Medical Use of Long-term Extended-release Opioid Analgesics in Commercially Insured Adults in the United States

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Abstract

Objectives. We examined the proportion of patients initiating extended-release (ER) opioids who become long-term users and describe how pain-related diagnoses before initiation of opioid therapy vary between drugs and over time. **Methods.** Using MarketScan (2006–2015), a US national commercial insurance database, we examined pain-related diagnoses in the 182-day baseline period before initiation of ER opioid therapy to characterize indications for opioid initiation. We report the proportion who became long-term users, the median length of opioid therapy, and the proportion with cancer and other noncancer chronic pain, by active ingredient. **Results.** Among 1,077,566 adults initiating ER opioids, 31% became long-term users, with a median length of use of 209 days. The most common ER opioids prescribed were oxycodone (26%) and fentanyl (23%), and the most common noncancer pain diagnoses were back pain (65%) and arthritis (48%). Among all long-term users, 16% had a diagnosis of cancer. We found notable variation by drug. Eighteen percent of patients initiating drugs approved by the Food and Drug Administration >10 years ago had evidence of cancer during baseline compared with only 8% of patients who received newer drugs. **Conclusions.** In a national sample of adults with private insurance, back pain was the most common diagnosis preceding initiation of opioid therapy. Opioids that have been approved within the last 10 years were more frequently associated with musculoskeletal pains and less frequently associated with cancer. Amid increasing concerns regarding long-term opioid therapy, our findings provide context regarding the conditions for which long-term opioid therapy is prescribed.

Key Words: Cancer Pain; Chronic Pain; Extended-release Opioids; Long-term Opioid Therapy; Opioid Prescribing

Introduction

Long-term opioid therapy is an important facet of modern pain medicine that has drawn widespread criticism, despite functional improvement in many patients [1–3]. The US Centers for Disease Control and Prevention estimates that 6% of patients who received outpatient

opioids between 2006 and 2015 continued using these medicines after one year [4]. Patients receiving extended-release/long-acting (ER/LA) opioids were most likely to have long-term therapy, with >27% continuing use after one year, and 21% continuing at three years [4]. The risks associated with long-term opioid therapy have been well documented, including immunosuppression, constipation, sleep apnea, androgen deficiency, impaired cognitive function, addiction and abuse, and hyperalgesia [5–12]. The continued use of these medications requires a better understanding of the range of conditions for which long-term opioid analgesic therapy is currently used, and if there are differences across opioid molecules.

Previous studies of long-term opioid therapy have largely focused on outcomes (usually negative) associated with prescribing. The few studies that have examined the prevalence of long-term opioid use have been limited to narrow populations and specialized treatment settings. Prevalence of long-term use has varied between patient populations, with estimates ranging from 6% of opioid-naïve patients having long-term use following elective surgery to 28% of those admitted for musculoskeletal rehab [13–18]. A recent study surveying patients with chronic opioid therapy found that while over a third of patients initiated opioid therapy for treatment of acute pain, the majority had transitioned to use of ER/LA opioids prescribed for different indications than the primary prescription [19].

ER/LA opioid analgesics have properties that make them suited for long-term therapy, especially in reducing patient pill burdens and maintaining steady physiologic concentrations. The risks associated with ER/LA opioids [5,20,21] have brought them under the scrutiny of the US Food and Drug Administration (FDA) via the Risk Evaluation and Mitigation Strategies (REMS). Although equianalgesic conversion factors seem to imply that opioid compounds are somewhat interchangeable, animal models [22] and advanced clinical practice [23] have long held that qualitative differences in clinical effect exist between the nine most commonly used ER/LA opioid compounds. We were interested in examining whether various opioid compounds in the ER/LA opioid REMS had different prescribing patterns for long-term use. Describing the types of patients and indications for which long-term opioid therapy is prescribed is critical to understanding the context of opioid prescribing in the United States. In particular, the exclusion of studies with malignant pain in the Centers for Disease Control and Prevention guidelines [24] led us to question what proportion of chronic pain patients would not be covered by the guidelines. We aim to use a large commercial claims database covering >148 million patients in the United States to examine the proportion of patients initiating ER/LA opioids who become long-term users and quantify the extent to which long-term opioid therapy is used to manage cancer vs other painful conditions.

Methods

Data Source

We used IBM Watson Health MarketScan databases from 2006 to 2015. The commercial claims data are constructed from privately insured employees and their dependents, and the Medicare supplemental database contains claims for individuals with Medicare supplemental insurance as an employee or retiree benefit. These data include inpatient and outpatient claims data with information on dates of service, diagnoses, and procedures billed, as well as outpatient prescription claims data.

