, however, a renewed surge in opioid overdose and opioid overdose death has been driven by fentanyl and synthetic opioids.[6]

The public-health response to increasing opioid overdoses has taken a multifaceted approach that includes local and state regulations, substance abuse treatment programs, prescription drug monitoring programs, "take back programs," and other measures. The US FDA required a Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioid analgesics on 09 July 2012 to reduce addiction, unintentional overdose, and death resulting from inappropriate prescribing, misuse, and abuse.[6,7] The REMS requires educational efforts that include: (1) Medication Guides, which are provided to patients at the point of medication dispensing, address issues specific to particular drugs and drug classes, and contain FDA-approved information that can help patients avoid serious adverse events; (2) Patient Counseling Documents to facilitate education of and discussions with patients by ER/LA opioid prescribers and other health-care providers; and (3) voluntary prescriber accredited continuing education on all ER/LA opioid analgesics. Class-wide safety labeling changes were also implemented. Annual REMS assessments submitted to the FDA have shown that approximately 66,219 healthcare providers completed training as of February 2016. Patient survey data found that 96.7% of respondents had received the medication guide.[8]

The purpose of this study was to describe the incidence of opioid overdose among commercially insured and Medicaid patients dispensed ER/LA opioids before and after REMS implementation.

Methods

We conducted a retrospective cohort study using the HealthCore Integrated Research Database[SM] (HIRD) as well as de-identified Medicaid data from four states. The HIRD contains longitudinal claims data for a population of over 40 million individuals with commercial insurance. With authorization from Medicaid plans in each participating state, similar claims data for individuals with Medicaid coverage administered through a private insurer were also accessed. We defined two time periods of interest: the REMS pre-implementation period (July 2010-June 2012) and the REMS active period (July 2013-September 2016). We included patients who received at least one ER/LA opioid analgesic dispensing of any duration during at least one REMS study period. Patients were required to have at least 6 months of continuous baseline health plan coverage prior to the first observed dispensing of an ER/LA opioid analgesic during a REMS study period. Subjects who were included in more than one REMS study period had different baseline periods and covariate profiles established for each applicable cohort entry date (Figure 1). Follow-up extended from the first ER/LA opioid dispensing until the end of the REMS period, the end of health plan coverage or a study outcome.

Treatment episodes were defined as beginning on the date an opioid medication was dispensed plus the number of days supplied, plus 30 days to account for intermittent use or use of medication still on hand from a prior dispensing. We assumed that concurrent or overlapping medication dispensings were used concurrently. Analyses included person-time during a treatment episode (ie, "exposed person-time").

In the HIRD, we defined patients as either new users or non-new users upon the start of their follow-up during each REMS period. New users were individuals for whom there were no prior recorded dispensings of ER/LA opioid analgesics identified in the administrative claims data at any time prior to the start of follow-up (noting that the baseline period was a minimum of 6 months long). Non-new users were individuals for whom pharmacy dispensings for ER/LA opioid analgesics were identified within the REMS period-specific baseline period. Patients were considered as new users only in the specific REMS period during which they

