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A Retrospective Cohort Study of Long-Term Immediate-Release Hydrocodone/Acetaminophen Use and Acetaminophen Dosing Above the Food and Drug Administration Recommended Maximum Daily Limit Among Commercially Insured Individuals in the United States (2008–2013)

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Abstract: Immediate-release (IR) hydrocodone/acetaminophen is the most prescribed opioid in the United States; however, patterns of use, including long-term treatment and dose, are not well described. Duration of use, including the percentage of patients on long-term treatment (>90 days of continuous use), was assessed for patients newly prescribed IR hydrocodone/acetaminophen compared to other opioid analgesics in a national commercial insurance database (January 2008–September 2013). Though only a small percentage of IR hydrocodone/acetaminophen patients continued treatment long-term (1.7%), the number was large (104,839) and was nearly 5 times the number receiving extended-release (ER) morphine (n = 22,338) and nearly 4 times the number receiving ER oxycodone (n = 26,946) long-term. Using a less conservative allowable gap in treatment increased the number of patients meeting the criteria for long-term use (approximately 160,000 for IR hydrocodone/acetaminophen vs <30,000 for ER morphine and ER oxycodone). Most patients meeting these criteria received IR hydrocodone doses between >20 and ≤60 mg/d (n = 56,220, 53.6%) in month 4; 5.5% (n = 5,743) received doses >60 mg/d. Moreover, approximately 15% of IR hydrocodone/acetaminophen patients (n > 900,000) were prescribed total daily acetaminophen doses exceeding 4 g (the limit recommended by the U.S. Food and Drug Administration) at their initial IR hydrocodone/acetaminophen prescription or any time during therapy.

***Perspective:** Although most patients were prescribed IR hydrocodone/acetaminophen for acute pain, the number of patients prescribed long-term therapy exceeds the number of patients prescribed ER opioids. It is important to consider the benefits and risks inherent with long-term opioid therapy, whether with IR or ER opioids, to ensure safe use of these products.*

***Key words:** Hydrocodone, acetaminophen, long-term opioid therapy, immediate-release opioids, utilization.*

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Immediate-release (IR) hydrocodone is the most highly prescribed opioid for pain in the United States, with more than 130 million prescriptions dispensed in 2011; virtually all of these prescriptions (98%) are for IR hydrocodone/acetaminophen.[5] Furthermore, the number of IR hydrocodone/acetaminophen prescriptions far exceeds that of extended-release (ER) opioids: 128 million IR hydrocodone/acetaminophen prescriptions were dispensed in 2011 versus 6.1 million ER morphine and 5.7 million ER oxycodone prescriptions.[5] Despite its importance in pain therapy, the epidemiology of IR hydrocodone/acetaminophen use is not well characterized.

IR opioids are commonly used for acute pain conditions; for example, IR hydrocodone/acetaminophen is indicated for relief of moderate to moderately severe pain, with a usual dosage of 1 or 2 tablets every 4 to 6 hours as needed.[24] In contrast, ER formulations are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative options are inadequate,[8] and require less-frequent administration (eg, every 8 to 12 hours). Though these indications differ and most patients receive IR opioids for acute treatment, a subset of patients use long-term IR opioid therapy for pain (ie, >90 days[3]). In a sample of opioid-treated patients in Group Health Cooperative (Washington) and Kaiser Permanente (Northern California) (1997–2005), IR hydrocodone combination products were the most commonly prescribed opioids not only for acute treatment episodes but also for episodic and long-term episodes.[25] Furthermore, in a U.S. Food and Drug Administration (FDA) drug use review, 10% of patients (approximately 1.6 million) continued hydrocodone combination products for >109 days.[5] Consequently, although most patients are prescribed IR opioids for short-term treatment (<14 days),[5] given the large number of patients prescribed IR opioids, the number treated long-term could approach or even exceed the number treated long-term with ER opioids.

Additionally, acetaminophen is associated with hepatotoxicity, and unintentional overdose can be the result of repeated doses higher than the prescribed dose over several days in an attempt at achieving greater pain relief or use of multiple acetaminophen-containing products.[13] The onset of liver injury can be difficult to identify, as it may be asymptomatic or symptoms may be nonspecific (eg, nausea, vomiting), and as a consequence it may not result in treatment discontinuation.[16] Unresolved hepatotoxicity can lead to multiple organ failure and death.[16] To reduce risk, the FDA has set a daily maximum limit (4 g/d) and a dosage unit limit (325 mg/unit).[7,9] With these dosing restrictions, when IR hydrocodone/acetaminophen is used as indicated, exposure will not exceed 4 g/d. However, if dosing exceeds the labeled dose, or if a product is used with other acetaminophen-containing products (which include more than 100 over-the-counter products or other prescription products), patients may be unintentionally ingesting supratherapeutic acetaminophen doses. Given the risks associated with acetaminophen use, it is critical to understand dosing patterns of acetaminophen associated with IR hydrocodone/acetaminophen combination products, including the prevalence of doses exceeding 4 g/d, which could have meaningful public health implications.[7,9]

To provide novel information about the epidemiology of this highly prescribed medication, this study describes treatment patterns among patients initiating therapy with IR hydrocodone/acetaminophen compared to IR oxycodone combination products (eg, IR oxycodone/acetaminophen), IR oxycodone single-entity (SE) products, ER oxycodone, and ER morphine. Specifically, the study aims were to evaluate the number and percentage of patients continuing therapy long-term (>90 days), dosing during long-term therapy, and pain diagnoses associated with the initial prescription.