Eligible Population

We identified patients initiating ER/LA opioid therapy between July 1, 2006, and September 30, 2015. Eligible patients were those initiated on any analgesic formulation containing the nine opioid active ingredients covered under the ER/LA opioid REMS: buprenorphine (transdermal only), fentanyl (transdermal only), hydrocodone, hydromorphone, methadone (solid oral only), morphine, oxycodone, oxymorphone, and tapentadol. For comparison, we also included ER analgesic tramadol. We required patients to be 18 years of age or older with at least 182 days of prior continuous enrollment in MarketScan to allow for collection of baseline health information, and we excluded patients with diagnosis codes indicating opioid poisoning, abuse, or dependence during baseline. In the present article, we focus on patients newly initiating ER/LA opioid therapy and describe pain-related diagnoses before initiation of therapy. To define incident use, patients must have had at least 182 days with no evidence of any ER/LA opioid prescription, as implemented in prior published literature [25]. The index date was defined as the first ER/LA prescription fill that occurred following 182 days with no ER/LA prescription. Patients were followed up to determine whether they became long-term users. We defined long-term therapy as at least 90 days of continuous medication supply, as calculated using the prescription fill date and days' supply reported on the prescription claim [4,26,27]. We allowed up to a seven-day gap allowance between subsequent prescriptions and required at least two distinct prescriptions to contribute to the 90-day minimum. ER/LA use episodes were defined as the date of first ER/LA prescription to the end of continuous medication supply. To determine the proportion of initiators with long-term use, we required patients to have at least 120 days of continuous enrollment after initiation. We first analyzed all ER/LA opioids combined, allowing long-term users to be on any ER/LA opioid during follow-up. We then conducted sub-analyses by each active pharmaceutical ingredient (API), where long-term use was defined using only the specific API. In the overall analysis, a long-term user could have switched between multiple ER opioids to reach 90 days of continuous use, whereas the drug-specific analysis

focused on long-term continuous use of the specific drug under study.

Baseline Cancer and Pain Diagnoses

We collected information on baseline cancer and pain-related diagnoses using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), diagnosis and procedure codes, Current Procedural Terminology (CPT) codes, and Healthcare Common Procedure Coding System (HCPCS) codes billed on any inpatient or outpatient claim in the 182-day baseline period before initiation of long-term opioid therapy. Categories of pain were abdominal pain, arthritis, back pain, cancer, chronic pain, connective tissue disorder, fibromyalgia, headache/migraine, neck pain, neuralgia, sickle cell anemia, and spinal cord injury (detailed code lists are available in the Supplementary Data). Although opioids may not be explicitly indicated for all these conditions, we included a broad range of pain-related diagnoses in an attempt to provide a comprehensive description of painful conditions observed before ER/LA opioid use. We also examined the prevalence of acute pain as an indicator of potential chronic therapy stemming from acute pain. Lastly, we examined the prevalence of selected baseline comorbidities and prescription medications of interest to contextualize the population of long-term users.

Statistical Analyses

We report the proportions of initiators with claims for each pain category during the baseline period and comparisons of proportions across APIs. As an indication of differences in the prevalence of diagnoses that were not due to random variation, we conducted chi-square tests comparing each API with morphine, the first FDA-approved ER/LA opioid with 12-hour dosing, noting those that were statistically different at $P < 0.001$. We additionally examined differences in API and pain-related diagnoses by age and sex.

Our main analysis focused on pain diagnoses in the 182 days before ER/LA initiation, as diagnoses for chronic conditions may occur months before initiation of ER/LA therapy. We conducted additional analyses examining more proximal pain diagnoses occurring within seven, 30, and 90 days before initiation in order to more closely link painful conditions to ER/LA initiation.

Prior Immediate-release Opioid Use

Guidelines recommend that patients initiate opioid therapy on immediate-release (IR) formulations [24]. We collected all IR opioid prescriptions filled during the baseline period and examined the proportion of patients who had evidence of prior IR use in the three months before ER/LA initiation. We use the days'
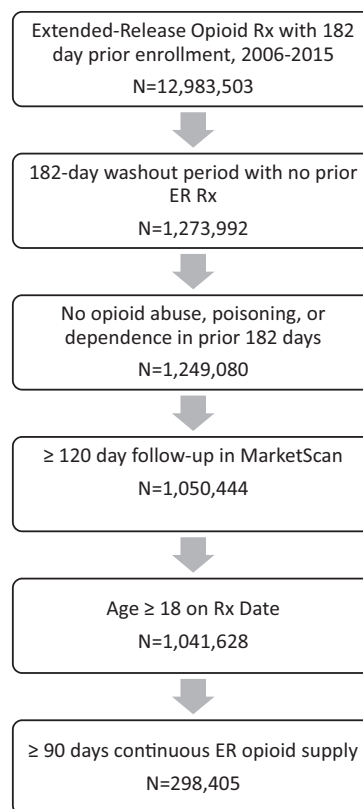
Figure 1. Flowchart for cohort inclusion.

supply, quantity dispensed, and dosage indicated on all prescriptions to describe the mean number of days and dosage in morphine milligram equivalents (MME) of IR use in the 90 days before ER/LA initiation.

Results

All Extended-release/Long-acting Opioids

We identified 1,249,080 patients initiating ER opioid therapy, of whom 1,041,628 (83%) had ≥120 days of enrollment following initiation and were 18 years of age or older. Among those meeting the eligibility criteria, 298,405 (29%) were classified as long-term users of ≥90 days (Figure 1). Compared with patients without long-term use, those with long-term users were more likely to be diagnosed with depression during baseline (17% vs 13%) and more likely to have prescription fills for anticonvulsants, anxiolytics, benzodiazepines, cyclic antidepressants, and SSRIs (Supplementary Data).

