Matching Study Design to Prescribing Intention: The Prevalent New-User Design for Studying Abuse-Deterrent Formulations of Opioids

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Abstract

Purpose: In drug studies, research designs requiring no prior exposure to certain drug classes may restrict important populations. Since abuse-deterrent formulations (ADF) of opioids are routinely prescribed after other opioids, choice of study design, identification of appropriate comparators, and addressing confounding by "indication" are important considerations in ADF post-marketing studies. **Methods**: In a retrospective cohort study using claims data (2006-2018) from a North Carolina private insurer [NC claims] and Merative MarketScan [MarketScan], we identified patients (18-64 years old) initiating ADF or non-ADF extended-release/long-acting (ER/LA) opioids. We compared patient characteristics and described opioid treatment history between treatment groups, classifying patients as traditional (no opioid claims during prior six-month washout period) or prevalent new users. **Results**: We identified 8,415 (NC claims) and 147,978 (MarketScan) ADF, and 10,114 (NC claims) and 232,028 (MarketScan) non-ADF ER/LA opioid initiators. Most had prior opioid exposure (ranging 64-74%), and key clinical differences included higher prevalence of recent acute or chronic pain and surgery among patients initiating ADFs compared to non-ADF ER/LA initiators. Concurrent immediate-release opioid prescriptions at initiation were more common in prevalent new users than traditional new users. **Conclusions**: Careful consideration of the study design, comparator choice, and confounding by "indication" is crucial when examining ADF opioid use-related outcomes.

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ABSTRACT

Purpose : In drug studies, research designs requiring no prior exposure to certain drug classes may restrict important populations. Since abuse-deterrent formulations (ADF) of opioids are routinely prescribed after other opioids, choice of study design, identification of appropriate comparators, and addressing confounding by "indication" are important considerations in ADF post-marketing studies.

Methods : In a retrospective cohort study using claims data (2006-2018) from a North Carolina private insurer [NC claims] and Merative MarketScan [MarketScan], we identified patients (18-64 years old) initiating ADF or non-ADF extended-release/long-acting (ER/LA) opioids. We compared patient characteristics and described opioid treatment history between treatment groups, classifying patients as traditional (no opioid claims during prior six-month washout period) or prevalent new users.

Results : We identified 8,415 (NC claims) and 147,978 (MarketScan) ADF, and 10,114 (NC claims) and 232,028 (MarketScan) non-ADF ER/LA opioid initiators. Most had prior opioid exposure (ranging 64-74%), and key clinical differences included higher prevalence of recent acute or chronic pain and surgery among patients initiating ADFs compared to non-ADF ER/LA initiators. Concurrent immediate-release opioid prescriptions at initiation were more common in prevalent new users than traditional new users.

Conclusions : Careful consideration of the study design, comparator choice, and confounding by "indication" is crucial when examining ADF opioid use-related outcomes.

Keywords: opioid analgesics, postmarketing evaluation studies, study design, opioid prescribing, opioid related disorder

Key points:

- Abuse-deterrent formulations (ADFs) of extended-release/long-acting (ER/LA) opioids were formulated with the goal of reducing opioid use disorder and opioid overdose among pain patients prescribed opioids.
- We evaluated the implications study design choice for estimating post-market effectiveness of ADFs and examined patterns of initiation.
- More than two-thirds of patients had claims for opioids before ADF or non-ADF ER/LA initiation, and it was common for patients that initiated ADF opioids to have previously or concurrently been prescribed non-ADF ER/LA or immediate-release opioids.
- Traditional new user designs may not adequately represent the intended patient population compared to the prevalent new user design.

Plain Language Summary

Post-marketing drug studies evaluate safety and effectiveness of medications in real-world patient populations, but study designs requiring no prior exposure to certain drug classes may exclude key patients. Using insurance claims data (2006-2018) from a North Carolina private insurer [NC claims] and Merative MarketScan [MarketScan], we evaluated the implications study design choice when studying post-market effectiveness of abuse-deterrent formulations (ADFs) of extended-release and long-acting (ER/LA) opioids, classifying patients as incident (no opioid claims six months before cohort entry) or prevalent users. We also examined prescribing patterns around the time of ADF or non-ADF ER/LA initiation, and described patient characteristics between the two exposure groups. We identified 8,415 (NC claims) and 147,978 (MarketScan) ADF, and 10,114 (NC claims) and 232,028 (MarketScan) non-ADF ER/LA initiators. Most had prior opioid exposure (ranging 64-74%), and prevalent users were more likely than incident users to have immediate-release opioids also prescribed at ADF or non-ADF ER/LA initiation. Patients starting ADFs were more likely to have recent acute pain, chronic pain, or surgery compared to patients starting non-ADF ER/LAs. Our findings suggest that important considerations must be made when selecting patients for inclusion based on prior drug use and identifying appropriate comparators post-marketing studies of ADFs.

INTRODUCTION

Beginning in 1999, the United States (US) experienced rapid increases in opioid-related mortality and diagnosed opioid use disorders (OUD) related to prescription opioid use,[1,2] particularly extended-release and long-acting (ER/LA) formulations of opioids.[3] Abuse-deterrent formulations (ADFs) of ER opioids were introduced as a "safer" alternative to ER/LA opioids, with the goal of curbing OUD and opioid overdose in patient populations treated for pain.[4] The first ADF (August 2010) was a reformulation of oxycodone hydrochloride controlled-release tablets (reformulated OxyContin® , Purdue Pharma), followed by several other ADFs introduced in subsequent years. By reformulating these medications to be harder for individuals to obtain immediate release of the active ingredient by crushing or dissolving, the goal was to deter use through non-intended routes of administration, e.g., injecting or snorting.[4,5] A crucial post-marketing research question has been whether these reformulations have met this goal of successfully reducing OUD and opioid overdose among patients prescribed opioids for pain management.[6-8]

