

# Prescription Opioid Registry Protocol in an Integrated Health System

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The use of prescription opioids has increased dramatically in the past 2 decades, with associated increases in opioid misuse/abuse and opioid overdose. These are among the most commonly prescribed medications,<sup>1</sup> with 259 million prescriptions written for opioid pain relievers in the United States in 2012.<sup>2</sup> However, effectiveness of these medications for long-term use has not been established,<sup>3</sup> and the risk of opioid-related abuse and overdose has led to a prescription opioid epidemic.<sup>4</sup> Close to 2 million Americans abused or were dependent on opioids in 2014.<sup>5</sup> From 2003 to 2013, the proportion of drug-abuse treatment admissions for non-heroin opiates tripled.<sup>6</sup> There were more than 18,000 fatal overdoses in 2014 related to prescription opioids, more than 4 times the number in 1999.<sup>7</sup> Sedative/hypnotics are frequently involved in overdose deaths, and their concurrent use with opioids is of high concern.<sup>8</sup>

The goal of the overall project was to use electronic health record (EHR) data from Kaiser Permanente Northern California (KPNC) to develop a patient prescription opioid registry with the potential to ultimately address several research inquiries: the characterization of opioid use and opioid users, identification of prescription opioid misuse, predictors of opioid overdose, and to describe patients' services utilization and costs. It drew on our, and others', previous research.<sup>9-11</sup> Our objective here was to describe our protocol to develop the registry and to address 3 initial research questions: 1) characterize all individuals who used prescription opioids in 2011; 2) analyze their opioid use and concurrent use of sedative/hypnotics; and 3) identify predictors of becoming a new long-term user of opioids. We provide detail and context for our methodological approach, which can be a foundation for future analyses and, we hope, a methodological resource for other research teams addressing these questions.

## METHODS

### Setting

KPNC is a nonprofit integrated healthcare delivery system providing comprehensive health services to approximately 3.8

## ABSTRACT

**OBJECTIVES:** To establish a prescription opioid registry protocol in a large health system and to describe algorithms to characterize individuals using prescription opioids, opioid use episodes, and concurrent use of sedative/hypnotics.

**STUDY DESIGN:** Protocol development and retrospective cohort study.

**METHODS:** Using Kaiser Permanente Northern California (KPNC) electronic health record data, we selected patients using prescription opioids in 2011. Opioid and sedative/hypnotic fills, and physical and psychiatric comorbidity diagnoses, were extracted for years 2008 to 2014. Algorithms were developed to identify each patient's daily opioid and sedative/hypnotic use, and morphine daily-dose equivalent. Opioid episodes were classified as long-term, episodic, or acute. Logistic regression was used to predict characteristics associated with becoming a long-term opioid user.

**RESULTS:** In 2011, 18% of KPNC adult members filled at least 1 opioid prescription. Among those patients, 25% used opioids long term and their average duration of use was more than 4 years. Sedative/hypnotics were used by 76% of long-term users. Being older, white, living in a more deprived neighborhood, having a chronic pain diagnosis, and use of sedative/hypnotics were predictors of initiating long-term opioid use.

**CONCLUSIONS:** This study established a population-based opioid registry that is flexible and can be used to address important questions of prescription opioid use. It will be used in future studies to answer a broad range of other critical public health issues relating to prescription opioid use.

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million members in Northern California. The membership reflects the region's general population, although it underrepresents individuals with very low levels of education and income.<sup>12</sup> Membership includes enrollees from Medicare, Medicaid, and the State Health Insurance Assistance Program.

Data Sources Membership, outpatient pharmacy, and medical encounter data are archived in KPNC's EHR. Demographic (eg age, race/ethnicity, sex, address), membership status, health services, diagnostic, and pharmacy data are regularly extracted from the EHR and stored in a Virtual Data Warehouse (VDW).<sup>13</sup> The VDW is a distributed data model that includes EHR data and other data, such as mortality and Census data. Although the current study only uses KPNC data, the VDW is a feature of the Health Care Systems Research Network, whose data are harmonized across 19 health systems.

KPNC pharmacy data in the VDW include generic name, strength, directions for use, date dispensed, quantity dispensed, days' supply, prescriber identification number, and National Drug Code. Surveys have found that more than 90% of members obtain all or almost all of their prescription medications through KPNC pharmacies.<sup>14</sup> KPNC does not have policies that impose mandatory opioid dosage limits or prior authorization.

Clinical diagnostic and health services utilization data include hospitalizations, and emergency department (ED) and outpatient clinic visits (primary and specialty care). Mortality data, including date of death and underlying cause of death, are created from the EHR and death certificates. The VDW tumor registry contains information on all new cancers for KPNC members diagnosed after January 1, 1997.

### Registry Inclusion

We extracted all opioid fills made at KPNC outpatient pharmacies during 2011 (eAppendix Table 1 [eAppendices available at [www.ajmc.com](http://www.ajmc.com)]). As prior researchers have,<sup>8,9,15,16</sup> we focused on formulations with higher likelihood of abuse, and those used primarily to treat pain. Thus, we excluded opioid formulations used primarily as antitussives, anesthetics, antihistamines, antidiarrheals, or opioid agonists/antagonists. Eligible registry participants were aged 19 years or older (on January 1, 2011) with at least 1 opioid fill during 2011, and without a cancer diagnosis between January 1, 1997, and December 31, 2014.