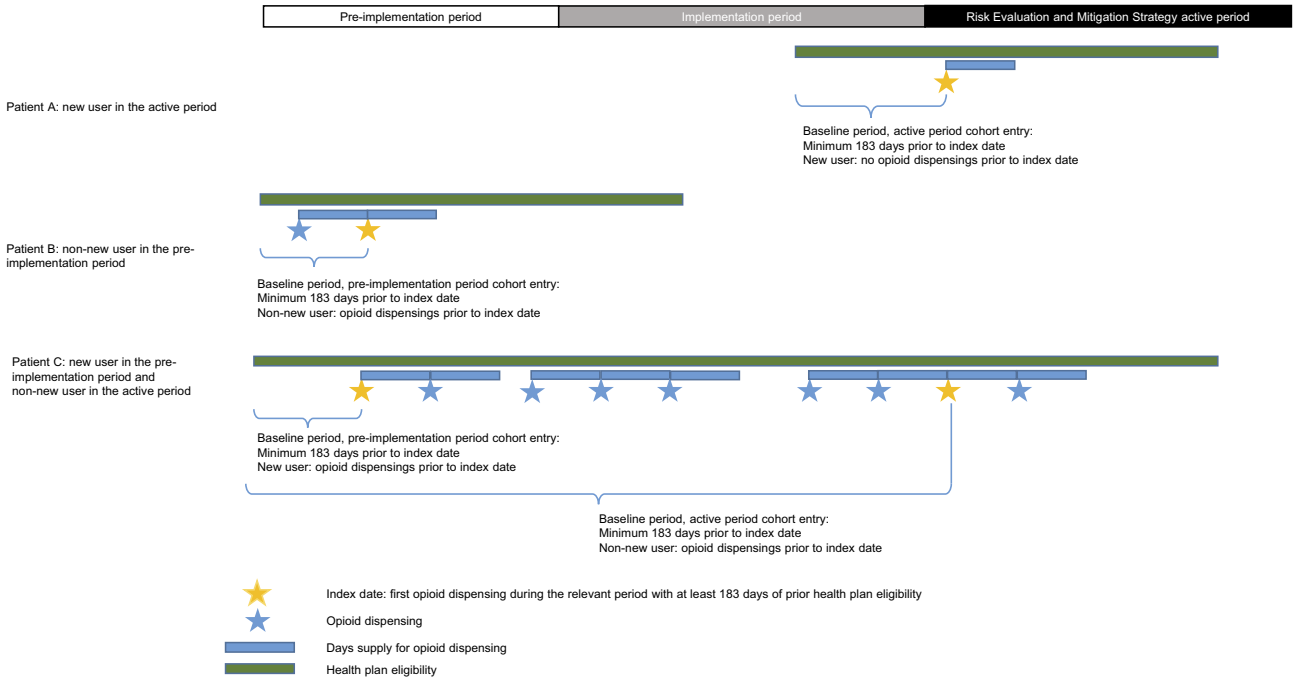

Figure 1 Examples of study entry and baseline covariate ascertainment windows.

first started follow-up. For example, a patient who initiated treatment during the pre-implementation period and continued to obtain dispensings during the active period was considered a new user during the pre-implementation period and a non-new user during the active period. Because of the small-available sample size for Medicaid, we did not stratify this group by new versus non-new user status.

Outcomes of interest included ED visits and hospitalizations due to opioid overdose or poisoning defined using diagnosis codes in any position from facility claims (Supplemental Table 1). Validation of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes 965 and E850 in Kaiser Permanente Northern California identified a positive predictive value of 83% for analgesic related overdoses or poisonings.[9] For commercially insured patients, we linked claims data electronically to the National Death Index (NDI). Patient identifiers were provided to NDI, and a probabilistic matching algorithm was applied to identify matched patients.[10] Because patient identifiers could not be used in this way for Medicaid, no overdose death data were available. Patients were then assigned as having a fatal overdose when any cause of death code indicated opioid overdose or poisoning.

Analyses

All analyses were performed separately for commercially insured and Medicaid patients. We first described demographics, medical history, pain conditions, psychiatric comorbidities, health-care utilization and medication use. We used these data to calculate propensity scores predicting ER/LA opioid use during the active period as compared to the pre-implementation period. We excluded patients whose propensity scores fell outside of the area of overlap between the groups by trimming the propensity score range asymmetrically using the 2.5 percentile of the propensity score distribution in the active period as a lower bound and the 97.5 percentile of the propensity score distribution in the pre-implementation period as an upper bound. The standardized difference in the distribution of each covariate included in the propensity score was reviewed within each propensity score decile to ensure balance. Any covariate that had a standardized difference of greater than 0.25 between REMS periods in any of the deciles was considered as a potential covariate along with the propensity score decile in the Poisson regression model. For the commercially insured, covariates were balanced and only indicator variables for propensity score deciles were included in the final models. For the Medicaid population, the number of prior immediate release opioid dispensings and prior use of sleep medications remained unbalanced within propensity score deciles (ie, standardized difference >0.25), and these variables were included in the regression models.

Within each REMS study period, we computed incidence rates as the number of opioid overdose events divided by the person time at risk, and for each rate, we computed an exact 95% confidence interval (CI). Rates were estimated during exposed person-time. For commercially insured patients, we also assessed rates for all users, new users and non-new users.

We presented the incidence rate ratios (IRRs) comparing the active period to the pre-implementation period, both crude and adjusted for propensity score deciles, using Poisson regression models with a generalized estimating equation correction to mitigate overdispersion (stemming from the statistical dependence introduced by having some of the same individuals appearing in both the active and the pre-implementation periods).

We performed all analyses using SAS® Enterprise Guide software version 9.4 (SAS Institute Inc., Cary, NC, USA).

This study was approved by the New England Institutional Review Board, which granted a waiver of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization under 45 CFR 164.512(i). The study was carried out in accordance with the principles of the Declaration of Helsinki and the International Society for Pharmacoepidemiology Guideline for Good Pharmacoepidemiology Practices.

Results

Among the commercially insured, we identified 99,074 individuals with at least one ER/LA opioid dispensing during the pre-implementation period and 92,925 with at least one dispensing during the active period. After restricting to those with at least 6 months of health plan enrollment prior to the first ER/LA opioid dispensing that occurred during the time frame, we retained 71,800 patients in the pre-implementation period and 59,465 in the active period. Numbers in the Medicaid from three states were smaller: 4889 pre-implementation period users and 7921 active period users were included in analyses (Table 1).