Post-marketing drug studies provide vital information about the safety and effectiveness of medications in real-world patient populations.[6] However, important considerations must be made when selecting patients for inclusion based on prior drug use and identifying appropriate comparators.[7,8] In drug studies, research designs requiring no prior exposure to specific drug classes, i.e., the active comparator new-user (ACNU) design,[9,10] may restrict research on important populations. For example, currently marketed ADFs are routinely used in patients with prior prescription opioid exposure.[11]Many implementations of the ACNU design in opioid research require no observed exposure to any or certain types of opioids in a pre-specified timeframe before cohort entry;[12] hence, people with incident ADF use in this type of study design may not be representative of the overall ADF patient population. The prevalent new-user (PNU) design[13,14] expands upon the traditional ACNU study, allowing for inclusion of patients previously prescribed a comparator treatment before starting

the new treatment, and may better represent the intended patient population.[15] Further, when designing pharmacoepidemiologic studies and selecting the study population it is important to identify appropriate comparators and address confounding by "indication"[16] observable in claims data.[7,8,17]

In this study, we evaluated the implications study design choice for estimating post-market effectiveness of ADFs and examined patterns of ADF and non-ADF ER/LA initiation. Further, we assessed demographic and clinical characteristics of patients initiating ADFs compared to patients initiating non-ADF ER/LA opioids to evaluate whether non-ADF ER/LA opioids represent an ideal comparator for ADF opioids.

METHODS

Data Sources

Available data spanned 13 years from 2006 through 2018 and was obtained from two sources: a large private health insurance provider in North Carolina (NC claims) and a commercially insured population from the Merative (formerly IBM®) MarketScan®Research Databases (MarketScan). The NC claims data source contained longitudinal demographic, outpatient, inpatient, and prescription claims data from individuals who received health and pharmaceutical coverage from a single private insurance provider, covering about one-fifth of NC residents from January 1, 2006 through September 30, 2018[18,19] (>1.4 million average member months of data per year). The MarketScan data source included longitudinal inpatient, outpatient, and prescription claims data from commercially insured individuals and their dependents. This nationally representative database includes more than 43.6 million individuals per year of data from January 1, 2006 through December 31, 2018.

Cohort selection & opioid analgesic treatment history

Adult patients (18-64 years old) were eligible for inclusion into analyses if they received an outpatient prescription for an ADF or non-ADF ER/LA opioid after August 1, 2010, when ADF opioids entered the market, following [?]six months of continuous enrollment before the prescription (**eFigures 1-5**). The filled date of the first prescription claim defining each cohort is hereafter referred to as the index date. Because treatment histories could span the period before August 1, 2010, we excluded patients who received their index ADF or non-ADF ER/LA prescription before August 1, 2010. Additionally, we excluded patients with evidence of overlapping ADF and non-ADF ER/LA prescriptions at the index date, defined as overlapping at least seven days or the duration of the ADF prescription. Patients were required to have [?]six months of continuous enrollment before their index date to characterize opioid treatment history before cohort entry.

We next categorized patients as traditional active comparator new users (incident users) or prevalent new users (prevalent users). Incident users of ADF and non-ADF ER/LA were identified as those with no prescription opioid claims of any type in the six-month washout period before the index date (**eFigures 1-5**). The PNU design allowed for non-ADF ER/LA or immediate-release (IR) opioid claims during the six months before ADF initiation, provided the patient's claim history also satisfied a six-month washout period with no opioid claims prior to the first non-ADF ER/LA or IR opioid claim. Similarly, prevalent users of non-ADF ER/LA opioids had evidence of IR or ADF opioid claims before the index date. We required a six-month washout period before the first opioid claim (between January 1, 2006 and the index date) in order to characterize each patient's opioid treatment history preceding their index ADF or non-ADF ER/LA prescription.

We further examined whether a patient had concurrent IR use at entry, defined as an overlap of the index prescription and an IR opioid that spanned [?]seven days of the treatment episode with an ADF (ADF cohort) or non-ADF ER/LA (ER/LA cohort). Among prevalent users, we examined whether patients had a direct switch ([?]7-day gap) between their previous opioid treatment and the index treatment versus a delayed switch (>7-day gap). We also identified the types of opioid analgesics (ADF cohort: IR and/or non-ADF ER/LA; non-ADF ER/LA cohort: IR and/or ADF) a patient had been exposed to between the most recent washout period and their index date, and time since the first opioid in the treatment episode (categorized as: 1-3, 4-6, 7-9, 10-12, 13-17, or 18+ months).

Patient Characteristics

Demographic and clinical characteristics were examined to identify potential confounding by "indication." Demographic characteristics (age and sex), and year of the index prescription date were included. We also identified outpatient pharmaceutical claims for benzodiazepines, gabapentin, and selective serotonin reuptake inhibitors (SSRIs) [?]six months before the index date as indications of physical and mental health status. Pain-related conditions (not mutually exclusive) were identified as invasive surgeries (using Current Procedural Terminology (CPT) codes[20]) or diagnosed acute pain, chronic pain, arthritis (rheumatoid or osteoarthritis) pain, back/neck pain, and neuropathic pain (using *International Classification of Disease, 9^{th} revision, Clinical Modification* (ICD-9-CM) and*10^{th} revision* (ICD-10-CM)) [?]30 days before the index date to capture potential clinical indications for pain management with ER/LA opioids. Finally, the Elixhauser comorbidity index[20,21] was used to identify comorbid conditions (Elixhauser conditions listed in Table 1) [?]six months before the index date based on ICD-9-CM and ICD-10-CM codes.