Among long-term users, the most common ER opioid prescribed at initiation was oxycodone (32% of initiators), followed by fentanyl (21%) and morphine (18%) (Table 1). Long-term users had a mean age of 54 years (Table 2). The median number of prescriptions dispensed per episode was seven, and the median length of prescribed use, which varied considerably by API, was 200 days (Table 1). Among this cohort of long-term ER

Table 1. Percentage of all extended-release opioid analgesic initiators with long-term use by active pharmaceutical ingredient

Active Ingredient	Total Initiators, No.	Long-term Users,* No.	% with Long-term Use	No. of Prescriptions[+]		Length of Continuous Supply, d[+]	
				Mean	Median	Mean	Median
Any ER/LA opioid	1,041,628	298,405	28.6	11.9	7	336.4	200
Buprenorphine	33,531	9,864	29.4	7.6	6	219.1	157
Fentanyl	216,308	65,583	30.3	10.5	7	293.8	178
Hydrocodone	1,975	621	31.4	6.2	5	183.9	157
Hydromorphone	3,783	1,367	36.1	9.5	7	276.5	194
Methadone	55,058	22,717	41.3	12.3	8	353.2	219
Morphine	190,374	55,290	29.0	11.6	7	337	203
Oxycodone	337,040	74,220	22.0	12.8	8	359.2	216
Oxymorphone	26,457	10,895	41.2	11	7	314.3	207
Tapentadol	12,554	3,146	25.1	9	6	269.8	179
Tramadol	160,359	29,741	18.5	6.8	5	252.2	177

ER/LA = extended-release/long-acting.

*Long-term use defined as ≥90 days.

[+]Among long-term users.

initiators, 16% had procedure or diagnosis codes for cancer in the 182-day baseline period, 88% of patients had non-cancer-related chronic pain, and 9% of patients had no pain-related diagnosis. The most common pain diagnoses were back pain (66%) and arthritis (49%) (Table 2). Most long-term users (62%) had more than one category of pain-related diagnosis (mean = 2.3), and 83% of the patients with cancer also had at least one diagnosis for non-cancer-related pain (data not shown).

We examined the proportion of ER/LA initiators who had evidence of prior IR opioid use in the 90 days before ER/LA initiation. We found that among long-term ER/LA users, 79% had an active IR prescription in the 90 days before ER/LA initiation. In contrast, among ER/LA initiators without long-term use, 64% had evidence of prior IR use. Among long-term ER/LA users, the median number of days in the prior 90 days covered by an opioid prescription was 76, with a median daily dosage of 68 MME (Table 3).

Drug-Specific Comparisons

The percentage of all initiators who were classified as long-term users ranged from 19% to 41%, by active ingredient. Patients initiating methadone (41%), oxymorphone (41%), and hydromorphone (36%) had the highest proportion continuing as long-term users, whereas those initiating tapentadol (25%), oxycodone (22%), and tramadol (19%) had the lowest proportion continuing therapy for at least 90 days (Table 1). Among long-term users, the median length of treatment was longest for methadone (219 days), followed by oxycodone (216 days), and was shortest for buprenorphine and hydrocodone (157 days) (Table 1). The percentage of long-term users with no pain diagnoses during baseline ranged from 4% to 15%. Patients on long-term therapy of tramadol (15%) and methadone (12%) had the highest proportion with no pain diagnoses during baseline,

whereas patients initiating hydromorphone (4%) and hydrocodone (4%) had the lowest proportion with no pain diagnoses (Table 2). Patients initiating long-term therapy of hydromorphone (5%) and tapentadol (4%) had the most acute pain diagnoses or surgery-related procedures codes during baseline, whereas methadone (3%) tramadol (2%) had the fewest. Across all opioid types, over 50% of patients on long-term opioid therapy had a diagnosis of back pain during baseline. The proportion of initiators with back pain ranged from 52% (tramadol) to 83% initiating hydrocodone. Fentanyl (24%) and oxycodone (17%) had the largest proportion of long-term patients with cancer during baseline, whereas hydrocodone (7%) and oxymorphone (7%) had the fewest long-term users with cancer diagnoses.

Table 2 displays the initial FDA approval date for each API and the percentage of all initiators with various pain diagnoses broken down by API. To highlight drug-specific variations, we compared the proportion of initiators with each type of pain to the reference group of morphine initiators and highlighted cells where the difference was statistically significantly different according to a chi-square test ($P < 0.0001$), illustrating that drugs approved more recently tended to be prescribed more often for non-cancer-related pain. Excluding methadone, whose use has changed significantly over time since initial approval in 1947, we found that overall, 9% of patients receiving APIs within 10 years of initial FDA approval had evidence of cancer, whereas 16% of patients who received an API that had been approved by the FDA >10 years ago had evidence of cancer at baseline. Among those initiating long-term therapy on the long-established APIs, the percentage with cancer ranged from 12% to 26%, whereas the percentage with cancer initiating APIs newer to the market ranged from 6% to 11% (Figure 2).