To compare the demographics of individuals with and without opioid use, we selected a comparison cohort of all individuals who were: KPNC members during 2011; aged 19 years or older on January 1, 2011; without a cancer diagnosis between 1997 and 2014; and without an opioid fill in 2011.

For each individual, we extracted gender, race/ethnicity, date of birth, and home address as of January 1, 2011. Using members'

## TAKEAWAY POINTS

We describe a protocol for developing a prescription opioid registry using electronic health record data and algorithms to characterize individuals using prescription opioids, opioid use episodes, and concurrent use of sedative/hypnotics.

- ▶ In 2011, 18% of adult members of a large integrated health plan filled at least 1 opioid prescription.
- ▶ Among these patients, 25% used opioids long term, and the average duration of use was more than 4 years. Sedative/hypnotics were used by 76% of long-term users.
- ▶ Being older and white; living in a more deprived neighborhood; having chronic pain, arthritis, chronic obstructive pulmonary disease, hypertension, or a psychiatric disorder diagnosis; and a history of sedative/hypnotic use were predictors of becoming a long-term opioid user.

home addresses in combination with the 2006 to 2010 American Community Survey collected by the US Census Bureau,<sup>17,18</sup> a neighborhood deprivation index (NDI) was generated at the Census tract level.<sup>19</sup> Chi-square tests and *t* tests were used to identify differences (at  $P < .05$ ) between the groups.

### Registry Structure

For the individuals who used prescription opioids, we extracted all outpatient opioid fills between January 1, 2008, and December 31, 2014. This allowed at least 3 years of opioid use before and after 2011, and facilitated analyses related to history and subsequent course of opioid use. We constructed a dataset of daily use: 1 record per person per day for each day of those 7 years; for each day, variables indicated if the person was considered to be using opioids, the opioid type, and the morphine equivalent of milligrams used. To identify opioid use on any given day, we assumed: 1) individuals used opioids according to the days' supply variable (ie, according to provider instructions); 2) if a person had 7 or more days remaining on a prior fill at dispensation, the new fill was assumed to be used concurrently with the prior fill; otherwise, the new fill was assumed to be used consecutively; and 3) stock from 3 fills could be used concurrently, or be held for future use.

### Opioid Episode Definition and Classification

Using the daily use dataset, we created episodes of opioid use, defined as the period from the start of any opioid use until a gap in use of more than 180 days.<sup>9-11</sup> For each episode, we calculated: 1) episode duration; 2) number of fills; 3) prescribed days' supply of opioids filled during the episode; 4) mean morphine daily-dose equivalent (MDDE) across the duration of the episode, by opioid type; 5) MDDE as prescribed, by opioid type (where the denominator is prescribed days' supply). Because episodes can include gaps in use, MDDE across episodes will typically be lower than MDDE as prescribed, since the latter's denominator does not include gaps in use.

Episodes were classified into 3 mutually exclusive types: 1) acute, 2) episodic, and 3) long-term, as in previous research.<sup>9-11</sup> Acute episodes were those lasting less than 90 days. Episodic episodes lasted 90 days or longer, during which the individual was dispensed less than 120 days' supply of opioids, and during which

there were fewer than 10 opioid fills. Long-term episodes lasted 90 days or more with either 120 days' supply or more of opioids, or at least 10 opioid fills. When describing episodes spanning any part of 2011, we retained only the most severe episode per individual and classified the individual according to that episode type. Thus, all individuals who had a long-term opioid episode covering any part of 2011 were classified as "persons with long-term opioid use." Among those remaining, individuals with at least 1 episodic episode were "persons with episodic opioid use," and the remaining individuals were "persons with acute opioid use."

### Comorbid Health Conditions, Mortality, and Sedative/Hypnotic Use

To examine comorbidities, we extracted from the VDW all diagnoses (*International Classification of Diseases, 9th Revision, Clinical Modification*) associated with healthcare encounters. As in prior research with other complex patient populations,<sup>20</sup> we identified whether individuals received a diagnosis for 1 or more of 13 chronic conditions: arthritis, asthma, congestive heart failure, chronic obstructive pulmonary disease, chronic pain, diabetes, epilepsy, end-stage renal disease, hypertension, ischemic heart disease, osteoporosis, Parkinson's disease, and stroke. We also identified individuals with the following psychiatric and substance use disorders<sup>20</sup>: attention-deficit disorders, anxiety disorder, autism, bipolar disorder, dementia, depression, other psychoses, personality disorder, schizophrenia, opioid abuse/dependence, and nonopioid substance use disorders (excluding tobacco). Date of death and underlying cause of death were also extracted, as was KPNC membership information for each month from 2008 to 2014.

For individuals with opioid use, we extracted all KPNC pharmacy fills for sedative/hypnotic medications (**eAppendix Table 2**) during 2008 to 2014. Using days' supply and the same approach as for opioid fills (without calculating dose), we identified daily use of sedative/hypnotics for each person. These records were merged with the opioid episodes to calculate the number of days of sedative/hypnotic use during each opioid episode.

### Predictors of Initiating Long-Term Opioid Use

Individuals who use opioids long term are at higher risk of adverse events (AEs) compared with individuals who use opioids over a shorter term.<sup>21</sup> To identify predictors of becoming a long-term user within 3 to 4 years of starting opioid use, we identified "opioid-naïve" individuals as those without an opioid fill prior to their first fill of 2011—in other words, having had at least 3 years without prior use of prescription opioids. We required continuous KPNC membership from 2008 to 2014, or death, subsequent to their first 2011 fill (allowing gaps in membership of  $\leq 3$  months). In the year prior to their first opioid fill, we examined medical diagnoses, sedative/hypnotic use, and 4 measures of utilization as proxies for severity and propensity to use resources: 1) number of inpatient days, 2)

number of ED visits, 3) number of office visits, and 4) number of nonopioid prescription fills.