Statistical Analyses

We compared sample sizes by study design and described opioid treatment histories prior to ADF or non-ADF ER/LA initiation by cohort. We created heat maps to visualize opioid dispensing patterns in the six months before and one year after treatment initiation and described opioid treatment histories using counts and frequencies. Further, we contrasted patient characteristics between cohorts, examining counts, frequencies, and absolute standardized mean differences (SMD) for evidence of differences between cohorts, using a cutoff of 0.1 as a meaningful SMD.[22]

Data management was completed in SAS version 9.4 (Cary, NC, USA), and analyses were conducted in SAS 9.4 and R version 3.6.0.[23]

RESULTS

In NC claims, we identified 8,815 eligible patients (meeting inclusion/exclusion criteria) who initiated ADFs and 10,114 patients who initiated non-ADF ER/LA opioids (**eFigures 2-3**). Of these, 2,306 (27.4%) ADF patients and 2,612 (25.8%) non-ADF ER/LA users were classified as incident users, while 6,109 (72.6%) ADF patients and 7,502 (74.2%) non-ADF ER/LA patients were classified as prevalent users.

In MarketScan, there were 147,978 ADF initiators and 232,028 non-ADF ER/LA initiators included who met inclusion/exclusion criteria (**eFigures 4-5**). Of these, 53,233 (36.0%) patients initiating ADFs and 71,310 (30.7%) patients initiating non-ADF ER/LAs were classified as incident users, whereas 94,745 (64.0%) patients in the ADF cohort and 160,718 (69.3%) patients in the non-ADF ER/LA cohort were classified as prevalent users (**Table 1)** .

Among ADF prevalent users, 17.2% and 8.4% had prior exposure to non-ADF ER/LA opioid analgesics in NC claims and MarketScan, respectively. In both study populations, concurrent use of IR opioids [?]7 days was more common among prevalent users (NC claims [ADF: 53.4%, non-ADF ER/LA: 52.7%]; MarketScan [ADF: 50.6%, non-ADF ER/LA: 52.4%]) than incident users (NC claims [ADF: 36.8%, non-ADF ER/LA: 25.0%]; MarketScan [ADF: 34.5%, non-ADF ER/LA: 45.0%]). The majority of prevalent users had a direct switch from IR opioids in both datasets (NC claims [ADF: 60.4%, non-ADF ER/LA: 64.0%]; MarketScan [ADF: 58.8%, non-ADF ER/LA: 61.8%]). Heat maps of opioid prescribing patterns (**Figures 1 and 2**) show that patients with prior exposure to opioids before starting an ADF or non-ADF ER/LA continued to have more claims for prescription opioids in the one year after the index ADF or non-ADF ER/LA opioid than patients without prior opioid exposure.

Patient Characteristics: NC Claims

Incident users : Average [SD] age was similar between patients initiating ADFs (46.8 [12.7] years) and those initiating non-ADF ER/LA opioids (46.2 [12.0] years; **Table 2)** . Patients initiating ADFs were less likely to be female (42.3% vs 48.3%, respectively) and there was a calendar trend in prescribing, with ADFs prescribed more after 2012. A recent history of invasive surgery (53.9% vs 18.2%), acute pain (50.6% vs 28.2%), or

chronic pain (78.8% vs 65.5%) [?]30 days before initiation were more prevalent among ADF initiators. Patients initiating ADFs were less likely to have had recent claims for benzodiazepines or gabapentin. When examining specific pain indications (acute or chronic), patients starting ADFs were more likely to have rheumatoid or osteoarthritis pain, but less likely to have back/neck pain or neuropathic pain. When examining Elixhauser comorbid conditions, history of metastatic cancer (2.5% vs 4.4%) and solid tumor without metastasis (5.1% vs 7.4%) were less prevalent among patients initiating ADFs compared to those initiating non-ADF ER/LA opioids in the six months before initiation. Likewise, a history of substance use disorders (SUD) and depression were less prevalent in patients initiating ADFs than those initiating non-ADF ER/LAs.

Prevalent users : Average age was similar between patients initiating ADFs (48.5 [11.0] years) and those initiating non-ADF ER/LA opioids (48.2 [11.0] years; **Table 3)** . Patients initiating ADFs were somewhat less likely to be female (45.7% vs 49.8%, respectively, SMD = 0.08). A recent history of invasive surgery (36.0% vs 13.5%), acute pain (37.2% vs 23.4%), or chronic pain (81.1% vs 76.1%) [?]30 days before initiation were more prevalent among patients starting ADFs. As with incident users, patients initiating ADFs were more likely to have rheumatoid or osteoarthritis pain, but less likely to have had back/neck pain or neuropathic pain. Also, recent claims for gabapentin were less prevalent in patients initiating ADFs than those starting non-ADF ER/LA opioids. When examining Elixhauser comorbid conditions, recent history of metastatic cancer (13.2% vs 17.2%) and solid tumor without metastasis (18.6% vs 23.7%) were less prevalent among patients initiating ADFs compared to those starting non-ADF ER/LA opioids.

Patient Characteristics: MarketScan

Incident users : Among patients classified as incident users, average age [SD] was similar between ADF initiators (48.7 [12.7]) and non-ADF ER/LA initiators (48.7 [11.9]), and patients initiating ADFs were less likely to be female than patients initiating non-ADF ER/LA opioids (47.1% vs. 54.2%, respectively; **Table 2**). A recent history of invasive surgery (34.6% vs. 16.1%), acute pain (40.1% vs. 22.7%), chronic pain (66.3% vs. 48.6%), and arthritis pain (31.7% vs. 13.7%) [?]30 days before initiation were more prevalent in patients initiating ADFs than patients initiating non-ADF ER/LAs; whereas prevalence of back/neck pain (12.5% vs. 17.9%) and neuropathic pain (5.1% vs 7.3%) were lower in patients initiating ADFs than patients initiating non-ADF ER/LAs. Also, patients starting ADF opioids had lower prevalence of gabapentin prescribing (4.0% vs. 6.7%) and benzodiazepines (11.2% vs. 14.6%) six months before the index date than patients initiating non-ADF ER/LAs. Patients initiating ADF opioids had lower prevalence of Elixhauser comorbid conditions than patients initiating non-ADF ER/LA opioids, including a history of metastatic cancer (2.3% vs. 5.2%), solid tumor without metastasis (5.6% vs. 9.1%), and weight loss (1.5% vs. 3.1%).