Methods

Data Source

This retrospective cohort study used data from a national commercial insurance database (MarketScan Commercial Claims and Encounters) from January 2008 through September 2013. The data set is a U.S. nationwide research database containing eligibility, pharmacy claims, and medical claims data representing more than 113 million individuals during the study period. Medical claims or encounter data are collected from all available health care sites (inpatient, outpatient, long-term care) for virtually all types of services provided, including specialty, preventive, and office-based treatments. Pharmacy data include National Drug Code, date of service, and days' supply, and are linkable to the Red Book, which includes information such as generic drug name and dosage forms. Claims are linkable based on a unique patient identification number. Individual-level, deidentified data were used for all analyses.

Index Opioid Prescription and Study Inclusion Criteria

Patients 18 to 64 years old with a new IR hydrocodone/acetaminophen, IR oxycodone combination, IR oxycodone SE, ER oxycodone, or ER morphine prescription ("index prescription") and 18 months' insurance enrollment (6 months before and 12 months after the index prescription) were eligible for the study. All patients with improbable opioid prescription data were excluded (>180 days' supply; >1,000 pills as described by Paulozzi et al[21]). ER oxycodone and ER morphine were selected as ER comparators as they are the 2 most commonly prescribed ER opioids.

Each sample was limited to new users, that is, patients with at least 6 months without prior prescriptions for the index opioid. Each sample was identified separately, so that patients newly prescribed IR hydrocodone/acetaminophen could have IR oxycodone combination products, IR oxycodone SE, ER oxycodone, or ER morphine prescriptions either before, concurrently, or after the qualifying index IR hydrocodone/acetaminophen prescription, and vice versa.

Daily Opioid/Acetaminophen Use

Daily use was determined based on days' supply from the pharmacy claims data. Prescriptions were assumed to be used as dispensed. However, to account for early refills, all overlapping prescriptions for the same product were assumed to be used sequentially; that is, for any overlapping prescriptions, the days' supply of the first prescription was added to the days' supply of the second prescription. The exception was for 2 prescriptions filled on the same day, which were assumed to be used concurrently.

Continuous Long-Term Opioid Use

The primary outcome of interest was the number and percentage of new users in each sample who were long-term users, defined as those who received >90 days of continuous therapy (adapted from definitions by Chou et al[3] and Von Korff et al[25]). Continuous use was defined as a period of opioid therapy with no gaps in supply of ≥15 days. For the primary analysis, any episode of continuous use after the initial prescription was included in the calculation of the number and percentage of patients meeting criteria for long-term use. Though additional episodes of use were identified in the primary analysis, patients could only meet criteria for long-term use once, such that all results reflect unique patients using treatment for >90 days. Because results may be sensitive to the duration of the allowable gap, a secondary analysis explored how results differed when the allowable gap was extended to 30 days.

In the primary analysis, any episode of continuous use was included because it is common to receive short courses of IR opioid therapy for acute pain or after certain procedures (eg, dental surgery). However, as a secondary analysis, only the first episode of continuous use was included (ie, if patients exceeded the 15-day allowable gap prior to meeting criteria for long-term continuous use, they were deemed to not be long-term opioid users regardless of any additional opioid use occurring after that initial treatment discontinuation).

Additional supplemental analyses provide results for 45- and 60-day allowable gaps using both any episode and the first episode of continuous use.

Long-Term Intermittent Opioid Use

Patients not meeting criteria for long-term use were further categorized into acute users (≤90 days during the 1-year follow-up period) and intermittent long-term users (>90 days of treatment during the 1-year follow-up period). Utilization for long-term intermittent users was examined (mean and median days of treatment per year, mean and median number of prescriptions per year), particularly as it compares to long-term continuous opioid use, to further explore this patient population.

Daily Opioid Dose

Daily opioid dose (quantity of pills dispensed multiplied by the tablet strength divided by the days' supply) was calculated for each patient based on prescriptions covering that day (see assumptions for daily opioid use described above, Daily Opioid/Acetaminophen Use). If a patient had 2 overlapping opioid prescriptions covering a single day, the total opioid dose on that day was designated as the sum of the doses. All doses were converted to morphine equivalent doses (conversion factors: oxycodone, 1.5; hydrocodone, 1.0).[15] Opioid dose was calculated at the index prescription and was categorized as follows: ≤20, >20 to 40, >40 to 60, >60 to 80, >80 to 100, and >100 mg/d; mean and median opioid dose at index were also calculated.

Additionally, average opioid dose was examined for each patient meeting the criteria for long-term continuous use in month 4 of the long-term treatment episode (ie, days 91–120 after meeting criteria for long-term continuous use). Month 4 was chosen to allow for sufficient time for up-titration of a new opioid. Average dose was calculated as the total opioid dose divided by the number of days with prescribed opioids in month 4, and was categorized as follows: ≤20, >20 to 40, >40 to 60, >60 to 80, >80 to 100, >100 mg/d. (Note: for this analysis there was no additional requirement for duration of use beyond the >90 days' continuous use described above; therefore, duration of use varied.)

Daily Acetaminophen Dose

Daily acetaminophen dose for patients on IR hydrocodone/acetaminophen was calculated in a similar manner based on prescriptions covering each day of therapy; if a patient had 2 overlapping IR hydrocodone/acetaminophen prescriptions covering a single day, the total acetaminophen dose was designated as the sum of the doses. The number and percentage of patients receiving acetaminophen doses >4 g at index prescription and on any day of the study was calculated. Additionally, the distribution of days used by dose was explored using the following acetaminophen dose levels: ≤.5, >.5 to 1, >1 to 1.5, >1.5 to 2, >2 to 3, >3 to 4, >4 to 5, >5 to 6, >6 to 7, >7 to 8, >8 g/d.

In January 2011, the FDA requested that by January 2014, the dose per unit in acetaminophen products and combinations be limited to no more than 325 mg.[9] Affected products may have been reformulated at different times, and some products could have been reformulated during the study period. Therefore, a sensitivity analysis was conducted in which it was assumed that the acetaminophen dose was 300 mg/tablet for all tablets containing >325 mg acetaminophen. No changes were made to the acetaminophen dose for tablets containing ≤325 mg acetaminophen.