Comparing the active versus pre-implementation period, ER/LA users within the HIRD were similar with respect to age (median 48 years in the active period and 51 in the pre-implementation period), gender (54.6% versus 55.4% female) and residence setting (72.4% versus 72.9% urban). Medicaid ER/LA users were also similar comparing the active versus pre-implementation period, however they were younger (median age 44 years in the pre-implementation period), more often female (63% female) and less often of urban residence (68.5%) than the commercially insured. Duration of follow-up was slightly longer in the active period than the pre-implementation period for the commercially insured (13

Table 1 Formation of the Study Cohorts*

	Pre-Implementation Period		Active Period	
	N	%	N	%
HIRD				
Patients with ≥1 ER/LA opioid analgesic dispensing during the study period**	174,233			
≥1 ER/LA opioid analgesic dispensing during the applicable REMS period	99,074	100.0	92,925	93.8
Enrolled in health plan 6 months prior to first ER/LA opioid analgesic dispensing during the exposure period	78,734	79.5	69,445	70.1
Retained after propensity score trimming	71,800	72.5	59,465	60.0
Medicaid				
Patients with ≥1 ER/LA opioid analgesic dispensing during the study period**	23,981			
≥1 ER/LA opioid analgesic dispensing during the applicable REMS period	7568	100.0	17,377	72.5
Enrolled in health plan 6 months prior to first ER/LA opioid analgesic dispensing during the exposure period	5688	75.2	10,686	61.5
Retained after propensity score trimming	4889	64.6	7921	45.6

Notes: Pre-implementation Period: 1 July 2010 to 30 June 2012. Active Period: 1 July 2012 to 30 September 2016. *For continuous variables, descriptive statistics other than N and % are shown as designated in the first column. **No patients were excluded due to missing or invalid gender or age at the ER/LA opioid dispensing.
Abbreviations: N, number; ER/LA, extended release/long-acting; HIRD, HealthCore Integrated Research DatabaseSM; REMS, Risk Evaluation and Mitigation Strategy.

months versus 11 months) and substantially longer for the Medicaid population (18 months versus 8 months, Table 2).

Across time periods, a large majority of patients were diagnosed with back pain at baseline (78.8% of the commercially insured and 87.2% of the Medicaid insured in the Active Period). Other common pain diagnoses included arthritis, abdominal pain, and chronic pain. Nearly all pain diagnoses were more often recorded during the active period than the pre-implementation period in both commercially insured and Medicaid patients (eg, fibromyalgia was recorded for 29.7% of the commercially insured in the active period and 27.1% in the pre-implementation period). Chronic pain was recorded for a higher proportion of Medicaid patients (60.8% active period, 56.4% pre-implementation period) than commercially insured patients (36.5% active period, 25.8% pre-implementation period). Conversely, malignancy was recorded for a higher proportion of commercially insured patients (31.0% active period, 28.3% pre-implementation period) than Medicaid patients (15.5% active period, 12.4% pre-implementation period). Health-care utilization was comparable when comparing the active versus pre-implementation period within each population (Table 2).

Psychiatric comorbidities were consistently more common in the active period than the pre-implementation period for both commercially insured and Medicaid insured individuals, but they were substantially more common in the Medicaid population. The most common psychiatric conditions recorded were anxiety disorders (commercially insured: 36.3% active period, 30.5% pre-implementation period, Medicaid: 51.4% active period, 46.5% pre-implementation period), depression (commercially insured: 32.4% active period, 28.4% pre-implementation period, Medicaid: 47.8% active period, 43.9% pre-implementation period), and sleep disorders (commercially insured: 34.6% active period, 30.7% pre-implementation period, Medicaid: 40.7% active period, 37.8% pre-implementation period). Opioid type dependence, other drug dependence, and history of overdose were also more prevalent at baseline in the active than pre-implementation period and were higher for Medicaid patients than for the commercially insured (eg, opioid type dependence: commercially insured: 7.4% active period, 5.6% pre-implementation period, Medicaid: 24.6% active period, 22.1% pre-implementation period, Table 2).