Prevalent users : Average age was similar between ADF initiators (49.6 [11.4]) and non-ADF ER/LA initiators (49.7 [11.1]), and patients initiating ADF opioids were less likely to be female than patients initiating non-ADF ER/LA opioids (50.2% vs. 54.4%, respectively; **Table 3**). In terms of recent history of surgery and pain diagnoses, the prevalence of invasive surgery (43.0% vs. 26.7%), acute pain (37.1% vs. 23.5%), chronic pain (69.7% vs. 59.5%), and arthritis pain (23.5% vs. 11.2%) [?]30 days before initiation were higher in patients initiating ADFs than patients initiating non-ADF ER/LAs; whereas, prevalence of back/neck pain (27.6% vs. 32.7%) was lower in patients initiating ADFs than patients initiating non-ADF ER/LAs. As above, patients initiating ADF opioids had lower prevalence of gabapentin claims (16.4% vs. 19.7%) and benzodiazepines (31.7% vs. 35.9%) six months before the index date than patients initiating non-ADF ER/LAs, and in both groups, patients classified as prevalent users were more likely to have a recent history of claims for gabapentin and benzodiazepines compared to incident users. Similar to Elixhauser comorbid conditions among incident users, patients initiating ADFs had lower prevalence of metastatic cancer (13.0% vs. 19.3%), solid tumor without metastasis (18.6% vs. 26.3%), and weight loss (4.2% vs. 6.9%).

DISCUSSION

In this study of patients initiating ADF or non-ADF ER/LA opioids in the US from 2010 through 2018 us-

ing two different claims-based datasets, more than two-thirds of patients had evidence of claims for opioids before ADF or non-ADF ER/LA initiation. These patients would subsequently be excluded from traditional ACNU studies requiring no prior opioid exposure. We found that it was common for patients that initiated ADF opioids to have previously or concurrently been prescribed non-ADF ER/LA or IR opioids. Clincially, this suggests that ADFs and non-ADF ER/LAs are not typically used as first-line treatment for pain management and reflect evolving adjustments to therapy through time. Thus, traditional ACNU designs may represent an idealized scenario that does not reflect the real-world nature of how ADFs are utilized with other opioid formulations. A PNU study,[13,14] wherein patients are prescribed similar treatments (or potential comparators) before starting the new treatment, likely better represents the intended patient population.

A recent study examining the risk of opioid-related harm associated with use of ADF formulations of oxycodone found an increased risk of opioid-related harms among patients exposed to ADF oxycodone compared to patients on non-ADF oxycodone formulations.[12] However, this study restricted the study population to incident users without any prior exposure to oxycodone in the 12 months before the start of study follow-up. Our findings indicate that a substantial proportion of ADF users could be excluded as a result of the choice of study design. Therefore, a study design that includes prevalent new users would increase sample size and capture a broader range of patients representing ADF initiators. These findings may apply to studies of other medications where prior exposure is a labeled prerequisite, such as higher-dose ER/LA opioids and second-line therapies. CDC guidelines from 2016[24] and 2022[25] recommend prescribing IR opioids for the shortest duration possible for acute pain episodes and also recommend that when initiating opioid therapy for chronic pain, physicians should start patients on IR opioids rather than ER/LA opioids. These guidelines also recommend against prescribing IR and ER/LA opioids concurrently.

Interestingly, in both patient populations in this study, patients initiating ADFs were more likely to have a history of recent surgery, acute pain, or chronic pain, regardless of study design type. However, when examining comorbid conditions, patients initiating non-ADF ER/LA opioids (new or prevalent) were more likely to have a history of cancer, and among patients classified as incident users, individuals initiating non-ADF ER/LA opioids were more likely to have a recent history of SUD, depression, or prescriptions for benzodiazepines. When investigating the impact of ADFs on opioid-related harms, non-ADF ER/LA opioids are likely a more suitable comparator choice than IR opioids due to opioid dosage, duration of action, and likely duration of treatment. However, observed differences in patient characteristics in this study indicate potential confounding by "indication" in analyses examining the relationship between ADF use and opioid-related harms that would need to be accounted for using weighting or other methods for confounding control.[26]

This study examines two large populations of patients initiating ADF and non-ADF opioids over nine years during the prescription opioid phase of the substance use epidemic using both a national and state data source. Notably, both data sources produced largely similar findings about opioid prescribing history and patient characteristics at ER/LA initiation. However, there are limitations to consider when interpreting these findings. The NC claims data source only includes data on patients <65 years old who were privately insured by a single insurance provider and the MarketScan data includes claims information from individuals with employer-sponsored insurance. Therefore, these findings may not generalize to all privately insured individuals in the US or to individuals covered by Medicare or Medicaid or those without health insurance. Additionally, due to the nature of pharmaceutical claims data, we could only analyze prescriptions that individuals filled from the pharmacy that were paid for by insurance, not what was paid for out-of-pocket or what was consumed by individuals included in this study.

Conclusions

In this large study of individuals initiating ADF and non-ADF ER/LA opioids in the US, we found that most individuals had prior opioid exposure in the six months before initiation and would be excluded in post-marketing study designs that required no prior opioid exposure. There are important considerations that must be made regarding comparator selection and adjusting for confounding by "indication" in ADF post-marketing studies. We found that individuals initiating ADF opioids (regardless of prior opioid exposure)

were more likely to have a recent acute or chronic pain diagnosis or surgery and were less likely to have a cancer diagnosis than those initiating non-ADF ER/LA opioids. Future work will further explore implementation of the PNU design and consider nuances in ADF initiation such as immediate versus delayed switching by incorporating opioid treatment history to address opioid tolerance.