We conducted logistic regression analysis with the dependent variable indicating whether or not the person subsequently had a long-term opioid episode, from initial fill to December 31, 2014. In addition to sex, age (in 7 groups), race/ethnicity, and NDI quartile, we included the following covariates measured in the year before the first opioid fill: dichotomous indicators for each of 13 chronic medical conditions; dichotomous indicators for any psychiatric disorder, opioid abuse/dependence, and nonopioid abuse/dependence; a dichotomous indicator of sedative/hypnotic use; the 4 utilization measures; and a class variable indicating the KPNC clinic where the patient received most of their care.

## RESULTS

Among 2,480,030 adult KPNC members in 2011, 455,693 (18.3%) had at least 1 opioid fill at a KPNC pharmacy. Individuals with opioid use were different from individuals without opioid use on every characteristic, including being more likely to be female, older, white, have a chronic medical or psychiatric condition, and to have a diagnosis of opioid abuse/dependence or nonopioid substance use disorder (**Table 1**).

The 455,693 individuals with opioid use had 474,045 unique episodes occurring in some part of 2011. Due to the 180-day gaps used when creating episodes, few individuals had more than 1 episode in 2011: 18,352 individuals had 2 episodes covering any part of 2011, and the rest had 1. After retaining the most severe episode per person, there were 112,089 long-term opioid episodes, 71,011 episodic episodes, and 272,593 acute episodes (**Table 2**). Long-term users were, on average, aged 56 years, and 61% were female. Forty percent of individuals with long-term opioid use received at least 1 diagnosis for a psychiatric disorder in 2011, 3% were diagnosed with opioid abuse/dependence, and 7% were diagnosed with a nonopioid substance use disorder.

On average, long-term episodes were 1609 days long and included 54 opioid fills (**Table 3**). Because the opioid data spanned 2008 to 2014, it is possible that some episodes began prior to 2008 or continued after 2014; thus, episode durations may be underestimated. Among long-term opioid episodes, 27% began prior to July 1, 2008, and ended after June 30, 2014, and may be both left and right truncated. Another 17% of long-term episodes may have been left truncated only, and 24% may have been right truncated only.

Among individuals with long-term use, the mean MDDE was 38.98 mg, with the highest MDDE for long-acting Schedule II opioids. However, use of those opioids was highly skewed (median MDDE was 0), with only 28% of long-term users using any long-acting Schedule II opioids. Among individuals with episodic and acute use, on the other hand, Schedule III opioids had the highest mean MDDE. Individuals with episodic use used at lower

**TABLE 1.** Description of Individuals With and Without Prescription Opioid Use, 2011<sup>a</sup>

Characteristic	With Prescription Opioid Use (n = 455,693)	Without Prescription Opioid Use (n = 2,024,337)	Characteristic	With Prescription Opioid Use (n = 455,693)	Without Prescription Opioid Use (n = 2,024,337)
Gender, n (%)			Diagnosed conditions, n (%) <sup>c</sup>		
Female	267,755 (58.8)	1,031,995 (51.0)	Any chronic medical condition <sup>d</sup>	287,436 (63.1)	627,085 (31.0)
Male	187,938 (41.2)	992,342 (49.0)	Arthritis	150,481 (33.0)	214,147 (10.6)
Age (years), mean (med)	50.35 (50.18)	45.52 (44.34)	Asthma	62,178 (13.6)	110,894 (5.5)
Age group, years, n (%)			Congestive heart failure	16,903 (3.7)	19,913 (1.0)
19 to 30	64,866 (14.2)	436,364 (21.6)	COPD	29,437 (6.5)	46,477 (2.3)
30 to <40	74,636 (16.4)	398,724 (19.7)	Diabetes	64,286 (14.1)	138,849 (6.9)
40 to <50	86,527 (19.0)	407,002 (20.1)	Epilepsy	4432 (1.0)	8050 (0.4)
50 to <60	95,702 (21.0)	371,768 (18.4)	End-stage renal disease	3108 (0.7)	2054 (0.1)
60 to <70	69,879 (15.3)	240,725 (11.9)	Hypertension	162,064 (35.6)	359,712 (17.8)
70 to <80	39,082 (8.6)	106,717 (5.3)	Ischemic heart disease	30,708 (6.7)	49,051 (2.4)
≥80	25,001 (5.5)	63,037 (3.1)	Osteoporosis	18,340 (4.0)	36,099 (1.8)
Race/ethnicity, n (%)			Pain (chronic)	64,421 (14.1)	32,421 (1.6)
Asian	41,920 (9.2)	356,773 (17.6)	Parkinson's disease	1789 (0.4)	3777 (0.2)
Black	43,378 (9.5)	126,310 (6.2)	Stroke	7364 (1.6)	10,105 (0.5)
Hispanic	80,540 (17.7)	342,260 (16.9)	Psychiatric disorders		
Pacific Islander	2203 (0.5)	11,445 (0.6)	Attention-deficit disorders	4491 (1.0)	10,529 (0.5)
Native American	2825 (0.6)	8230 (0.4)	Anxiety	56,311 (12.4)	96,373 (4.8)
Multiracial	19,092 (4.2)	53,735 (2.7)	Autism	112 (<0.1)	1043 (<0.1)
Other or unknown	10,958 (2.4)	214,133 (10.6)	Bipolar disorder	7371 (1.6)	10,882 (0.5)
White	254,777 (55.9)	911,451 (45.0)	Dementia	4580 (1.0)	8709 (0.4)
Member months in 2011, mean (median)	11.48 (12.00)	10.84 (12.00)	Depression	76,352 (16.8)	116,252 (5.7)
Died in 2011, n (%)	4761 (1.0)	8243 (0.4)	Personality disorder	2550 (0.6)	2770 (0.1)
Neighborhood deprivation, n (%) <sup>b</sup>			Psychoses (other)	2694 (0.6)	4105 (0.2)
Quartile 1 (least deprived)	101,499 (22.3)	523,074 (25.8)	Any psychiatric disorder	113,794 (25.0)	197,813 (9.8)
Quartile 2	132,226 (29.0)	579,802 (28.6)	Opioid abuse/dependence	4918 (1.1)	1880 (<0.1)
Quartile 3	127,979 (28.1)	524,327 (25.9)	Nonopioid substance use disorders	18,130 (4.0)	24,408 (1.2)
Quartile 4 (most deprived)	87,079 (19.1)	343,444 (17.0)			
Missing	6910 (1.5)	53,690 (2.7)			