The proportion of long-term ER/LA users with IR use in the prior 90 months was highest among those initiating

Table 2. Baseline pain diagnosis in the 182 days before initiation of long-term ER/LA therapy by active pharmaceutical ingredient

	All ER/LA Opioids	Morphine	Methadone	Fentanyl	Oxycodone	Tramadol	Oxymorphone	Hydromorphone	Buprenorphine	Tapentadol	Hydrocodone
Date of initial approval		May 1987	August 1947	August 1990	December 1995	September 2005	June 2006	March 2010	June 2010	August 2011	October 2013
Total No. of patients	298,405	55,290	22,717	65,583	74,220	29,741	10,895	1,367	9,864	3,146	621
Male, %	43.2	45.9	49.7	34.9	49.1	36.9	47.0	40.3	33.3	40.4	48.5
Age, mean (SD), y	53.9 (14.2)	53 (12.4)	50 (12.8)	59.4 (15.9)	52.6 (13.1)	55.7 (14.3)	48.7 (12)	49.8 (11)	51.7 (14)	50.3 (12.1)	50.4 (10.9)
No chronic pain diagnosis, %	8.9	7.3	12.1	8.6	9.8	14.8	6.1	3.7	4.6	3.8	3.5
Acute pain, %	3.5	3.2	2.5	3.8	4.0	1.6	3.4	5.0	3.5	4.2	3.1
Any noncancer pain, %	88.4	90.4	86.8	87.3	87.0	84.0	93.6	95.9	95.0	95.6	96.1
Chronic pain categories, No.	2.3	2.4	2.1	2.4	2.2	1.8	2.6	2.9	2.7	2.8	2.9
Back pain, %	65.8	70.9	64.5	62.2	64.4	52.3	79.7	82.3	76.0	79.8	82.6
Arthritis, %	49.4	48.3	42.3	50.8	47.4	53.0	51.6	54.2	56.5	55.7	57.3
Preop/anesthesia, %	23.8	22.2	16.3	27.5	24.8	17.6	21.0	28.7	22.9	24.1	25.4
Neck pain, %	18.6	20.2	16.9	16.5	17.6	14.7	26.6	27.0	27.1	27.5	33.8
Abdominal pain, %	17.8	16.8	14.1	22.7	16.4	12.1	15.2	19.8	17.6	15.9	15.3
Chronic pain, %	18.5	21.8	22.3	17.3	17.3	6.8	24.3	33.7	25.7	28.9	38.2
Cancer/neoplasm pain, %	16.4	15.4	8.4	23.6	17.3	8.8	6.8	8.3	8.8	9.6	6.6
Fibromyalgia, %	14.1	14.3	13.6	13.1	12.3	13.9	18.1	22.5	23.8	23.6	21.6
Neuralgia, %	13.6	13.6	14.1	14.3	12.4	10.0	15.1	20.9	17.9	19.0	17.2
Headache/migraine, %	12.9	12.8	12.6	12.8	11.6	10.7	15.4	19.8	18.4	16.6	16.9
Connective tissue disorder, %	1.9	1.7	1.4	2.1	1.7	2.4	2.0	2.8	2.9	2.4	2.1
Spinal cord injury, %	0.3	0.2	0.3	0.3	0.4	0.1	0.2	0.1	0.2	0.3	0.2
Sickle cell, %	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0

Column percentages do not add up to 100% because more than one diagnosis code could have been included. Bold text represents significant differences ($P < 0.001$) according to the chi-square (df = 1) test comparing each column with morphine as the referent. Dark cells represent a diagnosis that is significantly more common in patients initiating this API compared with the referent group of morphine; light gray cells represent a diagnosis that is significantly less common in patients initiating this API compared with the referent group of morphine.

API = active pharmaceutical ingredient; ER/LA = extended-release/long-acting.

Table 3. Proportion of ER/LA initiators with IR use in the prior 90 days

	Non-long-term Users	Long-term Users
Total No. of initiators	743,223	298,405
% with IR use	63.6	78.8
No. of days, median (IQR)	38 (12–78)	76 (42–90)
Dosage, median (IQR)	21.3 (6 –72)	67.7 (22.7–132)

ER/LA = extended-release/long-acting; IR = immediate-release.

hydromorphone (90%) and tapentadol (87%), whereas tramadol (64%), methadone (64%), and fentanyl (79%) had the smallest proportion of patients with evidence of IR use during baseline. The median dose per day of IR opioids during the baseline period was highest in those initiating hydromorphone (108 MME) and lowest in those initiating tramadol (37 MME) (Table 4).

Age- and Sex-Stratified Results

Older patients were more likely to receive fentanyl; 15% of patients aged 18–24 initiated fentanyl, compared with 41% of patients aged 65 years and older. Meanwhile, younger patients were more likely to initiate methadone, with 13% of patients aged 18–24 compared with 4% of patients aged 65 or older. The youngest and oldest age categories were most likely to have no chronic pain diagnosis before ER/LA initiation (12% for 18–24 years, 11% for 65 years and older). Patients in the youngest age group were most likely to have acute pain before initiation, whereas patients in the oldest age group were most likely to have a cancer diagnosis (Table 5).