In terms of opioid use among the commercially insured, a large majority of ER/LA opioid users also had past or present use of immediate-release opioids (89.1% active period, 88.8% pre-implementation period). The most commonly used ER/LA opioids were oxycodone (35.1% active period, 38.6% pre-implementation period) and fentanyl (21.5% active period, 27.2% pre-implementation period), and baseline history of benzodiazepine use was common (46.2% active period, 45.7% pre-implementation period [Table 3]). In Medicaid, immediate-release opioids were nearly universal (96.1% active period, 96.6% pre-implementation period), and the most commonly used ER/LA opioids were fentanyl (48.7% active period, 32.9% pre-implementation period) and morphine (47.9% active period, 41.1% pre-implementation period). During the active period, methadone was used by 31.1% of Medicaid, but by only 7.8% of commercially insured ER/LA opioid users (data not shown). Compared to the commercially insured, baseline history of benzodiazepine use was more common in the Medicaid population (53.7% active period, 55.0% pre-implementation period [Table 3]).

The commercially insured population had an IR for opioid overdose of 88.94 per 10,000 person years (95% CI 79.90–98.72) in the pre-implementation period and 102.60 (95% CI 93.00–112.93) during exposed person-time. This corresponded to an unadjusted IRR of 1.14 (95% CI 0.94–1.38) that decreased to 1.01 (95% CI 0.87–1.17) after propensity adjustment. Observed overdose rates were higher in new users than non-new users (active period incidence rate [IR] 140.03 vs 85.49). Rates appeared to decrease over time when comparing the active versus pre-implementation period for non-new users (propensity score adjusted IRR 0.87, 95% CI 0.72–1.05) and increase over time for new users (propensity score adjusted IRR 1.29, 95% CI 1.02–1.65). Opioid overdose mortality had an IR of 9.31 (95% CI 6.55–12.83) in the pre-implementation period and 7.08 (95% CI 4.74–10.17) during exposed person-time. This corresponded to an unadjusted IRR of 0.76 (95% CI 0.47–1.24) that decreased to 0.71 (95% CI 0.43–1.17) after adjusting for propensity score decile. (Table 4, Figure 2).

The rate of opioid overdose was strikingly higher in Medicaid with an IR for opioid overdose of 237.49 (95% CI 184.79–300.56) in the pre-implementation period and 192.00 (95% CI 162.60–255.18) during exposed person-time. This corresponded to an unadjusted IRR of 0.89 (95% CI 0.63–1.27) that decreased to 0.70 (95% CI 0.52–0.93) after adjusting for propensity score decile (Table 4, Figure 2).

Discussion

In this cohort study of commercially insured and Medicaid patients in a US administrative claims database, incidence

Table 2 Patient Characteristics by Study Period and Insurance Type

	HIRD				Medicaid			
	Pre-Implementation Period		Active Period		Pre-Implementation Period		Active Period	
	71,800		59,465		4889		7921	
	N*	%	N	%	N	%	N	%
Age category (years)								
Under 18	583	0.8	454	0.8	56	1.2	106	1.3
18 to 34	6930	9.7	4953	8.3	1159	23.7	1585	20.0
35 to 49	16,604	23.1	12,435	20.9	2158	44.1	3372	42.6
50 to 64	28,746	40.0	25,328	42.6	1470	30.1	2775	35.0
65 and over	18,937	26.4	16,295	27.4	46	0.9	83	1.1
Female	39,800	55.4	32,440	54.6	3082	63.0	4920	62.1
Geographic region of patient residence (US)								
Midwest	19,390	27.0	17,116	28.8	470	9.6	1149	14.5
Northeast	10,332	14.4	8091	13.6	<10		11	0.1
South	15,293	21.3	13,391	22.5	4328	88.5	6651	84.0
West	19,640	27.4	15,707	26.4	<10		<10	
Missing/unknown	7145	10.0	5160	8.7	84	1.7	101	1.3
Residence type								
Urban	52,358	72.9	43,039	72.4	3347	68.5	5497	69.4
Rural	12,292	17.1	11,263	18.9	1458	29.8	2323	29.3
Unknown	7150	10.0	5163	8.7	84	1.7	101	1.3
Year of cohort entry								
2010	34,060	47.4	0	0.0	2317	47.4	0.00	0.00
2011	26,909	37.5	0	0.0	1332	27.2	0.00	0.00
2012	10,831	15.1	0	0.0	1240	25.4	0.00	0.00
2013	0	0.0	26,300	44.2	0	0.0	3943	49.78
2014	0	0.0	15,334	25.8	0	0.0	1530	19.32
2015	0	0.0	11,794	19.8	0	0.0	1492	18.84
2016	0	0.0	6037	10.2	0	0.0	956	12.07
Duration of baseline period (months)								
Mean, SD	43.1	21.17	55.4	36.9	26.0	13.14	34.5	24.67
Median	51		48		28		27	
Range (min, max)	6	78	6	129	6	54	6	105
Duration of follow-up (months)								
Mean, SD	11.7	7.93	16	12.57	10.5	8.13	19.9	13.6
Median	11		13		8		18	
Range (min, max)	0	24	0	39	0	24	0	39
Pain diagnosis								
Abdominal pain	34,570	48.1	30,076	50.6	2629	53.8	4439	56.0
Amputation	5034	7.0	5199	8.7	222	4.5	421	5.3
Arthritis, arthropathies, osteoarthritis and musculoskeletal pain	42,609	59.3	37,899	63.7	2715	55.5	4652	58.7
Back pain	55,219	76.9	46,858	78.8	4315	88.3	6905	87.2
Chronic pain	18,519	25.8	21,701	36.5	2755	56.4	4816	60.8
Fibromyalgia	19,434	27.1	17,642	29.7	1544	31.6	2644	33.4
Headache	23,366	32.5	20,663	34.7	2285	46.7	3737	47.2
Malignancy	20,314	28.3	18,420	31.0	606	12.4	1228	15.5
Multiple sclerosis	967	1.3	811	1.4	72	1.5	122	1.5