COPD indicates chronic obstructive pulmonary disease; KPNC, Kaiser Permanente Northern California.

<sup>a</sup>An individual with opioid use refers to one with any fill at a KPNC pharmacy for an opioid. Some individuals defined as those without opioid use may have had an opioid fill at a non-KPNC pharmacy. All characteristics between opioid patients and individuals without opioid use were statistically different at  $P < .05$  based on  $\chi^2$  (for categorical variables) or  $t$  test (for continuous variables).

<sup>b</sup>Neighborhood deprivation index was created using data from the 2006 to 2010 American Community Survey collected by the US Census Bureau, and was generated through principal component analysis of 8 variables at the Census tract level, including percentages of males in the neighborhood working in management and professional occupations, residents living in crowded housing (more than 1 person per room), households in poverty, households headed by females with dependents, households receiving public assistance, households earning <\$30,000 per year, residents ≥25 years of age with less than a high school education, and residents ≥16 years of age who are unemployed. Quartiles based on all Census tracts within KPNC service area.

<sup>c</sup>Includes patients receiving at least 1 diagnosis for these conditions during the year 2011.

<sup>d</sup>Includes all the conditions listed below except psychiatric health disorders, opioid abuse/dependence, and nonopioid substance use disorders.

levels than long-term users, and tended to have substantial gaps between fills; therefore, they had a much lower mean MDDE (5.37 mg). Individuals with long-term use also had higher mean MDDE than episodic or acute users.

Sedative/hypnotics were used by 76% of individuals with long-term opioid use during their episodes, and for an average of 34% of episode days. Among individuals with acute use, 16% used sedative/hypnotics during their (much shorter) acute episode.

## CLINICAL

**TABLE 2.** Characteristics Among Persons with an Opioid Episode Spanning Any Part of 2011, by Episode Type<sup>a</sup>

Characteristic	Type of Opioid Use		
	Long-Term (n = 112,089)	Episodic (n = 71,011)	Acute (n = 272,593)
Female, n (%)	68,658 (61)	42,751 (60)	156,346 (57)
Age, years: mean (median)	56.41 (55.98)	51.32 (51.15)	47.61 (46.67)
Age group, years, n (%)			
19 to <30	5429 (5)	9310 (13)	50,127 (18)
30 to <40	11,363 (10)	11,039 (16)	52,234 (19)
40 to <50	20,984 (19)	13,359 (19)	52,184 (19)
50 to <60	30,012 (27)	14,758 (21)	50,932 (19)
60 to <70	22,285 (20)	11,481 (16)	36,113 (13)
70 to <80	13,207 (12)	6793 (10)	19,082 (7)
≥80	8809 (8)	4271 (6)	11,921 (4)
Race/ethnicity, n (%)			
Asian	3037 (3)	5104 (7)	33,779 (12)
Black	11,288 (10)	7993 (11)	24,097 (9)
Hispanic	14,493 (13)	13,123 (18)	52,924 (19)
Pacific Islander	256 (<1)	370 (1)	1577 (1)
Native American	972 (1)	470 (1)	1383 (1)
Multiracial	6133 (5)	3287 (5)	9672 (4)
Other or unknown	1370 (1)	1250 (2)	8338 (3)
White	74,540 (67)	39,414 (56)	140,823 (52)
Member months in 2011, mean (median)	11.48 (12.00)	11.52 (12.00)	11.47 (12.00)
Neighborhood deprivation, n (%)			
Quartile 1, least deprived	21,543 (19)	15,116 (21)	64,840 (24)
Quartile 2	32,303 (29)	20,350 (29)	79,573 (29)
Quartile 3	33,162 (30)	20,252 (29)	74,565 (27)
Quartile 4, most deprived	23,268 (21)	14,273 (20)	49,538 (18)
Missing	1813 (2)	1020 (1)	4077 (1)
Diagnosed conditions, n (%) <sup>b</sup>			
Any chronic medical condition <sup>c</sup>	92,894 (83)	49,355 (70)	145,187 (53)
Arthritis	52,274 (47)	28,155 (40)	70,052 (26)
Asthma	19,870 (18)	11,350 (16)	30,958 (11)
Congestive heart failure	7287 (7)	3121 (4)	6495 (2)
COPD	12,482 (11)	5014 (7)	11,941 (4)
Diabetes	22,565 (20)	11,388 (16)	30,333 (11)
Epilepsy	1654 (1)	779 (1)	1999 (1)
End-stage renal disease	1025 (1)	758 (1)	1325 (<1)
Hypertension	56,453 (50)	27,679 (39)	77,932 (29)
Ischemic heart disease	11,715 (10)	5497 (8)	13,496 (5)
Osteoporosis	6988 (6)	3092 (4)	8260 (3)
Pain (chronic)	41,238 (37)	8768 (12)	14,415 (5)
Parkinson's disease	640 (1)	324 (<1)	825 (<1)
Stroke	2602 (2)	1387 (2)	3375 (1)