Female patients were more likely to initiate fentanyl compared with males (27% vs 19%), whereas male patients were more likely to initiate oxycodone (30% vs 24%). Females patients were more likely to have fibromyalgia, headache, connective tissue disorder, and arthritis pain, whereas males were more likely to have no pain diagnosis recorded during the baseline period (Table 5).

Length of Baseline Period

Our main analysis focused on a 182-day baseline period in which pain-related diagnoses were summarized. We examined more proximal pain diagnoses, limiting the baseline period to 90, 30, and seven days before ER/LA initiation. As expected, shortening the lookback period increased the number of patients with no pain diagnosis before ER/LA initiation (15%, 27%, and 42% in the 90-, 30-, and seven-day lookback periods, respectively). Overall, trends were similar, with patients initiating morphine, fentanyl, and oxycodone having a higher proportion of cancer diagnosis, whereas patients initiating drugs approved within the past 10 years were more likely to have diagnoses of non-cancer-related pain (Table 6; Supplementary Data).

Discussion

This is the largest study of pain-related diagnoses before long-term opioid therapy that we are aware of to date. This research informs health care providers and researchers by describing the landscape of long-term opioid therapy, highlighting common pain diagnoses patients receive before long-term opioid use and differences by opioid molecule. Given that there are risks associated with any therapy, methods to reduce the need for long-term opioid use require an understanding of the conditions that give rise to opioid prescriptions in the first place.

By comparing each opioid API with morphine, which in 1987 became the first FDA-approved ER opioid with 12-hour dosing (and therefore chosen as the reference), certain patterns emerge that characterize the use of each molecule (Table 2, shaded cells). These patterns have important implications for postmarketing evaluation of these products, such as evaluations of abuse-deterrent/tamper-resistant formulations, as patients prescribed newer opioids may not be representative of patients on older opioids, and thus they are poor proxies for comparators under the counterfactual model of epidemiology [28]. Our results suggest that the underlying patient populations exposed to each opioid API may be clinically different, and may therefore have differing risks of outcomes. Under the counterfactual model in epidemiology, these patient populations may not be direct stand-ins for each other; for example, methadone appears to be used less for long-term care among cancer patients than the other ER/LA opioids, and cancer patients may have different risks of abuse outcomes than noncancer patients [29]. Amidst the opioid epidemic, the introduction of abuse-deterrent extended-release/long-acting opioids (ER/LA) aims to reduce risk associated with these medications by introducing tamper-resistant properties. However, these findings have important implications for both the approval and postmarket evaluation of newer drugs seeking approval and entering the market. Understanding the intended use and defining the relevant patient population are vital in assessing the safety and effectiveness of these drugs.

Lower-volume ER opioids approved in the past 10 years (hydrocodone, hydromorphone, buprenorphine, and tapentadol) were more commonly prescribed to patients with non-cancer-related pain compared with the rest of the ER/LA REMS products. These four drugs are also the most expensive, have little or no generic competition, tend to have been more recently approved by the FDA, and some have drug delivery platforms that may deter tampering. Although abuse-deterrent formulations for older APIs have more recently been approved (Embeda, reformulated OxyContin, etc.), the market share of these newer formulations is a small fraction of the initial, heavily generic APIs. For these newer more expensive APIs, the diagnosis codes that were more

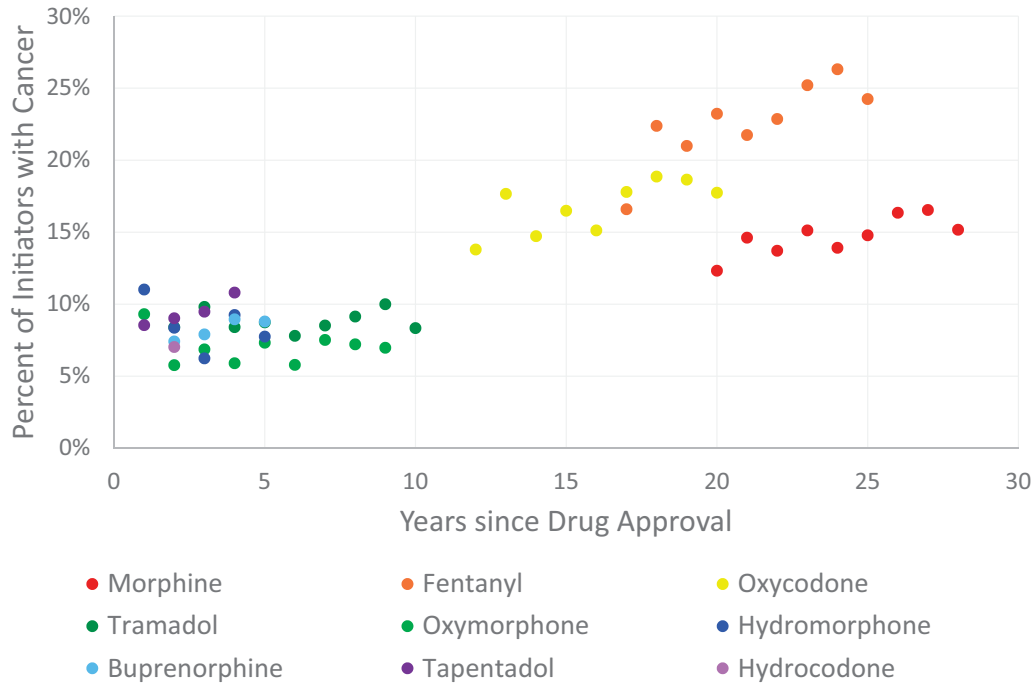## Cancer Patients by Years since Drug Approval