Additional Variables of Interest

Patient Demographics and Clinical Characteristics

Patient demographics and clinical characteristics, including pain diagnoses, were also described. Because pharmacy claims do not contain information about the condition for which drugs were prescribed, diagnoses were temporally linked to medication claims by identifying diagnoses that occurred in the 1 month prior or subsequent to the index date. Index diagnoses were stratified by duration of opioid use, for example, ≤90 days versus >90 days (see above for details on classifications of patients into long-term users).

Statistical Analyses

Descriptive analyses were performed, including the calculation of frequency and percentage for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables. All analyses were conducted using SAS, version 9.2 (SAS Institute, Cary, NC).

Results

Study Population

Between January 2008 and September 2013, there were 6,053,149 IR hydrocodone/acetaminophen users, 2,280,196 IR oxycodone combination users, 269,613 IR oxycodone SE users, 121,289 ER oxycodone users, and 65,831 ER morphine users who met the study inclusion criteria. In general, the IR opioid samples had a greater percent of patients in the youngest age categories in comparison to the ER opioid samples (Table 1). Patients initiating ER oxycodone and ER morphine were more likely to have prior opioid exposure (72.2% of ER oxycodone patients and 86.4% of ER morphine patients compared to 55.6% of IR oxycodone SE patients, 32.3% of IR oxycodone combination patients, and 13.2% of IR hydrocodone/acetaminophen patients), particularly IR opioids. All samples comprised a majority of females, ranging from 51.0% to 59.0%.

At the initial prescription, 53.0% of IR hydrocodone/acetaminophen patients were prescribed a daily dose of >20 to 40 mg/d, compared to 22.0% of IR oxycodone combination patients, 16.6% of IR oxycodone SE patients, 38.7% of ER oxycodone patients, and 39.8% of ER morphine patients (Table 1). Although only 2.5% of IR hydrocodone/acetaminophen patients received hydrocodone doses exceeding 100 mg/d at their initial prescription, this represented almost 150,000 patients, compared to 11.5% of IR oxycodone combination patients (n = 260,982), 23.0% of IR oxycodone SE patients (n = 61,921), 13.6% of ER oxycodone patients (n = 16,496), and 13.2% of ER morphine patients (n = 8,686). The mean and median opioid doses at the index prescription were as follows: IR hydrocodone/acetaminophen, 37.6 and 33.3 mg/d, respectively; IR oxycodone combination products, 72.5 and 56.3 mg/d, respectively; IR oxycodone SE, 92.1 and 75.0 mg/d, respectively; ER oxycodone, 67.5 and 60.0 mg/d, respectively; and ER morphine, 67.1 and 45.0 mg/d, respectively (results not shown).

The most common diagnosis at the initiation of treatment (ie, first prescription) among long-term (>90 days) and short-term (≤90 days) IR hydrocodone/acetaminophen users was back/neck pain, which was more common for long- versus short-term users (36.6% vs 14.1%, respectively) (Table 2). The 3 most common pain conditions among patients treated with IR hydrocodone/acetaminophen were back/neck pain, fractures, and arthropathies; back/neck pain and arthropathies were more common among long-term versus short-term IR hydrocodone/acetaminophen users, whereas a similar percentage had fractures. The comparator opioid treatment groups had a similar pattern of results in terms of the most common pain conditions.

Continuous Long-Term Use

Using a 15-day allowable gap in treatment, only a small percentage of patients continued long-term (>90 days) treatment with IR hydrocodone/