(*Continued*)

Table 2 (Continued).

	HIRD				Medicaid			
	Pre-Implementation Period		Active Period		Pre-Implementation Period		Active Period	
	71,800		59,465		4889		7921	
	N*	%	N	%	N	%	N	%
Neuropathic pain	5472	7.6	6137	10.3	379	7.8	924	11.7
Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers	16,855	23.5	15,294	25.7	937	19.2	1778	22.4
Stroke	7900	11.0	7297	12.3	315	6.4	591	7.5
None of the above	3047	4.2	1743	2.9	99	2.0	170	2.1
Psychiatric comorbidities								
Alcoholism	3629	5.1	3565	6.0	608	12.4	1109	14.0
Anxiety disorder	21,900	30.5	21,593	36.3	2272	46.5	4069	51.4
Bipolar disorder	3125	4.4	2791	4.7	861	17.6	1505	19.0
Depressive disorder	20,397	28.4	19,243	32.4	2147	43.9	3783	47.8
History of suicide attempt	550	0.8	552	0.9	155	3.2	248	3.1
Post-traumatic stress disorder	1226	1.7	1276	2.1	274	5.6	598	7.5
Sleep disorder	22,022	30.7	20,571	34.6	1846	37.8	3221	40.7
Somatoform disorder	125	0.2	141	0.2	10	0.2	17	0.2
Drug dependence								
Opioid type dependence	4015	5.6	4372	7.4	1080	22.1	1948	24.6
Other drug dependence	4494	6.3	4852	8.2	1371	28.0	2408	30.4
ADHD	2172	3.0	2182	3.7	363	7.4	678	8.6
History of overdose/poisoning	556	0.8	686	1.2	102	2.1	220	2.8
Conditions that may affect opioid metabolism								
Liver disease	11,499	16.0	10,781	18.1	351	7.2	638	8.1
Renal disease	6845	9.5	6642	11.2	363	7.4	678	8.6
Deyo-Charlson comorbidity index								
Mean, SD	2.8	3.46	3.2	3.69	2.2	7.18	3	3
Median	1		2		1		1	
Range (min, max)	0	20	0	23	0	18	0	20
History of healthcare utilization								
All cause ED visits								
Mean, SD	0.4	0.88	0.4	0.94	8.4	5.07	8.6	5.39
Median	0		0		8		8	
Range (min, max)	0	40	0	44	0	40	0	56
All cause office visits								
Mean, SD	7.2	5.68	7	6	1.2	2.44	1.2	2.23
Median	6		6		0		0	
Range (min, max)	0	98	0	94	0	40	0	44
All cause hospitalizations								
Mean, SD	0.5	0.96	1	1	0.5	1.09	0.5	1.04
Median	0		0		0		0	
Range (min, max)	0	36	0	20	0	11	0	13
Distinct medication classes dispensed								
Mean, SD	9.5	6.08	9.6	6.03	12.7	7.18	12.8	7.26
Median	9		9		12		12	
Range (min, max)	0	52	0	59	0	50	0	57

Note: *For continuous variables, descriptive statistics other than N and % are shown as designated in the first column.

Abbreviations: HIRD, HealthCore Integrated Research Database; SD, standard deviation; min, minimum; max, maximum; US, United States; ADHD, attention-deficit/hyperactivity disorder; ED, emergency department; N, number.