Figure 2. Proportion of initiators with cancer by years since drug approval upon initiation of long-term extended-release opioid therapy. *Truven MarketScan Commercial Claims and Medical Supplemental Insurance from 2006 to 2015.

Table 4. Proportion of long-term ER/LA users with prior IR use by percentage of all extended-release opioid analgesic initiators with long-term use by active pharmaceutical ingredient

Active Ingredient	Long-term Users,* No.	% with IR Use in Prior 90 Days	No. of Days Median	IQR	Dose (MME)/d Median	IQR
Any ER/LA opioid	298,405	78.8	76	(42–90)	67.7	(22.7–132)
Buprenorphine	9,864	83.1	75	(54–90)	56.7	(20–107.6)
Fentanyl	65,583	78.7	70	(50–90)	52.1	(15.2–111.8)
Hydrocodone	621	84.4	81	(30–88)	73.5	(33.8–116.1)
Hydromorphone	1,367	90.1	84	(27–86)	108.4	(55.4–188.1)
Methadone	22,717	63.8	81	(47–90)	76	(27.3–150)
Morphine	55,290	82.2	81	(64–90)	79.1	(32–144.3)
Oxycodone	74,220	82.0	78	(64–90)	76.5	(28.5–149.9)
Oxymorphone	10,895	86.9	85	(42–88)	97.1	(46.4–180.4)
Tapentadol	3,146	87.3	81	(58–90)	94.7	(42.6–180)
Tramadol	29,741	63.5	61	(58–90)	36.7	(11.1–79.1)

ER/LA = extended-release/long-acting; IR = immediate-release.

common than those for the morphine group clustered around musculoskeletal pains and were less often used in the presence of cancer. One possible explanation is that oncologists may use more well-understood and long-established drugs in efforts to minimize harmful drug interactions in patients undergoing complex medical treatments [30, 31]. In addition, transdermal formulations may have distinct clinical benefits in patients with cancer who are managing many other medications simultaneously or have no recourse to curing the underlying physical conditions that give rise to their pain. Oncologists may also use older generic formulations to reduce the out-of-pocket financial costs to cancer patients who are burdened with paying for expensive chemotherapy.

The pharmaceutical marketing industry may also explain some of this observed variation, with pharmaceutical companies seizing upon the idea of differences in clinical effects between common ER compounds to differentiate their products, often with more recent approvals targeting the noncancer pain market [32–34]. Postmarketing requirements by the FDA for evaluation of abuse-deterrent or tamper-resistant property claims have recently suggested that sponsors need to first

Table 5. Opioids initiated and pain diagnoses among patients on long-term ER/LA opioid therapy by age category and sex