Table 1. Demographics and Clinical Characteristics

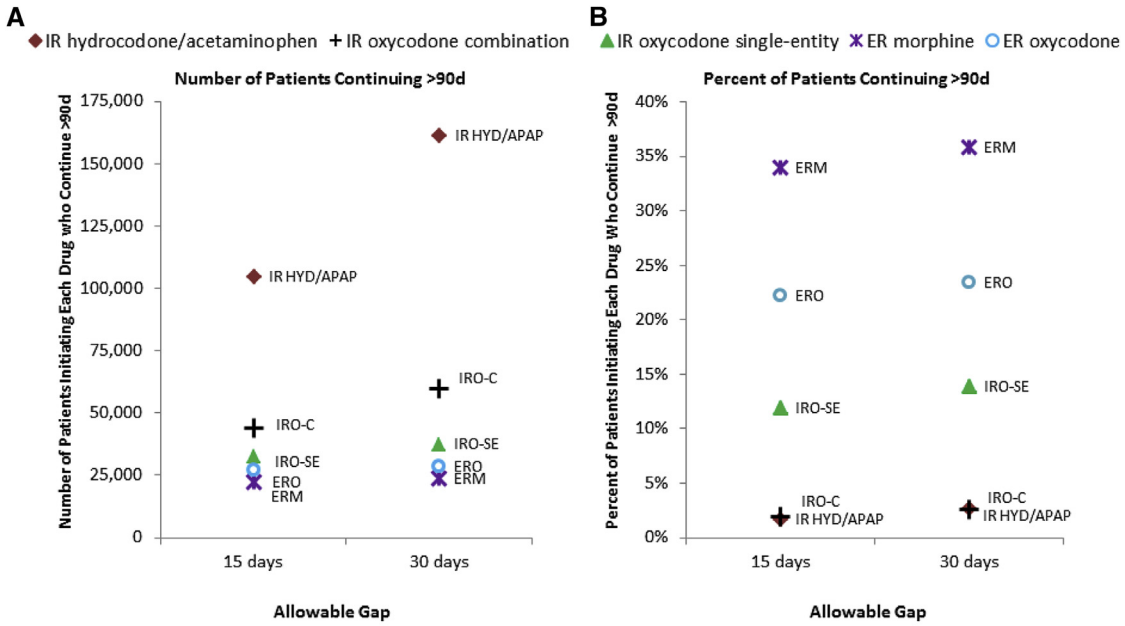
	IR Hydrocodone/ Acetaminophen (N = 6,053,149)		*IR Oxycodone Combination (N = 2,280,196)*		*IR Oxycodone Single-Entity (N = 269,613)*		*ER Oxycodone (N = 121,289)*		*ER Morphine (N = 65,831)*	
Characteristic	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Prior opioid use										
None	5,246,669	86.8	1,535,589	67.7	118,368	44.4	33,425	27.8	8,809	13.6
IR	751,601	12.4	694,693	30.6	118,542	44.4	71,578	59.6	38,809	59.9
ER/LA	14,148	.2	7,118	.3	3,600	1.4	790	.7	1,210	1.9
ER/LA + IR	30,312	.5	32,063	1.4	26,245	9.8	14,306	11.9	15,951	24.6
Age category (y)										
18–24	695,276	11.5	235,542	10.3	18,521	6.9	5,752	4.7	2,054	3.1
25–34	1,013,214	16.7	407,053	17.9	34,946	13.0	11,523	9.5	6,209	9.4
35–44	1,340,294	22.1	520,227	22.8	53,809	20.0	22,364	18.4	13,082	19.9
45–54	1,646,916	27.2	611,939	26.8	82,350	30.5	40,694	33.6	23,452	35.6
55–64	1,357,449	22.4	505,435	22.2	79,987	29.7	40,956	33.8	21,034	32.0
Gender										
Male	2,711,358	44.8	935,411	41.0	122,540	45.5	59,450	49.0	30,115	45.8
Female	3,341,791	55.2	1,344,785	59.0	147,073	54.6	61,839	51.0	35,716	54.3
Morphine equivalent opioid dose (mg/d) at first prescription										
≤20	1,120,522	18.5	61,785	2.7	9,573	3.6	3,410	2.8	4,825	7.3
>20–40	3,208,448	53.0	502,642	22.0	44,659	16.6	46,931	38.7	26,208	39.8
>40–60	1,171,360	19.4	806,580	35.4	66,207	24.6	44,223	36.5	20,630	31.3
>60–80	366,505	6.1	430,060	18.9	38,879	14.4	2,166	1.8	824	1.3
>80–100	36,594	.6	218,147	9.6	48,374	17.9	8,063	6.7	4,658	7.1
>100	149,720	2.5	260,982	11.5	61,921	23.0	16,496	13.6	8,686	13.2

Abbreviation: LA, long acting.
NOTE. Morphine equivalent conversion factors: 1.5 (oxycodone), 1.0 (hydrocodone).

Table 2. Pain Conditions at Initiation by Duration of Continuous Use (≤90 Days Versus >90 Days)

	IR Hydrocodone/Acetaminophen		*IR Oxycodone Combination*		*IR Oxycodone Single-Entity*		*ER Oxycodone*		*ER Morphine*	
Diagnoses	*≤90 d (N = 6,000,197)*	*>90 d (N = 52,952)*	*≤90 d (N = 2,254,091)*	*>90 d (N = 26,105)*	*≤90 d (N = 246,643)*	*>90 d (N = 22,970)*	*≤90 d (N = 98,914)*	*>90 d (N = 22,375)*	*≤90 d (N = 47,214)*	*>90 d (N = 18,617)*
Back/neck pain	14.1	36.6	19.5	62.8	29.5	63.3	35.0	61.5	55.7	66.6
Fracture	11.8	11.8	18.0	14.9	22.2	10.6	29.4	11.0	16.5	9.0
Arthropathies*	11.2	18.9	18.8	24.6	29.3	21.5	45.2	22.8	27.6	21.9
Rheumatism†	10.1	14.4	16.9	20.6	24.0	18.4	34.6	20.2	24.5	18.9
Abdominal pain	7.3	5.0	13.9	7.7	15.2	9.2	8.5	9.6	13.1	9.6
Other injuries	6.8	5.5	9.3	7.9	12.0	6.5	12.0	7.2	10.3	5.6
Osteoarthritis	3.4	9.1	7.2	11.7	14.7	10.1	29.7	10.7	14.0	10.0
Neuropathic pain	3.2	6.8	4.7	11.3	7.2	11.4	8.5	12.5	12.0	13.2
Osteopathies‡	3.2	4.1	5.7	5.6	9.0	5.1	13.4	7.7	8.9	6.4
Headache	3.1	4.4	4.7	6.8	6.4	6.7	5.6	7.3	8.1	7.4
Cancer	2.6	2.4	4.8	3.7	10.7	4.8	7.2	10.6	10.1	8.5
Kidney stones	2.1	.7	5.2	1.0	3.1	1.0	1.2	1.1	1.6	1.1
Dental pain	2.0	.6	2.5	.9	1.5	1.0	1.1	1.2	1.4	1.1
Pain—female genital organs	2.0	.9	4.9	1.5	3.0	1.4	1.4	1.5	1.8	1.3
Other pain	1.8	4.6	6.5	12.4	14.5	15.5	23.9	17.4	19.2	19.6
Hernia	1.7	.8	3.5	1.1	3.1	1.1	1.6	1.2	1.5	1.1
Acute pain	1.4	1.8	5.4	3.8	10.8	2.7	18.7	3.6	7.3	2.2
Fibromyalgia	1.1	4.0	1.7	8.1	3.2	8.7	4.0	9.2	7.6	10.7
Rheumatoid arthritis	.4	1.8	.8	2.2	1.5	2.3	2.1	2.5	2.4	2.8
Chronic pain	.3	1.6	.8	5.2	2.5	7.1	3.7	7.7	7.4	10.1

NOTE. Values are percentages.
*Arthropathies excludes rheumatoid arthritis and osteoarthritis (disorders of joint, dislocation, etc).
†Rheumatism, excluding the back (also excluding fibromyalgia and neuralgia).
‡Osteopathies, chondropathies, and acquired musculoskeletal deformities.