Table 3 Baseline Medication Use by Study Period and Insurance Type

	HIRD				Medicaid			
	Pre-Implementation Period		Active Period		Pre-Implementation Period		Active Period	
	71,800		59,465		4889		7921	
	N	%	N	%	N	%	N	%
New ER/LA opioid analgesic user	45,896	63.9	37,905	63.7	2952	60.4	4473	56.5
Prior use of opioid analgesics								
ER/LA opioid analgesic only	1329	1.9	1164	2.0	74	1.5	101	1.3
IR opioid analgesic only	39,195	54.6	32,617	54.9	2858	58.5	4264	53.8
Both ER/LA and IR opioid analgesics	24,575	34.2	20,396	34.3	1863	38.1	3347	42.3
Number of different ER/LA opioid analgesic dispensings								
Mean, SD	1.5	0.79	1.5	0.80	1.4	0.66	1.5	0.81
Median	1		1		1		1	
Range (min, max)	1	7	1	7	1	6	1	6
Duration of ER/LA opioid analgesic use (months)								
Mean, SD	20.7	18.01	26.8	26.83	13.0	9.34	15.5	15.68
Median	15		17		10		10	
Range (min, max)	0	57	0	92	0	32	0	67
Time since last ER/LA opioid analgesic use (months)								
Mean, SD	5.2	11.87	7.4	17.67	3.1	7.64	3.3	9.53
Median	0		0		0		0	
Range (min, max)	0	73	0	122	0	49	0	84
Number of ER/LA opioid analgesics dispensed								
Mean, SD	21.0	20.26	26.9	29.12	14.4	12.56	0.0	18.26
Median	14		16		11		10	
Range (min, max)	1	7	1	383	1	131	1	192
Prescribing physician specialty (on index date)								
Pain specialist	27,644	38.5	22,711	38.2	1642	33.6	2553	32.2
General, internal medicine or family practice physician	20,944	29.2	16,367	27.5	960	19.6	1731	21.9
Other specialist	6807	9.5	5365	9.0	725	14.8	1207	15.2
Unknown	3583	5.0	3164	5.3	338	6.9	655	8.3
Non-physician	12,822	17.9	11,858	19.9	1224	25.0	1775	22.4
Number of prescribers of opioid analgesics								
Mean, SD	2.8	2.24	3.3	2.90	2.5	7.64	2.7	2.38
Median	2		2		2		2	
Range (min, max)	1	73	1	39	1	49	1	31
Number of pharmacies where patient obtained opioid analgesics								
Mean, SD	20.7	18.01	26.8	26.83	13.0	9.34	15.5	15.68
Median	15		17		10		10	
Range (min, max)	0	7	0	92	0	131	0	67
Number IR opioid analgesics dispensed								
Mean, SD	18.5	24.42	21.9	31.58	24.2	20.27	27.0	27.22
Median	8		9		20		17	
Range (min, max)	0	371	0	458	0	191	0	388

(*Continued*)

Table 3 (Continued).

	HIRD				Medicaid			
	Pre-Implementation Period		Active Period		Pre-Implementation Period		Active Period	
	71,800		59,465		4889		7921	
	N	%	N	%	N	%	N	%
Non-opioid medications of abuse potential								
Depressants								
Benzodiazepines	32,807	45.7	27,495	46.2	2689	55.0	4250	53.7
Barbiturates	247	0.3	178	0.3	21	0.4	36	0.5
Other sleep medications	22,702	31.6	17,881	30.1	1736	35.5	2629	33.2
Stimulants								
Amphetamines	2887	4.0	2648	4.5	271	5.5	462	5.8
Methylphenidate	1908	2.7	1565	2.6	72	1.5	117	1.5

Abbreviations: ER/LA, extended release/long-acting; HIRD, HealthCore Integrated Research Database; IR, immediate-release; SD, standard deviation; min, minimum; max, maximum; N, number.

rates of opioid overdose or poisoning did not meaningfully decrease after introduction of the REMS among the commercially insured patient cohort, and declined slightly in the Medicaid population. A slight numerical decrease in overdose mortality was also observed for the commercially insured.

Although substantially elevated rates of opioid overdose in Medicaid patients have been previously described,[11] the comparatively higher incidence in Medicaid patients compared to commercially insured patients observed here is striking. Our inability to assess mortality data for Medicaid patients is a limitation of the study. One of the reasons for higher incidence rates among the Medicaid patients could be differences in the distributions of certain patient characteristics associated with increased opioid overdose risk that are typical of commercially insured and Medicaid insured patients, such as a higher prevalence of psychiatric comorbidities among the Medicaid insured compared to the commercially insured. It is also plausible, given substantially higher rates of diagnosed opioid type dependence and use of methadone in Medicaid patients, that a higher proportion of Medicaid patients than commercially insured patients were receiving ER/LA opioids for maintenance therapy rather than pain management. Because administrative claims do not directly capture the indication for which a medication is prescribed, it is not possible to differentiate analgesic use from use for maintenance therapy.