	Age 18–24 y	Age 25–34 y	Age 35–44 y	Age 45–54 y	Age 55–64 y	Age 65+ y	Female	Male
Total No. of beneficiaries	3,984	20,190	47,196	86,903	84,272	55,860	169,460	128,945
Region, %								
Northeast	11.6	13.3	13.4	14.7	15.0	15.6	14.2	15.2
North Central	22.5	20.9	21.4	22.9	24.3	34.4	25.3	24.7
South	37.7	43.6	44.7	42.5	40.2	30.5	40.0	39.9
West	26.6	21.0	19.1	18.5	19.2	18.8	19.4	18.8
Unknown	1.6	1.3	1.5	1.5	1.4	0.8	1.2	1.4
Opioid initiated, %								
Buprenorphine	5.1	5.0	4.7	3.7	3.5	2.6	4.4	2.9
Fentanyl	15.4	15.2	17.8	19.4	22.3	40.5	26.8	19.3
Hydrocodone	0.3	0.2	0.3	0.3	0.3	0.1	0.2	0.3
Hydromorphone	0.6	0.8	0.8	0.7	0.5	0.2	0.6	0.5
Methadone	12.8	11.4	10.2	9.1	7.4	4.3	7.2	9.3
Morphine	17.1	20.0	21.5	22.6	22.1	15.9	19.7	22.2
Oxycodone	29.1	29.2	27.5	28.1	27.3	21.1	23.9	30.1
Oxymorphone	6.7	6.7	5.9	4.8	3.5	1.7	3.9	4.5
Tapentadol	1.9	1.6	1.6	1.3	1.2	0.5	1.2	1.1
Tramadol	10.4	9.2	8.9	9.1	11.0	12.6	11.4	8.8
Pain-related diagnoses, %								
No chronic pain diagnosis	12.0	8.1	7.9	8.4	8.5	11.3	8.0	10.1
Acute pain	7.5	4.8	3.8	3.3	3.4	3.0	3.6	3.3
Any noncancer pain	87.2	91.3	91.0	89.6	87.9	84.3	89.9	86.6
Back pain	59.2	70.5	71.0	68.5	64.1	58.4	66.0	65.5
Arthritis	39.6	41.0	42.6	47.3	52.2	57.8	53.2	44.3
Preop/anesthesia	24.7	21.1	21.6	22.8	25.5	25.2	24.4	22.9
Neck pain	17.4	21.3	23.0	22.0	17.5	10.4	20.0	16.8
Abdominal pain	23.2	21.0	18.6	16.6	16.7	18.8	20.1	14.7
Chronic pain	22.7	22.2	21.2	19.7	18.4	12.9	18.9	18.0
Cancer/neoplasm pain	7.3	5.8	7.6	12.6	20.8	27.5	15.6	17.5
Fibromyalgia	15.0	17.6	17.9	16.2	13.7	7.0	18.6	8.2
Neuralgia	18.1	17.9	16.6	14.0	12.7	9.9	15.7	10.8
Headache/migraine	21.4	20.5	18.4	14.0	10.4	6.7	16.1	8.5
Connective tissue disorder	1.7	2.3	2.3	2.1	2.0	1.2	2.9	0.6
Spinal cord injury	1.2	0.5	0.3	0.3	0.3	0.2	0.2	0.4
Sickle cell	0.9	0.4	0.2	0.1	0.0	0.0	0.1	0.1

ER/LA = extended-release/long-acting.

identify when market penetration for a new product has reached a sufficient threshold before proceeding to a formal evaluation of the abuse/tamper-deterring properties in the community. As such, baseline diagnosis codes from claims provide insight into how the use of newer products changes over time and can inform relevant comparator groups for newer products under evaluation. These patterns in prescribing also highlight the need for careful confounder analyses if pain diagnoses are differentially associated with adverse outcomes under study.

In addition to pharmaceutical companies, insurance companies and pharmacy benefit managers may play a significant role in determining the types of pain management treatments (pharmacotherapy and others) available to patients by defining coverage rules, prices, reimbursements, and formulary benefits. In the case of ER/LA opioids, insurance carriers may be less likely to cover newer abuse-deterrent/tamper-resistant formulations, thus influencing prescribing trends as described above [35].

We caution that these are administrative claims data originating from >40 health insurance providers across the country [36]. In these types of data, certain diagnosis codes may be required in order for the patient to receive authorization for particular opioids; the diagnosis codes described in this paper should not be treated as prevalence or incidence measures. Still, as claims data are routinely used for safety studies of opioid analgesics, the baseline patient diagnoses codes should be considered in assessing the potential for confounding bias in the study design.

We recognize that opioids play an important role in the health care system and that patients receiving long-term opioid therapy may have well-managed, stable pain management plans under the supervision of a prescriber. These patients may use opioids to manage chronic pain, resulting in improved quality of life and allowing patients to lead productive lives while minimizing the interference of pain and unmanaged side effects [35]. However, increasing evidence of side effects associated with long-term use, coupled with the growing crisis in the United States, warrants a closer look at the landscape of long-term opioid therapy.

Other notable limitations of our analysis exist. First, out-of-pocket transactions for medications are not

Table 6. Baseline pain diagnosis in the 90, 30, and seven days before initiation of long-term ER/LA therapy by active pharmaceutical ingredient

	All ER/LA opioids	Morphine	Methadone	Fentanyl	Oxycodone	Tramadol	Oxymorphone	Hydromorphone	Buprenorphine	Tapentadol	Hydrocodone
Date of initial approval		May 1987	August 1947	August 1990	December 1995	September 2005	June 2006	March 2010	June 2010	August 2011	October 2013
Total No. of patients	298,405	55,290	22,717	65,583	74,220	29,741	10,895	1,367	9,864	3,146	621
90-d baseline, %											
No chronic pain diagnosis	14.5	12.3	19.1	14.1	15.7	23.4	10.2	5.8	7.7	7.3	6.0
Any noncancer pain	81.9	84.3	79.5	80.3	79.8	75.2	89.4	93.9	91.8	92.1	93.7
Back pain	58.5	63.9	56.5	54.6	57.0	44.4	73.6	77.2	69.9	73.5	78.7
Arthritis	38.6	37.5	32.2	39.8	36.9	42.2	40.6	41.2	45.3	44.7	47.7
Cancer/neoplasm pain	14.2	13.4	6.6	20.9	15.3	6.3	4.9	5.1	6.4	7.1	4.3
30-d baseline, %											
No chronic pain diagnosis	26.6	24.5	35.2	26.3	28.6	37.6	21.0	13.3	15.6	15.8	12.2
Any noncancer pain	68.3	70.7	63.1	65.8	65.2	61.3	78.5	86.4	83.9	83.1	87.0
Back pain	46.8	51.7	42.8	42.6	44.6	34.6	62.0	67.4	60.6	62.3	69.9
Arthritis	25.6	24.6	20.2	25.8	24.2	29.4	27.1	27.7	32.3	30.6	36.1
Cancer/neoplasm pain	11.6	11.1	4.5	17.6	12.8	3.6	2.7	3.1	3.5	4.6	2.9
7-d baseline, %											
No chronic pain diagnosis	42.0	39.6	51.2	42.2	44.3	54.6	36.1	30.4	27.9	32.2	26.7
Any noncancer pain	52.0	54.7	47.2	48.2	48.6	44.6	63.4	69.2	71.6	67.0	72.5
Back pain	35.2	39.6	31.7	30.8	33.0	24.6	49.0	53.0	49.8	48.2	55.9
Arthritis	15.6	15.1	12.3	14.7	14.5	18.8	17.3	17.3	22.5	20.3	24.6
Cancer/neoplasm pain	9.0	8.7	2.8	14.1	10.1	1.6	1.2	1.6	1.6	2.0	1.3