IR HYD/APAP: immediate-release hydrocodone/acetaminophen; IRO-C: immediate-release oxycodone combination; IRO-SE: immediate-release oxycodone single-entity; ERM: extended-release morphine; ERO: extended-release oxycodone

Figure 1. Number **(A)** and percentage **(B)** of patients initiating each drug receiving long-term (>90 days) treatment using a 15- and 30-day allowable gap.

acetaminophen (1.7%), IR oxycodone combination (1.9%), or IR oxycodone SE (11.9%), compared with a much larger percentage of ER oxycodone (22.2%) and ER morphine (33.9%) (Fig 1B). However, as the total number of patients newly starting IR hydrocodone/acetaminophen was approximately 6 million, the absolute number of patients continuing IR hydrocodone/acetaminophen treatment long-term was large (n = 104,839), almost 5 times the number of ER morphine patients (n = 22,338), more than 3 times the number of IR oxycodone SE (n = 32,184) or ER oxycodone patients (26,946), and approximately twice the number of IR oxycodone combination patients (n = 43,816) (Fig 1A).

To explore the sensitivity of these results to changes in the definition of long-term use, secondary analyses examined a longer allowable gap in therapy. For IR hydrocodone/acetaminophen, the percentage of patients considered long-term users nearly doubled when the allowable treatment gap was increased from 15 to 30 days (1.7–2.7%). Although the increase was comparable for IR oxycodone combination products (1.9% for 15 days, 2.6% for 30 days), it was smaller for IR oxycodone SE (11.9% for 15 days, 13.9% for 30 days), ER oxycodone (22.2% for 15 days, 23.4% for 30 days), and ER morphine (33.9% for 15 days, 35.8% for 30 days) (Fig 1B). As the number of patients initiating IR hydrocodone/acetaminophen therapy was large, the absolute number of patients treated long-term was >160,000 patients using the 30-day allowable gap, as compared to <30,000 for ER oxycodone or ER morphine (Fig 1A). These differences were even greater when using a 45- or 60-day allowable gap (Supplementary Table 1).

A similar pattern was observed when only the first episode of continuous use was considered (vs any episode); though the number of patients on therapy long-term (and the associated percentage) was lower than for any episode of continuous use (Supplementary Table 1). The absolute number of patients treated long-term using the 15-day allowable gap and the first episode of continuous use was almost 53,000 for IR hydrocodone/acetaminophen versus ≤23,000 for ER oxycodone or ER morphine. Comparing results for the first versus any episode, the number of patients using therapy long-term was higher for all samples when any episode of continuous use was captured, although the difference between the numbers for first versus any episode was greatest for IR hydrocodone/acetaminophen and lowest for ER oxycodone and ER morphine (Supplementary Table 1).

Intermittent Long-Term Therapy

Almost 50,000 patients (n = 49,063) had at least 91 days of IR hydrocodone/acetaminophen treatment during the 1-year follow-up period that did not meet criteria for long-term use (>90 days of therapy with no gaps exceeding 15 days) (Table 3). Among these patients, the mean (standard deviation) days of use during the 1-year follow-up period was 126 (31) (compared to 220 [90] for patients meeting criteria for long-term continuous use and 9 [11] for patients defined as acute users). The results were generally similar for the comparator opioids. Long-term users were dispensed more prescriptions per year than acute users, and patients meeting criteria for long-term continuous use were dispensed more prescriptions per year than those on long-term intermittent treatment.

Table 3. Days of Opioid Use and Number of Opioid Prescriptions per Year Stratified by Acute, Long-Term Intermittent, and Long-Term Continuous Use

		Days' Supply/Year		Prescriptions/Year	
Opioid Prescription	N	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
IR hydrocodone/acetaminophen (n = 6,053,149)					
Acute	5,899,247	9 (11)	5 (3, 10)	3 (4)	1 (1, 3)
Long-term intermittent	49,063	126 (31)	120 (102, 143)	16 (12)	12 (8, 20)
Long-term continuous	104,839	220 (90)	213 (145, 300)	23 (17)	19 (12, 30)
IR oxycodone combination (n = 2,280,196)					
Acute	2,221,323	8 (11)	5 (3, 8)	2 (2)	1 (1, 2)
Long-term intermittent	15,057	128 (32)	120 (103, 146)	14 (10)	10 (7, 17)
Long-term continuous	43,816	232 (92)	231 (150, 317)	20 (14)	16 (10, 25)
IR oxycodone SE (n = 269,613)					
Acute	231,663	13 (16)	7 (4, 15)	2 (3)	1 (1, 2)
Long-term intermittent	5,766	133 (34)	122 (105, 150)	13 (10)	10 (6, 16)
Long-term continuous	32,184	266 (89)	288 (193, 351)	21 (14)	17 (11, 27)
ER oxycodone (n = 121,289)					
Acute	91,858	23 (20)	15 (10, 30)	2 (2)	1 (1, 2)
Long-term intermittent	2,485	136 (35)	120 (110, 150)	9 (8)	6 (4, 10)
Long-term continuous	26,946	275 (93)	311 (195, 362)	18 (14)	15 (8, 24)
ER morphine (n = 65,831)					
Acute	41,368	32 (21)	30 (15, 35)	2 (3)	1 (1, 2)
Long-term intermittent	2,125	141 (37)	127 (118, 164)	9 (7)	6 (4, 10)
Long-term continuous	22,338	273 (91)	304 (195, 360)	18 (13)	15 (8, 24)

Abbreviations: SD, standard deviation; IQR, interquartile range.