(continued)

**TABLE 2.** Characteristics Among Persons with an Opioid Episode Spanning Any Part of 2011, by Episode Type<sup>a</sup> (continued)

Characteristic	Type of Opioid Use		
	Long-Term (n = 112,089)	Episodic (n = 71,011)	Acute (n = 272,593)
Psychiatric disorders			
Attention-deficit disorders	1392 (1)	788 (1)	2311 (1)
Anxiety	22,288 (20)	9556 (13)	24,467 (9)
Autism	13 (<1)	7 (<1)	92 (<1)
Bipolar disorder	3352 (3)	1204 (2)	2815 (1)
Dementia	1709 (2)	839 (1)	2032 (1)
Depression	31,890 (28)	13,069 (18)	31,393 (12)
Personality disorder	1291 (1)	433 (1)	826 (<1)
Psychoses (other)	1229 (1)	406 (1)	1059 (<1)
Any psychiatric disorder	44,437 (40)	19,461 (27)	49,896 (18)
Opioid abuse/dependence	3656 (3)	434 (1)	828 (<1)
Nonopioid substance use disorders	7372 (7)	3042 (4)	7716 (3)

COPD indicates chronic pulmonary obstructive disease.

<sup>a</sup>All opioid fills were extracted from 2008 to 2014 for persons with at least 1 opioid fill in 2011. Using these fills, opioid-use episodes were constructed. For this table, only 1 episode (the most severe) per person was retained. For episodes that began prior to 2008, the episode start date will be identified here as being the first fill after January 1, 2008. For episodes that ended, or continued, after 2014, the episode stop date will only include fills through December 31, 2014. Therefore, some episodes are left truncated, and some are right truncated. All characteristics between long-term opioid patients and episodic opioid patients were statistically different at *P* < .05 based on  $\chi^2$  (for categorical variables) or *t* test (for continuous variables), except for autism. All characteristics between episodic opioid patients and acute opioid patients were statistically different at *P* < .05.

<sup>b</sup>Includes patients receiving at least 1 diagnosis for these conditions during the year 2011.

<sup>c</sup>Includes all the conditions listed below except psychiatric disorders, opioid abuse/dependence, and nonopioid substance use disorders.

Among all individuals using prescription opioids in 2011, 175,558 (39%) were opioid naïve. Of these, 85,305 had continuous KPNC membership from 2008 to 2014 (n = 81,809), or until death (n = 3496), and were the analytic sample for initiating long-term opioid use (Table 4). Multivariate analysis indicated that individuals at least 80 years of age were more likely to become long-term users than individuals younger than 50 years of age. Compared with whites, Asians and Hispanics were less likely to become long-term users (odds ratio [OR], 0.41; 95% confidence interval [CI], 0.35-0.47, and OR, 0.67; 95% CI, 0.60-0.75, respectively) (Table 5). Individuals in more-deprived neighborhoods were more likely to become long-term users than those in the least-deprived neighborhoods (most-deprived neighborhood: OR, 1.26; 95% CI, 1.12-1.43).

Numerous conditions were associated with long-term opioid use, including chronic pain (OR, 2.57; 95% CI, 2.26-2.93), nonopioid substance use disorders (OR, 2.25; 95% CI, 1.89-2.69), psychiatric disorders (OR, 1.22; 95% CI, 1.12-1.33), and arthritis (OR, 1.41; 95% CI, 1.31-1.52). Use of sedatives/hypnotics was associated with increased odds of becoming a long-term user (OR, 1.67; 95% CI, 1.54-1.81, vs no use). Even after adjusting for diagnosed conditions, inpatient hospital days and use of nonopioid medications in the prior year remained predictive of the long-term user. On the other hand, outpatient office visits in the prior year were associated with lower odds of becoming a long-term user.

## DISCUSSION

This study developed a protocol for an EHR-based prescription opioid registry that can be used to address important research questions about prescription opioid use in noncancer patients on a population level. The current paper also addressed initial questions about the characteristics of prescription opioid users and what predicts initiating long-term use.

Consistent with prior literature,<sup>3,22,23</sup> individuals who used opioids were older, more likely to be white, and were more clinically complex patients, with more medical and psychiatric conditions and substance use disorders than individuals not using opioids. Further, a considerable portion of patients was using opioids long term. Patients using opioids long term are especially important to identify, because duration of use is associated with abuse, overdose, and other AEs.<sup>3,16,21,24-26</sup> As prior researchers found,<sup>22,27</sup> we found individuals with long-term opioid use to be more likely than those with shorter-term use to have higher daily dosages, chronic medical or psychiatric conditions, and opioid or other substance use disorders. Given the current epidemic of misuse and overdose, identifying long-term users with population-based data can help health systems identify patients early, monitor them, and refer them to specialty services (eg, substance use treatment, pain management) as needed.