Although some medications used for maintenance therapy are dispensed outside of routine care and may not be captured in administrative data, rates of methadone and buprenorphine use were higher in Medicaid than commercially-insured patients. If this is the case, some of the observed ER/LA use may be comingled with illicit opioid use where individuals may relapse due to use of opioids from non-medical sources. Administrative claims cannot define whether the medication that caused an overdose was prescribed or non-prescribed; the observed rate in these patients may reflect overdoses caused by illicit use. Further, the Medicaid population included in this study derives from only four states, and we cannot exclude the possibility that they are not fully representative of other Medicaid plans.

Higher rates of opioid overdose or poisoning in new users compared to non-new users warrant further investigation. The influence of confounding by unmeasured or poorly captured characteristics such as use of medication from non-medical sources and addiction disorder may play a role. Management of patients for whom long-term pain treatment is required also may differ from new users, who may include a higher proportion of patients for whom ER/LA opioid analgesic treatment is not indicated. It is plausible, for example, that pain physicians managing long-term users are more experienced in prescribing these medications. Their patients could be more aware of the serious risks of these medications as suggested by a recent survey of commercially insured ER/LA opioid users. Further, medication tolerance, which is more likely in chronic users[12] but cannot be well measured in administrative data, may have an impact on differences in findings between new and non-new users. Additionally, opioid overdose risk may not be constant over the course of treatment, with higher rates of overdose (1) early on in the course of treatment, and (2) later on for a subset

Table 4 Opioid Overdose or Poisoning Events

	Pre-Implementation Period					Active Period					Unadjusted			Adjusted for Propensity Score Decile		
	Cases	Person-Years	Incidence Rate	95% CI		Cases	Person-Years	Incidence Rate	95% CI		Incidence Rate Ratio	95% CI		Incidence Rate Ratio	95% CI	
HIRD																
Overdose emergency department visits or hospitalizations																
All ER/LA opioid analgesic users	353	39,689	88.94	79.90	98.72	418	40,740	102.60	93.00	112.93	1.14	0.94	1.38	1.01	0.87	1.17
New ER/LA opioid analgesic users	116	12,458	93.11	76.94	111.68	179	12,783	140.03	120.26	162.11	1.31	0.96	1.78	1.29	1.02	1.65
Non-new ER/LA opioid analgesic users	237	27,231	87.03	76.31	98.85	239	27,956	85.49	74.99	97.04	1.03	0.80	1.31	0.87	0.72	1.05
Overdose deaths																
All ER/LA opioid analgesic users	37	39,748	9.31	6.55	12.83	29	40,972	7.08	4.74	10.17	0.66	0.34	1.28	0.60	0.30	1.21
Medicaid																
Overdose emergency department visits or hospitalizations																
All ER/LA opioid analgesic users	69	2905	237.49	184.79	300.56	151	7865	192.00	162.60	225.18	0.89	0.63	1.27	0.70	0.52	0.93

Abbreviations: HIRD, HealthCore Integrated Research Database; ER/LA, extended release/long-acting; CI, confidence interval.