Opioid Dose During Long-Term Therapy

Dose in month 4 of the long-term treatment episode was also examined for the subset of patients who continued therapy long-term (ie, >90 days); month 4 was chosen to allow a period of up-titration, which is common among patients newly starting an opioid, usually within the first 3 months of therapy. The number and percentage of patients in each dose category was calculated for each sample (Fig 2). Among the subset prescribed long-term IR hydrocodone/acetaminophen therapy, 41.3% (n = 43,317) had doses between >20 and 40 mg/d, 12.3% (n = 12,903) between >40 and 60 mg/d, and 5.5% (n = 5,743) >60 mg/d in month 4. At month 4, the number of long-term IR hydrocodone/acetaminophen patients on doses between >20 and 40 mg/d exceeded the number on any other opioid comparator, and the number on >40 to 60 mg/d exceeded those for all comparators except IR oxycodone combination. Only a small percentage of IR hydrocodone/acetaminophen patients were prescribed doses >60 mg/d (n = 5,743, 5.5%), whereas between 40 and 70% of patients on IR oxycodone SE, ER oxycodone, or ER morphine were prescribed doses >60 mg/d.

Acetaminophen Dose During Therapy

At the index prescription, almost one-sixth of the IR hydrocodone/acetaminophen patients (15.1%, n = 910,888) were prescribed >4 g of acetaminophen per day; a similar number (16.3%; n = 986,149) received >4 g of acetaminophen on at least 1 day of treatment during the study. Overall, the 4-g limit was exceeded on 7.2% of continuous usage days (Fig 3). Moreover, 16.3% of all days were at doses between >3 and 4 g/d. In January 2011, the FDA requested that by January 2014, the dose per unit of acetaminophen in acetaminophen products and combinations be limited to no more than 325 mg. In the sensitivity analysis where all unit doses ≥325 mg/tablet were assumed to be 300 mg/tablet, the percentage dropped to below 5% (4.2% at index and 4.7% on at least 1 day of treatment; 1.6% of days at doses >4 g/d). However, the absolute number of patients and usage days on >4 g/d acetaminophen were still substantial (>280,000 patients; 759,152 days).

Discussion

The current study examined IR hydrocodone/acetaminophen use among adults in a large U.S. commercial insurance database. Although only 1.7% of individuals initiating IR hydrocodone/acetaminophen therapy continued long-term (ie, >90 days), the number of patients was approximately 4 and 5 times the number of ER oxycodone and ER morphine patients, respectively. Using a less restrictive allowable treatment gap (30 days), the number was 6 to 7 times the number of patients prescribed the ER opioid comparators. Although IR hydrocodone/acetaminophen was generally prescribed at lower doses than the ER opioids for long-term treatment (ie, month 4 of the long-term episode), with very few patients receiving doses exceeding 60 mg/d, there was overlap in the dosing distribution, suggesting that some patients receive IR hydrocodone/acetaminophen long-term at doses comparable to the ER opioids. The observed dosing patterns may reflect differences in product labeling; IR hydrocodone/acetaminophen has a

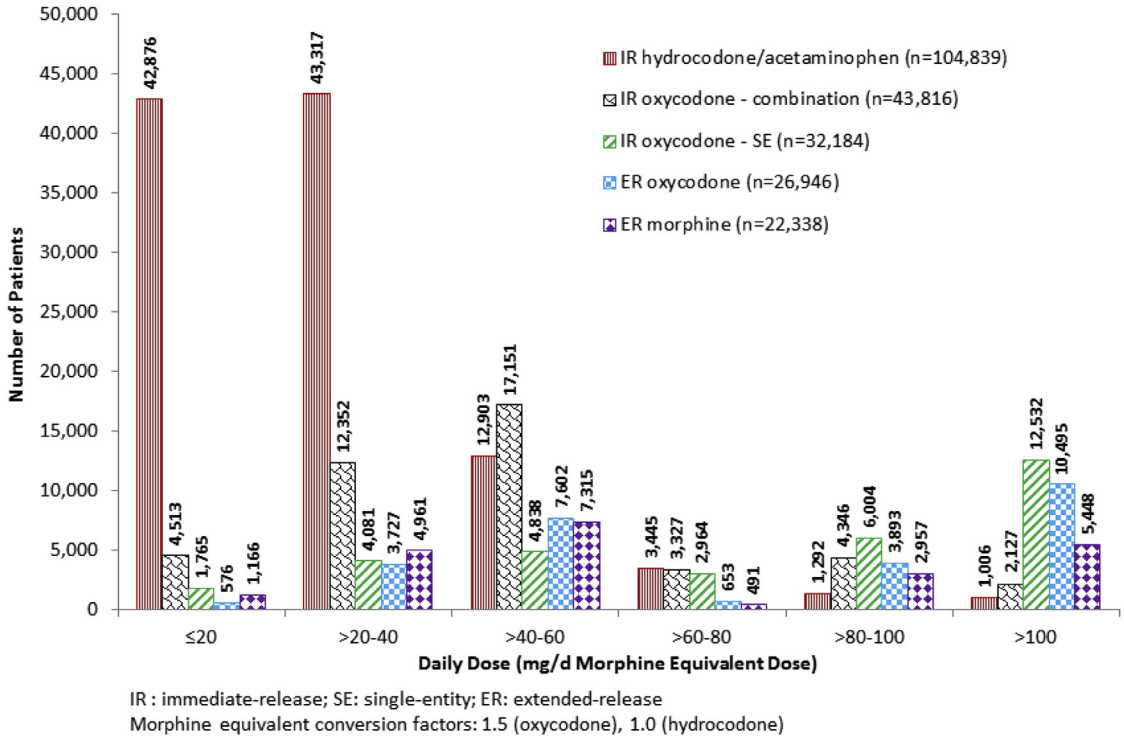


Figure 2. Number of patients in each opioid dose category at month 4 of long-term treatment (among patients treated >90 days only).

maximum daily dose of 60 mg/d, whereas ER opioids and IR oxycodone SE have no such maximum.[18,19,22,24] Most importantly, these results underscore the importance of understanding not only the percentage of patients continuing long-term therapy but also the absolute number. To ensure the safe use of IR and ER opioids, it is important for physicians treating pain long-term to consider their benefits and risks.