Our analysis of “opioid-naïve” users indicated that only 4.2% went on to long-term use within 3 years, although at any given time, the percentage of long-term opioid users is quite high (25%).

## CLINICAL

**TABLE 3.** Characteristics of Opioid Episodes Spanning Any Part of 2011\*

Episode Characteristic	Mean (Median), Except Where Noted Otherwise			
	Long-Term Episodes (n = 112,089)	Episodic Episodes (n = 71,011)	Acute Episodes (n = 272,593)	All Episodes (n = 455,693)
Days' duration <sup>b</sup>	1608.68 (1576.00)	226.29 (179.00)	11.90 (6.00)	438.07 (17.00)
Opioid fills during episode	53.87 (42.00)	3.86 (3.00)	1.28 (1.00)	14.62 (2.00)
Prescribed days' supply of fills during episode <sup>c</sup>	1144.98 (787.00)	30.85 (22.00)	7.83 (6.00)	291.13 (10.00)
MDDE across episode, n (%) <sup>d</sup>				
<20	66,218 (59)	68,773 (97)	45,963 (17)	180,954 (40)
20 to <50	26,746 (24)	2,012 (3)	143,659 (53)	172,417 (38)
50 to <120	11,915 (11)	218 (<1)	76,741 (28)	88,874 (20)
≥120	7210 (6)	8 (<1)	6230 (2)	13,448 (3)
MDDE across episode, by opioid type, mg <sup>d</sup>				
Schedule III opioids	15.16 (9.57)	4.36 (2.83)	36.28 (25.00)	26.11 (20.00)
Short-acting Schedule II opioids	4.54 (0.00)	0.87 (0.00)	4.36 (0.00)	3.86 (0.00)
Long-acting Schedule II opioids	19.27 (0.00)	0.15 (0.00)	0.21 (0.00)	4.89 (0.00)
Total	38.98 (15.25)	5.37 (3.34)	40.85 (30.00)	34.87 (21.43)
MDDE as prescribed, n (%) <sup>e</sup>				
<20	18,319 (16)	7,196 (10)	20,459 (8)	45,974 (10)
20 to <50	64,807 (58)	48,188 (68)	157,484 (58)	270,479 (59)
50 to <120	23,772 (21)	14,672 (21)	87,792 (32)	126,236 (28)
≥120	5191 (5)	955 (1)	6858 (3)	13,004 (3)
MDDE as prescribed, by opioid type, mg <sup>e</sup>				
Schedule III opioids	35.32 (30.00)	38.12 (30.00)	43.37 (30.00)	40.53 (30.00)
Short-acting Schedule II opioids	61.98 (48.00)	65.17 (52.50)	68.08 (57.50)	64.12 (50.23)
Long-acting Schedule II opioids	101.11 (60.00)	49.93 (30.00)	54.26 (30.00)	97.66 (60.00)
Total	46.53 (33.88)	39.33 (31.67)	45.09 (33.33)	44.54 (33.33)
Episodes during which sedatives/hypnotics were used, n (%)	85,262 (76)	29,063 (41)	44,271 (16)	158,596 (35)
Among opioid episodes with sedative/hypnotic use				
Days' duration of opioid episodes	1675.85 (1675.00)	251.61 (198.00)	17.02 (7.00)	951.80 (581.00)
Proportion of days in episode that sedatives/hypnotics were used	0.35	0.24	0.57	0.35

MDDE indicates morphine daily-dose equivalent.

\*All opioid fills were extracted from 2008 to 2014 for persons with at least 1 opioid fill in 2011. Using these fills, opioid-use episodes were constructed. For this table, only 1 episode (the most severe) per person was retained. For episodes that began prior to 2008, the episode start date will be identified here as being the first fill after January 1, 2008. For episodes that ended, or continued, after 2014, the episode stop date will only include fills through December 31, 2014. Therefore, some episodes are left truncated, and some are right truncated. All characteristics between long-term opioid patients and episodic opioid patients were statistically different at  $P < .05$  based on  $\chi^2$  (for categorical variables) or  $t$  test (for continuous variables). All characteristics between episodic opioid patients and acute opioid patients were statistically different at  $P < .05$  except MDDE as prescribed, long-acting Schedule II opioids.

<sup>b</sup>Episode duration includes gaps in use of up to 180 days. As noted above, episodes may be right or left truncated.

<sup>c</sup>The days' supply prescribed during the period. Due to the allowance of gaps in use and/or the concurrent use of multiple opioid fills on the same day, prescribed days' supply for an episode can be greater or less than the episode duration.

<sup>d</sup>Total dose assumed to be used during the episode, divided by episode duration (which may include gaps in use).

<sup>e</sup>Total dose of this opioid type assumed to be used during the episode, divided by the prescribed days' supply for this opioid type.