ETHICS STATEMENT

This analysis was part of a larger study approved by the Institutional Review Board (IRB), Office of Human Research Ethics, the University of North Carolina at Chapel Hill. The University of Kentucky's IRB has approved the use of de-identified claims data from MarketScan for research purposes; therefore, no further approval for this study was required.

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CONFLICT OF INTEREST STATEMENT

ND is on the Scientific Advisory Board of the non-profit RADARS System of Denver Health and Hospitals Authority, which had no knowledge of or involvement in this research.

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Table 1. Opioid treatment histories for patients prescribed a non-ADF ER/LA or ADF opioid between August 1, 2010 and September 30, 2018 identified using insurance claims data from a private insurer in North Carolina (N = 17,140) and MarketScan (N = 380,006)

			NC claims N (%)	NC claim
			NC claims N (%)	NC claim
			ER/LA N = 10,114	**ADF** N =
Traditional New-User	**Traditional New-User**	**Traditional New-User**	2,612 (25.8)	2,306 (27.4
	Concurrent IR use at index	*Concurrent IR use at index*		
		No concurrent IR	1,958 (75.0)	1,457 (63.9
		Concurrent IR	654 (25.0)	849 (36.8)
Prevalent New-User	**Prevalent New-User**	**Prevalent New-User**	7,502 (74.2)	6,109 (72.6
	Concurrent IR use at index	*Concurrent IR use at index*		
		No concurrent IR	3,546 (47.3)	2,846 (46.6
		Concurrent IR	3,956 (52.7)	3,263 (53.4
	Treatment Switch	*Treatment Switch*		
		Direct switch from ADF	271 (3.6)	-
		Direct switch from IR	4,798 (64.0)	3,690 (60.4
		Delayed switch from ADF	86 (1.2)	-
		Delayed switch from IR	2,347 (31.3)	1,758 (28.8
		Direct switch from ER/LA	-	487 (8.0)
		Delayed switch from ER/LA	-	174 (2.9)
	Historical opioid use by type	*Historical opioid use by type*		
		ADF only or ADF & IR	567 (7.6)	-
		IR only	6,935 (92.4)	5,061 (82.8
		ER/LA & IR	-	1,025 (16.8
		ER/LA only	-	23 (0.4)
	Months since first opioid	*Months since first opioid*		
		1-3	2,485 (33.1)	2,250 (36.8
		4-6	1,192 (15.9)	956 (15.7)
		7-9	815 (10.9)	612 (10.0)
		10-12	547 (7.3)	369 (6.0)
		13-17	655 (8.7)	441 (7.2)
		18+	1,808 (24.1)	1,481 (24.2

[a]Abbreviations: ADF: Abuse-deterrent formulation; ER/LA: Extended-release/long-acting; IR: Immediate-release

Table 2. Baseline characteristics of traditional new users. Comparing baseline characteristics[a] of patients newly initiating an ADF or non-ADF ER/LA opioid between August 1, 2010 and September 30, 2018 in insurance claims data from North Carolina (N = 17,140) and MarketScan (N = 380,006)

	NC claims	**NC claims**	**NC claims**	**MarketScan**	**MarketScan**	**MarketScan**
	ER/LA N = 2,612	**ADF** N = 2,306	**SMD**	**ER/LA** N =71,310	**ADF** N =53,233	**SMD**
Age, mean [SD]	46.2 [12.0]	46.8 [12.7]	0.047	48.7 [11.9]	48.7 [12.7]	0.002
Female	1261 (48.3)	975 (42.3)	0.121	38,620 (54.2)	25,091 (47.1)	0.109
Index Year			0.139			0.275

	NC claims	**NC claims**	**NC claims**	**MarketScan**	**MarketScan**	**MarketScan**
2010	271 (10.4)	71 (3.1)		8,326 (11.7)	2,762 (5.2)	
2011	355 (13.6)	298 (12.9)		13,952 (19.6)	10,768 (20.2)	
2012	332 (12.7)	314 (13.6)		11,608 (16.3)	10,349 (19.4)	
2013	330 (12.6)	374 (16.2)		7,972 (11.2)	7,698 (14.5)	
2014	414 (15.8)	374 (16.2)		10,242 (14.4)	8,333 (15.7)	
2015	358 (13.7)	377 (16.3)		6,861 (9.6)	5,331 (10.0)	
2016	289 (11.1)	276 (12.0)		5,990 (8.4)	4,110 (7.7)	
2017	217 (8.3)	175 (7.6)		4,364 (6.1)	2,755 (5.2)	
2018	46 (1.8)	47 (2.0)		1,995 (2.8)	1,127 (2.1)	
Other Prescriptions						
Benzodiazepines	596 (22.8)	355 (15.4)	0.190	10,384 (14.6)	5,950 (11.2)	0.101
Gabapentin	326 (12.5)	211 (9.2)	0.107	4,783 (6.7)	2,130 (4.0)	0.120
SSRIs	392 (15.0)	279 (12.1)	0.085	8,842 (12.4)	6,177 (11.6)	0.024
Surgery and pain diagnoses						
Surgery	475 (18.2)	1,242 (53.9)	0.800	11,451 (16.1)	18,428 (34.6)	0.437
Acute Pain	736 (28.2)	1,167 (50.6)	0.472	16,184 (22.7)	21,355 (40.1)	0.382
Chronic Pain	1,713 (65.6)	1,816 (78.8)	0.297	34,644 (48.6)	35,270 (66.3)	0.363
Arthritis Pain	373 (14.3)	817 (35.4)	0.505	9,791 (13.7)	16,879 (31.7)	0.439
Back/Neck Pain	675 (25.8)	288 (12.5)	0.344	12,781 (17.9)	6,674 (12.5)	0.150
Neuropathic Pain	252 (9.6)	109 (4.7)	0.191	5,168 (7.3)	2,729 (5.1)	0.088
Elixhauser Comorbid Conditions						
Congestive Heart Failure	41 (1.6)	30 (1.3)	0.023	1,713 (2.4)	898 (1.7)	0.051
Cardiac Arrhythmia	207 (7.9)	217 (9.4)	0.053	5,614 (7.9)	4,275 (8.0)	0.006
Valvular Disease	81 (3.1)	49 (2.1)	0.061	2,192 (3.1)	1,584 (3.0)	0.006