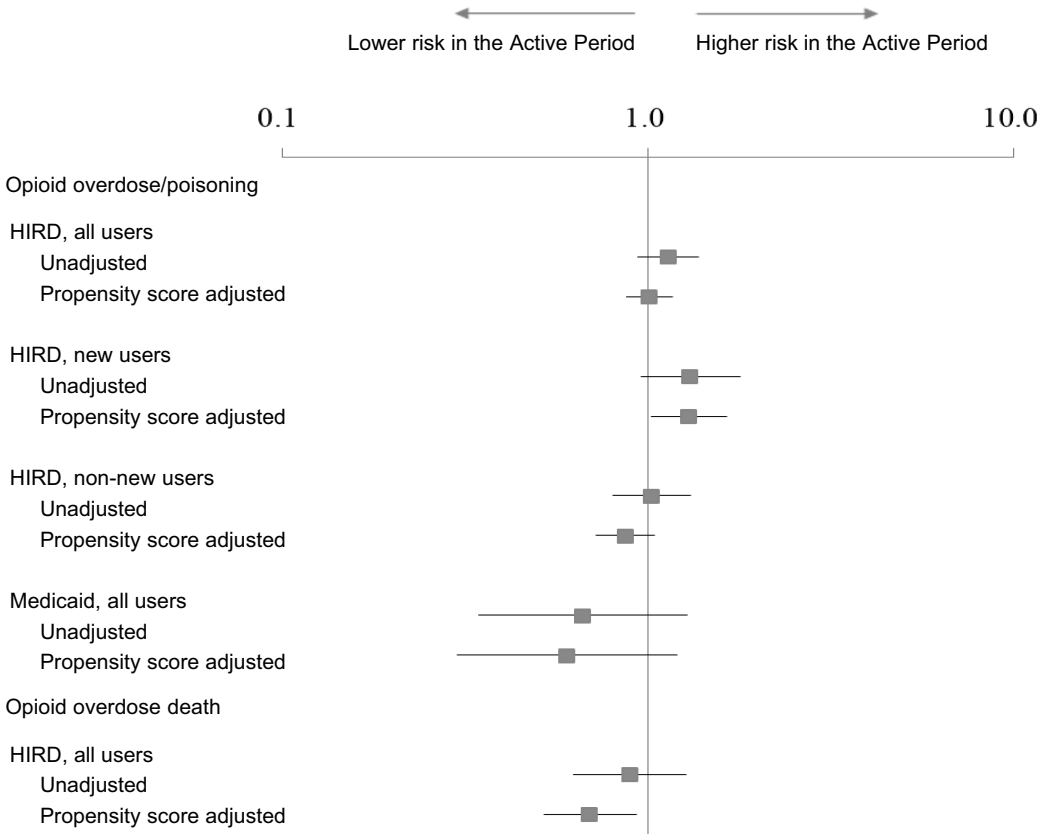

Figure 2 Incidence rate ratio of opioid overdose and opioid overdose death.
Abbreviation: HIRD, HealthCore Integrated Research Database.

of patients who develop opioid use disorders. It should be noted that the high-risk period early in the course of treatment is missed in non-new users, so this subgroup may be limited to those who did not experience adverse events early on. This may explain some differences between new and non-new users and differences in the observed overdose rates in the active and pre-implementation period for Medicaid given that follow-up was longer in the active period.

Because the REMS study periods are perfectly correlated with calendar time, the influence of the REMS on study results is difficult to disentangle from other contemporaneous factors, and results cannot be attributed solely to the REMS. Along with the implementation of the REMS, many other interventions targeting opioid analgesics have occurred. Efforts to develop abuse-deterrent formulations, enhanced requirements from both the FDA and Drug Enforcement Administration (DEA) and legislative changes at all levels of government have proceeded alongside REMS implementation. Prescription drug monitoring programs have been established in 49 states to address misuse, abuse and diversion of these controlled substances.[13,14] The National Governors Association State Policy Academy on Reducing Prescription Drug Abuse is among entities promoting state-based efforts to address the "opioid epidemic." In Oregon, for example, a task force is implementing strategies to reduce the number of pills in circulation, educate prescribers and the public on risks, improve safe disposal, and provide treatment for addicted patients.[15] Health system and health plan interventions on prescribing have also been implemented.[16] Given that the study REMS periods occurred during implementation of these and other measures, the extent to which any other concomitant effort has influenced rates of overdose over time is unknown. Further, whether or not each patient's opioid prescriber(s) had completed REMS-compliant continuing education is unknown in this assessment. Given that this is one of the primary mechanisms through which the education-focused REMS may impact opioid harm, a more informative future approach may be to directly compare opioid overdose rates in patients whose health-care providers did versus did not complete continuing education activities.

Our estimates of incidence may be subject to diagnostic bias. It is plausible, for example, that increased awareness of the serious risks of ER/LA opioid analgesics among the medical community could result in more

widespread attribution of overdose events to opioids and the familiarity with and use of opioid-specific ICD-9-CM or International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis overdose codes. Were that the case, an opioid overdose event may be more likely to be recorded as such in the active period, which would tend to mask an effect of the REMS. Additional code availability in ICD-10 may also result in more sensitive but less specific capture of overdose in this coding system, which was implemented in 2015 in the US. The plausibility of this is increased given that the observed incidence of overdose identified by administrative claims-based sources increased sharply after the introduction of ICD-10,[17] however formal validation studies have not been completed to date.

This study utilized an administrative claims database, and it is subject to the limitations inherent in the use of such data. The majority of analyses were conducted using a database that is representative of the commercially insured population in the US and is therefore not representative of individuals without medical insurance. Given differences in patient characteristics between commercially and Medicaid insured individuals and a substantially higher rate of overdose in Medicaid patients, better characterization of this at-risk population is important.

Finally, although all patients were required to have a pharmacy benefit, patients for the main analyses of ER/LA opioid analgesic users were identified on the basis of submitted pharmacy claims, excluding patients who chose not to use their pharmacy benefit from the cohort. Insurance coverage typically presents a strong financial incentive for use of the pharmacy benefit; however, it is possible that patients more likely to abuse opioids (who are therefore at higher risk for overdose, poisoning and death) could choose to pay for some or all of their prescriptions with cash.[18]

Conclusion

Despite these limitations, this study provides insight on the incidence of opioid overdose and poisoning in the context of the class-wide ER/LA opioid analgesic REMS in a large population. Continued efforts to reduce opioid harm are needed both overall and to reduce disparities between those with Medicaid and commercial insurance.

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