Because IR hydrocodone/acetaminophen is a widely used opioid analgesic and acetaminophen is associated with increased risk of liver injury,[7,9] patterns of acetaminophen exposure are an important clinical consideration. In this study, more than 15% of patients (n > 900,000) were prescribed doses >4 g/d at the index prescription or during follow-up, and almost 25% of all person-days of treatment were at prescribed doses >3 g/d. These results are similar to a retrospective claims study conducted in the United States, where 18.9% of patients (n = 255,123) filled a prescription for opioids/acetaminophen combinations exceeding 4 g/d

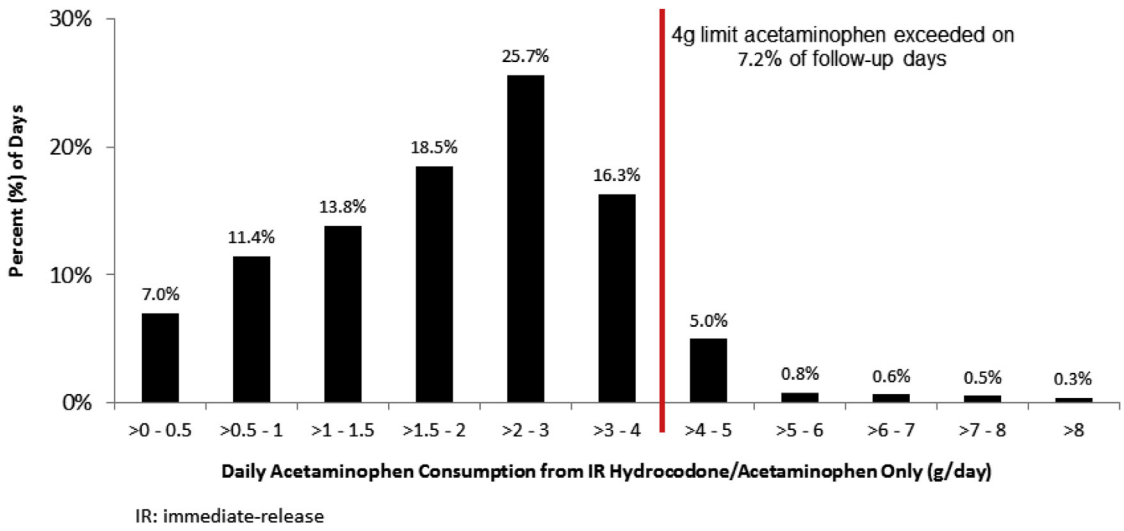


Figure 3. Distribution of total acetaminophen dose during IR hydrocodone/acetaminophen treatment (total person-time of exposure = 48,615,038 days).

acetaminophen.[17] However, this is higher than in a Canadian retrospective claims study where 6.4% of patients filled prescriptions for opioid/acetaminophen combinations exceeding 4 g/d acetaminophen.[4] These results are also higher than the past 7-day acetaminophen use described previously, likely because of differences in study population (pain patients vs general population) and study methodology (administrative claims vs survey data).[10] In the sensitivity analysis accounting for reduction in per unit acetaminophen dose, the percentage of patients on >4-g/d acetaminophen dropped considerably, though the number of patients was still large (n > 280,000). It is noteworthy that although this analysis provides insight into acetaminophen exposure, it is unknown whether the unit dose change will affect use patterns. It is also notable that dosing included only IR hydrocodone/acetaminophen use; patients could also use other prescription or over-the-counter products, further increasing daily acetaminophen dose. As over-the-counter medications are not captured within this claims database, their inclusion was not feasible. However, over-the-counter acetaminophen use is common,[11,12,20] and as a result, prescription acetaminophen analyses likely represent an underestimation of its actual use. Despite these limitations, the present study suggests that many prescribers may not be aware of the risks associated with acetaminophen use at daily doses exceeding 4 g despite efforts by the FDA to publicize this issue, and additional efforts may be necessary to ensure that prescribers are educated on the risk associated with acetaminophen use that exceeds the recommended maximum daily dose.

In addition to the risk associated with acetaminophen-related liver injury, opioids are subject to intentional abuse, medication errors by patients, prescribing errors or prescribing more than is appropriate, and accidental exposures of nonpatients. Although many IR opioids are formulated as combination products with nonopioid analgesics and ER opioids are available in equal or higher unit dosage strengths, IR opioids remain attractive to abusers. Oral abuse is the most common route of abuse for IR combination products; however, reports of snorting IR hydrocodone combination products range from approximately 20% of individuals entering substance abuse treatment[1] to almost 75% in a cohort of individuals identified for abusing OxyContin (ER oxycodone) in rural Kentucky.[26] Although only a small proportion of individuals entering substance abuse treatment centers report snorting IR hydrocodone/acetaminophen, the number of patients exceeds that of other opioids (data on file). Although the rescheduling of IR hydrocodone products from Schedule III to Schedule II may affect its availability for abuse and diversion, understanding both the use of IR hydrocodone/acetaminophen and the potential for abuse is important for prescribers.