	NC claims	**NC claims**	**NC claims**	**MarketScan**	**MarketScan**	**MarketScan**
Pulmonary Circulation Disorders	39 (1.5)	31 (1.3)	0.013	1,203 (1.7)	706 (1.3)	0.030
Peripheral Vascular Disorders	60 (2.3)	46 (2.0)	0.021	1,934 (2.7)	1,140 (2.1)	0.037
Hypertension Uncomplicated	777 (29.7)	668 (29.0)	0.017	19,952 (28.0)	15,753 (29.6)	0.036
Hypertension Complicated	64 (2.5)	79 (3.4)	0.058	1,495 (2.1)	995 (1.9)	0.016
Paralysis	23 (0.9)	10 (0.4)	0.055	805 (1.1)	476 (0.9)	0.023
Other Neurological Disorders	91 (3.5)	60 (2.6)	0.051	2,266 (3.2)	1,114 (2.1)	0.068
Chronic Pulmonary Disease	272 (10.4)	191 (8.3)	0.073	7,342 (10.3)	4,737 (8.9)	0.047
Diabetes Uncomplicated	289 (11.1)	202 (8.8)	0.077	8,397 (11.8)	5,327 (10.0)	0.057
Diabetes Complicated	85 (3.3)	59 (2.6)	0.041	2,577 (3.6)	1,420 (2.7)	0.054
Hypothyroidism	229 (8.8)	173 (7.5)	0.046	6,358 (8.9)	5,109 (9.6)	0.024
Renal Failure	67 (2.6)	43 (1.9)	0.048	1,723 (2.4)	878 (1.7)	0.054
Liver Disease	134 (5.1)	98 (4.2)	0.042	3,352 (4.7)	1,669 (3.1)	0.081
Peptic Ulcer Disease excl. bleeding	17 (0.7)	18 (0.8)	0.015	423 (0.6)	183 (0.3)	0.037
AIDS/HIV	2 (0.1)	0 (0.0)	0.039	202 (0.3)	111 (0.2)	0.015
Lymphoma	17 (0.7)	11 (0.5)	0.023	773 (1.1)	355 (0.7)	0.045
Metastatic Cancer	116 (4.4)	57 (2.5)	0.108	3,710 (5.2)	1,239 (2.3)	0.151
Solid Tumor without Metastasis	194 (7.4)	117 (5.1)	0.097	6,506 (9.1)	2,984 (5.6)	0.135
Rheumatoid Arthritis/collagen	138 (5.3)	76 (3.3)	0.098	3,466 (4.9)	1,894 (3.6)	0.065
Coagulopathy	64 (2.5)	61 (2.6)	0.012	1,775 (2.5)	1,211 (2.3)	0.014
Obesity	277 (10.6)	287 (12.4)	0.058	6,013 (8.4)	5,599 (10.5)	0.071
Weight Loss	100 (3.8)	60 (2.6)	0.070	2,174 (3.1)	797 (1.5)	0.104

	NC claims	**NC claims**	**NC claims**	**MarketScan**	**MarketScan**	**MarketScan**
Fluid and Electrolyte Disorders	250 (9.6)	189 (8.2)	0.048	5,293 (7.4)	3,084 (5.8)	0.066
Blood Loss Anemia	29 (1.1)	16 (0.7)	0.044	559 (0.8)	427 (0.8)	0.002
Deficiency Anemia	80 (3.1)	53 (2.3)	0.047	2,324 (3.3)	1,245 (2.3)	0.056
Alcohol Use Disorder	73 (2.8)	76 (3.3)	0.029	1,285 (1.8)	977 (1.8)	0.002
Substance Use Disorder	168 (6.4)	62 (2.7)	0.180	1,293 (1.8)	600 (1.1)	0.057
Psychoses	24 (0.9)	10 (0.4)	0.059	644 (0.9)	287 (0.5)	0.043
Depression	461 (17.6)	307 (13.3)	0.120	9,236 (13.0)	6,218 (11.7)	0.039

[a]All results presented are N (%) unless otherwise noted

[b]Abbreviations: ADF: Abuse-deterrent formulation; ER/LA: Extended-release/long-acting; IR: Immediate-release; SMD: standardized mean difference; IQR: interquartile range; SSRI: selective serotonin reuptake inhibitor

Table 3. Baseline characteristics of prevalent new users. Comparing baseline characteristics[a] of patients initiating an ADF or non-ADF ER/LA opioid between August 1, 2010 and September 30, 2018 in insurance claims data from North Carolina (N = 17,140) and MarketScan (N = 380,006)

	NC claims	**NC claims**	**NC claims**	**MarketScan**	**MarketScan**	**MarketScan**
	ER/LA N = 7,502	**ADF** N = 6,109	**SMD**	**ER/LA** N =160,718	**ADF** N =94,745	**SMD**
Age, mean [SD]	48.2 [11.0]	48.5 [11.0]	0.032	49.7 [11.1]	49.6 [11.4]	0.011
Female	3,737 (49.8)	2,789 (45.7)	0.083	87,474 (54.4)	47,562 (50.2)	0.134
Index Year			0.096			0.113
2010	657 (8.8)	394 (6.4)		13,392 (8.3)	5,398 (5.7)	
2011	1,143 (15.2)	833 (13.6)		28,148 (17.5)	17,386 (18.4)	
2012	1,068 (14.2)	809 (13.2)		29,380 (18.3)	18,022 (19.0)	
2013	951 (12.7)	817 (13.4)		21,352 (13.3)	13,410 (14.2)	
2014	995 (13.3)	859 (14.1)		22,340 (13.9)	14,031 (14.8)	