Column percentages do not add up to 100% because more than one diagnosis code could have been included. Bold text represents significant differences ($P < 0.001$) according to the chi-square (df = 1) test comparing each column with morphine as the referent. Dark cells represent a diagnosis that is significantly more common in patients initiating this API compared with the referent group of morphine; light gray cells represent a diagnosis that is significantly less common in patients initiating this API compared with the referent group of morphine.

API = active pharmaceutical ingredient; ER/LA = extended-release/long-acting.

captured in the claims data. Although state prescription monitoring program (PMP) data could be useful in this regard, the use of commercial claims data allowed us to glean detailed information on diagnoses that are not available in PMPs. Second, although health insurance claims records are used for administrative and reimbursement processes, they do not posit a direct link between diagnosis and receipt of a medication. The lack of any pain diagnosis in 9% of patients is a curious finding and may be an artifact of claims data. This is consistent with a recent study conducted using claims data in Ontario, Canada, which used procedure and diagnosis codes to classify opioid initiators into indications and found that 12% of opioid initiators had an "unknown" reason for initiation [37]. Another study using insurance claims data conducted among working-age adults in the United States found that only 32% of adults initiating opioids had a diagnosis for pain-related conditions; however, the time-window for capture of diagnoses was unclear, making comparisons with the current study difficult [38]. To mitigate difficulties in linking indications for use with prescriptions, electronic health record data could be a useful adjunct in future analyses. Third, the employer-based insurance beneficiaries are a subset of all patients receiving opioid analgesics. In 2015, employer-sponsored insurance covered the largest group of Americans at an estimated 49% of the total US population, followed by Medicaid, covering 20% of the US population. The employer-sponsored population is likely younger and healthier than the overall US population. We sought to increase the generalizability of our study by including Medicare supplemental data to cover elderly patients. However, according to estimates from the 2015 American Community Survey, 15% of the US population was 65 years or older, whereas 9% of the employee-sponsored population was 65 years or older, suggesting that the older population is underrepresented in the current analysis [39]. Fourth, this analysis relies on prescription opioids being used as dispensed. There was no way to verify if an individual ingested the medication or the amount and rate of consumption. It is also unknown if patients received prescriptions that were paid for out-of-pocket, if they consumed medications from prior prescriptions, or if they received diverted medication from other sources (family members, etc.). However, our analysis was limited to the diagnoses at the time of initiation of opioid pharmacotherapy and did not focus on risk outcomes (e.g., overdose, abuse) that make assumptions about which opioids were ingested. Finally, ER hydrocodone product(s) were available only intermittently during the observation period and have lower sample sizes than the others. Future analyses using data for 2015 and later are needed to better describe the use of hydrocodone and changing trends across all APIs in response to heightened awareness surrounding the opioid crisis. Finally, the transition from immediate-release to extended-release opioid use, as would be expected in some properly clinically managed patients, was not examined in depth in this manuscript, but has been reported elsewhere [40].

We were able to examine opioid usage patterns in a large insurance database covering adults from all regions in the United States. This research fills a gap in the current literature, describing the proportion of incident ER opioid users who go on to continue treatment for at least three months in a population-level analysis, characterizing the pain-related diagnoses before initial ER/LA opioids prescriptions.

In conclusion, we found that over a quarter of all patients initiating ER/LA opioids continued therapy for ≥90 days and that the most common pain diagnoses before initiation were back pain, arthritis, and postoperative pain. We observed drug-specific differences in the percentage of initiators who went on to become long-term users, as well as differences in baseline pain diagnoses. Medical use of newly marketed ER opioid analgesics tended to focus on back and joint pain, with less use for cancer pain. Understanding the prevalence of long-term opioid use and the reasons for which patients are initiating long-term therapy would inform future research and policy-makers in efforts to reduce the need for long-term therapy and implement changes to aid the safety of opioid therapy in pain management.

Supplementary Data

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