In the current analysis, the number of patients on long-term treatment increased with a longer allowable treatment gap, and these increases were of a greater magnitude for the IR opioid combination products. This may reflect the identification of additional patient types, such as those receiving extended periods of intermittent (as-needed) treatment, or alternatively could reflect patients who used less than the prescribed dose, or who were not adherent to timely prescription refills. Although the 15-day allowable treatment gap was selected to increase confidence that continuous long-term use was identified, the gap is shorter than applied in other utilization analyses[6,23]; therefore, the results from the primary analysis may be conservative. However, as-needed (or p.r.n.) prescriptions cannot be ascertained from claims data, and because all prescriptions were assumed to be used as written, use could be overestimated if a longer gap was used and prescriptions were intended for long-term intermittent or as-needed use.

Although long-term continuous treatment resembles use of ER opioids (ie, around-the-clock therapy for an extended period of time), long-term intermittent treatment reflects a distinct use pattern. Intermittent therapy has been described previously, based on duration of gaps between prescriptions (regardless of duration of therapy[2]), or days' supply and number of prescriptions (>90–<120 days' supply, <10 prescriptions).[25] In this study, long-term intermittent use was defined as >90 days of opioid therapy during the 1-year follow-up not meeting criteria for long-term continuous use. Among patients identified as potential long-term intermittent IR hydrocodone/acetaminophen users, the mean number of prescriptions/year was 16, and the mean days of use/year was 126, suggesting relatively high usage among this subgroup, though less than that of long-term continuous users. This could reflect daily use at lower doses for longer periods than the days' supply indicated on the prescription or periods of use/no use. Because use was based on claims data and not medication taken, it is not possible to further differentiate the possible usage patterns. However, these results are informative because some studies of long-term opioid use select patients based on 90 days of use in a set time period, often 6 months[14] or 1 year,[6] and the current study suggests that such a subject selection criteria could result in a heterogeneous patient population, particularly for drugs that can be prescribed as needed, making these results informative despite the aforementioned limitations.

Administrative claims databases provide a rich resource, with large sample sizes and detailed prescription refill patterns; however, the results should be considered in light of potential limitations. First, prescription medication use is not accounted for during hospitalizations, which could lead to misclassification of patients as "new" users if individuals were hospitalized prior to the index prescription or to underestimation of use if individuals were hospitalized during follow-up. Second, each opioid was considered separately, and overall duration of continuous opioids or monotherapy versus multiple pain medications was not evaluated. Third, although this sample reflects a large population of insured patients across the United States, 18 months of continuous insurance coverage was required for inclusion in the analyses; as a result, the sample may not be generalizable to all patients newly dispensed opioids. Though the assumptions made about use could

influence the results, the sensitivity analyses demonstrate that varying the allowable gap or limiting the analysis to the first episode of continuous use does not impact the conclusions of the study, that is, more IR hydrocodone/acetaminophen was used to treat pain beyond 90 days' duration than the ER opioid comparators. Fourth, this data set only included adults 18 to 64 years of age, and it is possible that use patterns in patients older than 65 years would differ. Finally, this study was not designed to address the relative benefits and risks of IR versus ER opioids, or the appropriate selection of an IR versus ER opioid among patients for whom opioid therapy is indicated.

In conclusion, this study provides novel information on the use of the most highly prescribed opioid medication, IR hydrocodone/acetaminophen. Although most patients were prescribed IR hydrocodone/acetaminophen for acute pain, the population encompassed different treatment types (acute, long-term intermittent, long-term continuous use). Although the percentage of patients prescribed continuous long-term treatment with IR hydrocodone/acetaminophen was small, the number of patients was large, up to 7 times that of ER oxycodone or ER morphine. Overall, it is important that physicians and patients consider the benefits and risks inherent with long-term opioid therapy, whether with IR or ER opioids, to ensure safe use of these products.

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Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpain.2015.03.004.

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Supplementary Table 1. Number of Patients Receiving Long-Term Treatment (>90 Days Continuous Use): Results of Varying the Allowable Gap and First Episode of Continuous Use Versus Any Episode of Continuous Use

	Number (%) of Patients Continuing Long-Term (>90 d) With Varying Allowable Gaps			
Episode of Continuous Use	*15 d*	*30 d*	*45 d*	*60 d*
First episode of continuous use only*				
IR hydrocodone/acetaminophen (n = 6,053,149)	52,952 (.9)	98,855 (1.6)	146,269 (2.4)	197,617 (3.3)
IR oxycodone combination (n = 2,280,196)	26,105 (1.1)	41,692 (1.8)	55,093 (2.4)	68,055 (3.0)
IR oxycodone SE (n = 269,613)	22,970 (8.5)	30,188 (11.2)	34,601 (12.8)	37,967 (14.1)
ER oxycodone (n = 121,289)	22,375 (18.4)	25,255 (20.8)	27,048 (22.3)	28,254 (23.3)
ER morphine (n = 65,831)	18,617 (28.3)	21,119 (32.1)	22,617 (34.4)	23,566 (35.8)
Any episode of continuous use at any time after index prescription*				
IR hydrocodone/acetaminophen (n = 6,053,149)	104,839 (1.7)	161,173 (2.7)	215,232 (3.6)	270,405 (4.5)
IR oxycodone combination (n = 2,280,196)	43,816 (1.9)	59,668 (2.6)	73,167 (3.2)	86,153 (3.8)
IR oxycodone SE (n = 269,613)	32,184 (11.9)	37,398 (13.9)	40,729 (15.1)	43,235 (16.0)
ER oxycodone (n = 121,289)	26,946 (22.2)	28,423 (23.4)	29,552 (24.4)	30,294 (25.0)
ER morphine (n = 65,831)	22,338 (33.9)	23,595 (35.8)	24,537 (37.3)	25,113 (38.2)

*By design, any episode of continuous use was included in the primary analysis. As a secondary analysis, only the first episode of continuous use was included (ie, if patients exceeded the allowable gap prior to meeting criteria for long-term continuous use, they were deemed to not be long-term opioid users regardless of any additional opioid use occurring after that initial treatment discontinuation). Patients were only counted as long-term users once regardless of analysis.