	NC claims	**NC claims**	**NC claims**	**MarketScan**	**MarketScan**	**MarketScan**
2015	1,048 (14.0)	931 (15.2)		16,002 (10.0)	10,123 (10.7)	
2016	771 (10.3)	729 (11.9)		14,140 (8.8)	7,952 (8.4)	
2017	615 (8.2)	537 (8.8)		10,057 (6.3)	5,336 (5.6)	
2018	254 (3.4)	200 (3.3)		5,907 (3.7)	3,087 (3.3)	
Other Prescriptions						
Benzodiazepines	3,094 (41.2)	2,352 (38.5)	0.056	57,712 (35.9)	30,067 (31.7)	0.088
Gabapentin	1,826 (24.3)	1,230 (20.1)	0.101	31,724 (19.7)	15,527 (16.4)	0.087
SSRIs	1,574 (21.0)	1,281 (21.0)	<0.001	32,290 (20.1)	18,175 (19.2)	0.023
Surgery and pain diagnoses						
Surgery	1,011 (13.5)	2,202 (36.0)	0.542	42,830 (26.7)	40,761 (43.0)	0.349
Acute Pain	1,756 (23.4)	2,270 (37.2)	0.303	37,823 (23.5)	35,147 (37.1)	0.298
Chronic Pain	5,707 (76.1)	4,956 (81.1)	0.123	95,607 (59.5)	66,067 (69.7)	0.215
Arthritis Pain	1,043 (13.9)	1,511 (24.7)	0.277	17,958 (11.2)	22,303 (23.5)	0.331
Back/Neck Pain	3,213 (42.8)	2,095 (34.3)	0.176	52,573 (32.7)	26,153 (27.6)	0.111
Neuropathic Pain	1,402 (18.7)	884 (14.5)	0.114	23,355 (14.5)	11,682 (12.3)	0.065
Elixhauser Comorbid Conditions						
Congestive Heart Failure	237 (3.2)	181 (3.0)	0.011	5,798 (3.6)	2,898 (3.1)	0.031
Cardiac Arrhythmia	839 (11.2)	659 (10.8)	0.013	18,486 (11.5)	10,667 (11.3)	0.008
Valvular Disease	318 (4.2)	223 (3.7)	0.03	7,210 (4.5)	3,993 (4.2)	0.013
Pulmonary Circulation Disorders	185 (2.5)	151 (2.5)	<0.001	4,856 (3.0)	2,497 (2.6)	0.023
Peripheral Vascular Disorders	369 (4.9)	273 (4.5)	0.021	7,307 (4.6)	3,579 (3.8)	0.039

	NC claims	**NC claims**	**NC claims**	**MarketScan**	**MarketScan**	**MarketScan**
Hypertension Uncomplicated	3,018 (40.2)	2,545 (41.7)	0.029	59,805 (37.2)	35,700 (37.7)	0.010
Hypertension Complicated	262 (3.5)	236 (3.9)	0.020	5,226 (3.3)	2,778 (2.9)	0.018
Paralysis	97 (1.3)	72 (1.2)	0.010	2,192 (1.4)	1,112 (1.2)	0.017
Other Neurological Disorders	328 (4.4)	231 (3.8)	0.030	7,455 (4.6)	3,491 (3.7)	0.048
Chronic Pulmonary Disease	1,168 (15.6)	851 (13.9)	0.046	24,076 (15.0)	13,024 (13.8)	0.035
Diabetes Uncomplicated	1,112 (14.8)	865 (14.2)	0.019	25,487 (15.9)	13,853 (14.6)	0.034
Diabetes Complicated	367 (4.9)	289 (4.7)	0.008	8,952 (5.6)	4349 (4.6)	0.045
Hypothyroidism	810 (10.8)	625 (10.2)	0.018	17,035 (10.6)	10,252 (10.8)	0.007
Renal Failure	276 (3.7)	218 (3.6)	0.006	6,158 (3.8)	3,038 (3.2)	0.034
Liver Disease	796 (10.6)	570 (9.3)	0.043	15,724 (9.8)	7,562 (8.0)	0.063
Peptic Ulcer Disease excl. bleeding	111 (1.5)	74 (1.2)	0.023	2,176 (1.4)	902 (1.0)	0.038
AIDS/HIV	16 (0.2)	14 (0.2)	0.003	706 (0.4)	318 (0.3)	0.017
Lymphoma	181 (2.4)	154 (2.5)	0.007	4,680 (2.9)	2,352 (2.5)	0.027
Metastatic Cancer	1,287 (17.2)	805 (13.2)	0.111	30,933 (19.3)	12,320 (13.0)	0.170
Solid Tumor without Metastasis	1,781 (23.7)	1,134 (18.6)	0.127	42,245 (26.3)	17,575 (18.6)	0.186
Rheumatoid Arthritis/collagen	746 (9.9)	481 (7.9)	0.073	13,087 (8.1)	6,562 (6.9)	0.046
Coagulopathy	332 (4.4)	254 (4.2)	0.013	7,219 (4.5)	3,912 (4.1)	0.018
Obesity	1,016 (13.5)	927 (15.2)	0.047	17,884 (11.1)	12,146 (12.8)	0.052
Weight Loss	608 (8.1)	390 (6.4)	0.066	11,104 (6.9)	3,933 (4.2)	0.121
Fluid and Electrolyte Disorders	1,143 (15.2)	806 (13.2)	0.059	23,920 (14.9)	11,284 (11.9)	0.087