**TABLE 4.** Persons With and Without Subsequent Long-Term Opioid Use After an Initial Opioid Fill<sup>a</sup>

Characteristic	Had a Long-Term Opioid Episode 2011-2014 (n = 3605)	Did Not Have a Long-Term Opioid Episode 2011-2014 (n = 81,700)	Characteristic	Had a Long-Term Opioid Episode 2011-2014 (n = 3605)	Did Not Have a Long-Term Opioid Episode 2011-2014 (n = 81,700)
Gender, n (%)			Diagnosed conditions in the year prior to initial 2011 opioid fill, n (%) <sup>c</sup>		
Female	1988 (55.1)	44,785 (54.8)	Any chronic medical condition <sup>b,d</sup>	2668 (74.0)	42,256 (51.7)
Male	1617 (44.9)	36,915 (45.2)	Arthritis <sup>b</sup>	1311 (36.4)	18,032 (22.1)
Age, years: mean (median) <sup>b</sup>	60.75 (61.04)	52.73 (52.65)	Asthma <sup>b</sup>	457 (12.7)	7310 (8.9)
Age group, years, n (%) <sup>b</sup>			Congestive heart failure <sup>b</sup>	203 (5.6)	2176 (2.7)
19 to <30	147 (4.1)	8430 (10.3)	COPD <sup>b</sup>	371 (10.3)	3627 (4.4)
30 to <40	242 (6.7)	11,981 (14.7)	Diabetes <sup>b</sup>	700 (19.4)	9495 (11.6)
40 to <50	490 (13.6)	15,620 (19.1)	Epilepsy	26 (0.7)	509 (0.6)
50 to <60	833 (23.1)	17,582 (21.5)	End-stage renal disease <sup>b</sup>	24 (0.7)	273 (0.3)
60 to <70	802 (22.2)	14,136 (17.3)	Hypertension <sup>b</sup>	1873 (52.0)	25,731 (31.5)
70 to <80	613 (17.0)	8594 (10.5)	Ischemic heart disease <sup>b</sup>	369 (10.2)	4646 (5.7)
≥80	478 (13.3)	5357 (6.6)	Osteoporosis <sup>b</sup>	207 (5.7)	2697 (3.3)
Race/ethnicity, n (%) <sup>b</sup>			Chronic pain <sup>b</sup>	322 (8.9)	2085 (2.6)
Asian	200 (5.5)	12,130 (14.8)	Parkinson's disease <sup>b</sup>	34 (0.9)	316 (0.4)
Black	295 (8.2)	6157 (7.5)	Stroke <sup>b</sup>	107 (3.0)	1215 (1.5)
Hispanic	420 (11.7)	13,888 (17.0)	Any psychiatric disorder <sup>b</sup>	890 (24.7)	11,030 (13.5)
Pacific Islander	11 (0.3)	367 (0.4)	Opioid abuse/dependence <sup>b</sup>	9 (0.2)	51 (<0.1)
Native American	17 (0.5)	339 (0.4)	Nonopioid substance use disorders <sup>b</sup>	174 (4.8)	1364 (1.7)
Multiracial	195 (5.4)	3255 (4.0)	1 or more sedative/hypnotic fills, n (%) <sup>b,e</sup>	1118 (31.0)	12,384 (15.2)
Other or unknown	25 (0.7)	1475 (1.8)	Number of hospital days, mean (median) <sup>b,e</sup>	1.35 (0.00)	0.66 (0.00)
White	2442 (67.7)	44,089 (54.0)	Number of ED visits, mean (median) <sup>b,e</sup>	0.50 (0.00)	0.33 (0.00)
Neighborhood deprivation, n (%) <sup>b</sup>			Number of office visits, mean (median) <sup>b,e</sup>	9.02 (6.00)	6.78 (5.00)
Quartile 1 (least deprived)	824 (22.9)	22,223 (27.2)	Number of pharmacy fills, mean (median) <sup>b,e</sup>	18.57 (15.00)	10.06 (6.00)
Quartile 2	1122 (31.1)	24,680 (30.2)			
Quartile 3	1022 (28.3)	21,292 (26.1)			
Quartile 4 (most deprived)	597 (16.6)	12,475 (15.3)			

COPD indicates chronic obstructive pulmonary disease; ED, emergency department; KPNC, Kaiser Permanente Northern California.

<sup>a</sup>Persons included were those who had no outpatient fills for opioids ("opioid naive") at a KPNC pharmacy between January 1, 2008, and their initial 2011 opioid fill.

<sup>b</sup>Persons with a long-term opioid episode between index fill and December 31, 2014, were significantly different from persons who did not have a long-term opioid episode, at  $P \leq .05$

<sup>c</sup>Includes patients receiving at least 1 diagnosis for these conditions in the year prior to their initial 2011 opioid fill.

<sup>d</sup>Includes all the conditions listed below except any psychiatric disorder, opioid abuse/dependence, and other substance abuse.

<sup>e</sup>Measured in the year prior to initial 2011 opioid fill.

Although individual risk is low, at a population level, this is consistent with the high level of AEs observed in recent years.

Predictors of developing long-term use included chronic pain, sedative/hypnotic use, psychiatric disorders, and nonopioid substance use disorders. Concurrent use of sedative/hypnotics and opioids has been shown to be associated with a substantial

increased risk of death from drug overdose.<sup>8,25,26,28</sup> Federal and health-system guidelines have focused on reducing high daily dosages, and also on restricting concurrent opioid and sedative/hypnotic use.<sup>2,29</sup> Individuals who lived in more-deprived neighborhoods were also more likely to develop long-term opioid use; to our knowledge, this is a relationship not previously identified in other