	NC claims	**NC claims**	**NC claims**	**MarketScan**	**MarketScan**	**MarketScan**
Blood Loss Anemia	117 (1.6)	82 (1.3)	0.018	2,042 (1.3)	1,140 (1.2)	0.006
Deficiency Anemia	404 (5.4)	282 (4.6)	0.035	8,872 (5.5)	4,309 (4.6)	0.044
Alcohol Use Disorder	308 (4.1)	238 (3.9)	0.011	4,153 (2.6)	2,363 (2.5)	0.006
Substance Use Disorder	581 (7.7)	382 (6.3)	0.058	6,657 (4.1)	3,487 (3.7)	0.024
Psychoses	91 (1.2)	78 (1.3)	0.006	2,212 (1.4)	1,042 (1.1)	0.025
Depression	1,882 (25.1)	1,441 (23.6)	0.035	31,885 (19.8)	18,283 (19.3)	0.014

[a]All results presented are N (%) unless otherwise noted

[b]Abbreviations: ADF: Abuse-deterrent formulation; ER/LA: Extended-release/long-acting; IR: Immediate-release; SMD: standardized mean difference; IQR: interquartile range; SSRI: selective serotonin reuptake inhibitor

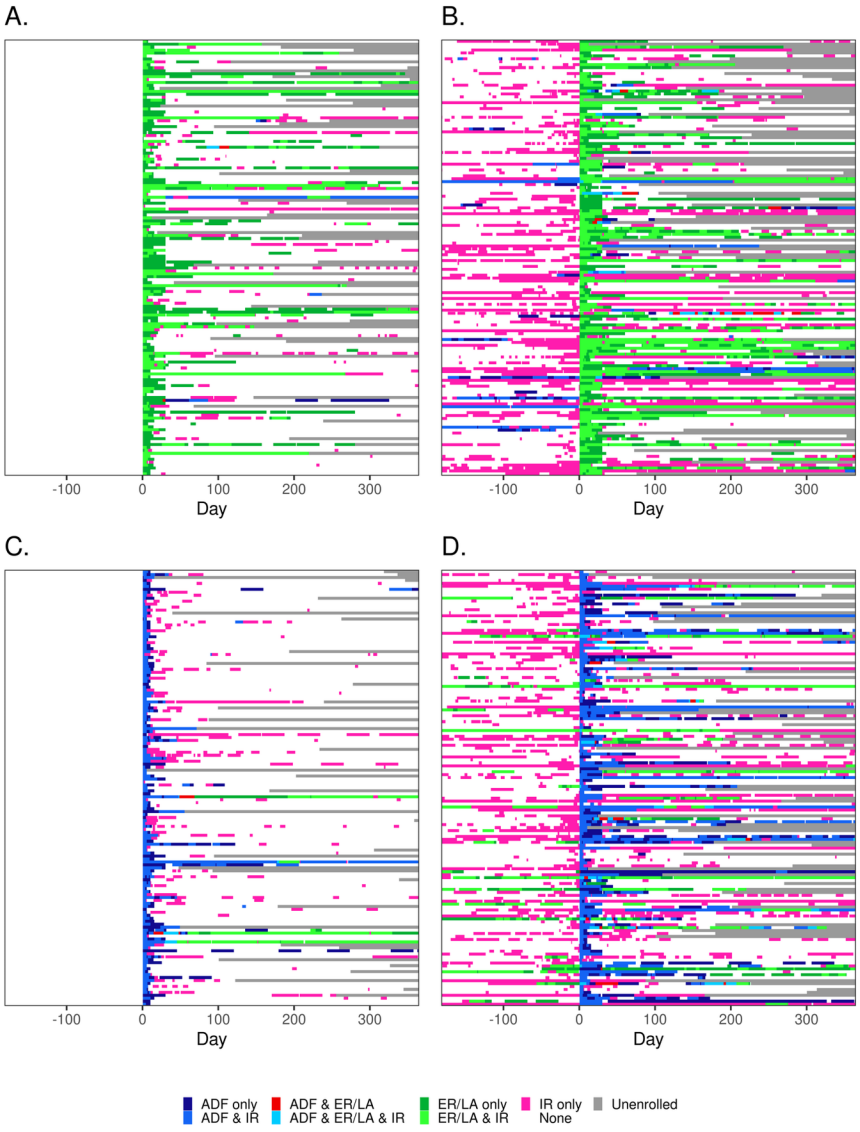

Figure 1. Patterns of pharmaceutical claims for opioids among patients in the NC claims data source , 2010-2018. For each group, 150 patients were randomly selected. A) Traditional new users initiating non-ADF ER/LA, B) Prevalent new users initiating non-ADF ER/LA, C) Traditional new users initiating ADFs, D) Prevalent new users initiating ADFs. Abbreviations: ADF: Abuse-deterrent formulation; ER/LA: Extended-release/long-acting; IR: Immediate-release.

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Figure 2. Patterns of pharmaceutical claims for opioids among patients in the MarketScan data source , 2010-2018. For each group, 150 patients were randomly selected. A) Traditional new users initiating non-ADF ER/LA, B) Prevalent new users initiating non-ADF ER/LA, C) Traditional new users

initiating ADFs, D) Prevalent new users initiating ADFs. Abbreviations: ADF: Abuse-deterrent formulation; ER/LA: Extended-release/long-acting; IR: Immediate-release.

FIGURE LEGENDS

Figure 1. Patterns of pharmaceutical claims for opioids among patients in the NC claims data source , 2010-2018. For each group, 150 patients were randomly selected. A) Traditional new users initiating non-ADF ER/LA, B) Prevalent new users initiating non-ADF ER/LA, C) Traditional new users initiating ADFs, D) Prevalent new users initiating ADFs. Abbreviations: ADF: Abuse-deterrent formulation; ER/LA: Extended-release/long-acting; IR: Immediate-release.

Figure 2. Patterns of pharmaceutical claims for opioids among patients in the MarketScan data source , 2010-2018. For each group, 150 patients were randomly selected. A) Traditional new users initiating non-ADF ER/LA, B) Prevalent new users initiating non-ADF ER/LA, C) Traditional new users initiating ADFs, D) Prevalent new users initiating ADFs. Abbreviations: ADF: Abuse-deterrent formulation; ER/LA: Extended-release/long-acting; IR: Immediate-release.