**TABLE 5.** Predictors of Becoming an Individual With Long-Term Opioid Use<sup>a</sup>

Characteristic <sup>b</sup>	OR (95% CI) <sup>c</sup>	Characteristic <sup>b</sup>	OR (95% CI) <sup>c</sup>
Gender		Missing	1.03 (0.73-1.44)
Female	0.94 (0.87-1.01)	Quartile 1, least deprived	ref
Male	ref	Diagnosed conditions <sup>d</sup>	
Age group, years		Arthritis	1.41 (1.31-1.52) <sup>f</sup>
19 to <30	0.57 (0.46-0.70) <sup>f</sup>	Asthma	0.95 (0.85-1.06)
30 to <40	0.66 (0.54-0.79) <sup>f</sup>	Congestive heart failure	0.86 (0.72-1.02)
40 to <50	0.81 (0.69-0.94) <sup>f</sup>	COPD	1.25 (1.11-1.42) <sup>f</sup>
50 to <60	0.96 (0.84-1.11)	Diabetes	0.91 (0.82-1.01)
60 to <70	0.93 (0.81-1.06)	Epilepsy	0.63 (0.42-0.95) <sup>f</sup>
70 to <80	0.96 (0.84-1.10)	End-stage renal disease	1.06 (0.68-1.65)
≥80	ref	Hypertension	1.28 (1.17-1.39) <sup>f</sup>
Race/ethnicity		Ischemic heart disease	0.86 (0.75-0.98) <sup>f</sup>
Asian	0.41 (0.35-0.47) <sup>f</sup>	Osteoporosis	1.13 (0.96-1.33)
Black	0.93 (0.81-1.07)	Pain (chronic)	2.57 (2.26-2.93) <sup>f</sup>
Hispanic	0.67 (0.60, 0.75) <sup>f</sup>	Parkinson's disease	1.14 (0.79-1.66)
Pacific Islander	0.75 (0.41-1.39)	Stroke	0.96 (0.78-1.20)
Native American	0.99 (0.60-1.63)	Psychiatric disorders	1.22 (1.12-1.33) <sup>f</sup>
Multiracial	0.99 (0.85-1.16)	Opioid abuse/dependence	1.92 (0.88-4.17)
Other or unknown	0.52 (0.35-0.77) <sup>f</sup>	Nonopioid substance use disorders	2.25 (1.89-2.69) <sup>f</sup>
White	ref	Sedative/hypnotic fill (any vs none) <sup>e</sup>	1.67 (1.54-1.81) <sup>f</sup>
Neighborhood deprivation		Hospital days (per 10 hospital days) <sup>e</sup>	1.18 (1.10-1.26) <sup>f</sup>
Quartile 2	1.16 (1.05-1.28) <sup>f</sup>	Emergency department visits (per 10 ED visits) <sup>e</sup>	0.56 (0.38-.83) <sup>f</sup>
Quartile 3	1.21 (1.09-1.34) <sup>f</sup>	Office visits (per 10 office visits) <sup>e</sup>	0.93 (0.89-0.97) <sup>f</sup>
Quartile 4 (most deprived)	1.26 (1.12-1.43) <sup>f</sup>	Pharmacy fills (per 10 pharmacy fills) <sup>e</sup>	1.33 (1.29-1.37) <sup>f</sup>

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; KPNC, Kaiser Permanente Northern California; OR, odds ratio; ref, reference.

<sup>a</sup>Population included persons with an opioid fill in 2011 and no prior fill after January 1, 2008. Persons were also required to have been continuous KPNC members for the entire 7 years from 2008 to 2014, or to have died after their initial fill.

<sup>b</sup>Also included in the model as an adjuster variable was the KPNC clinic at which the patient received most of their healthcare. There were 49 such clinics; results not shown.

<sup>c</sup>Calculated from results of a logistic regression model in which the dependent variable was a flag indicating that the patient had a long-term opioid episode subsequent to their initial opioid fill.

<sup>d</sup>Includes patients receiving at least 1 diagnosis for these conditions in the year prior to initial 2011 fill.

<sup>e</sup>Measured in the year prior to initial 2011 opioid fill.

<sup>f</sup>Odds ratio was significantly different compared to reference group at  $P < .05$ , after adjusting for covariables.

research studies. Our data do not contain information on pain severity or control. However, findings may suggest that individuals residing in more-deprived neighborhoods (which may also be a proxy for individual deprivation) have more complex health status, or fewer nonmedication treatment alternatives available—these hypotheses deserve further study.

There is increased interest in using registries to address critical clinical and policy questions.<sup>30</sup> A goal of this project was to develop a protocol that can serve as a reference for other clinical and research teams addressing similar questions. Study algorithms can be used in health systems with pharmacy dispensation data and encounter data. For example, because our approach used the VDW, investigators from 19 other health systems in the Health

Care Systems Research Network can also use the VDW to similarly address important questions about prescription opioid use. We recognize this is not without challenges, and would require adaptations, particularly for systems that have dissimilar EHR data elements or claims data. However, by sharing details about our methodology, we hope to contribute to developing harmonized approaches across systems to address the opioid epidemic.

**Limitations**

Our measures of opioid and sedative/hypnotic use depend on pharmacy dispensation data, which is commonly used in the literature, and which we consider a reasonable proxy for use. Uncertainty also exists about calculating use for overlap-

ping fills. However, in contrast to some prior studies, we make explicit our assumptions for overlapping fills. The vast majority of KPNC members fill prescriptions at KPNC pharmacies,<sup>14</sup> but we miss potential non-KPNC pharmacy fills. Although all registry members filled an opioid prescription at KPNC, it is possible that individuals using opioids may be more likely to seek opioid prescriptions externally. Identification of medical and psychiatric conditions, and substance use disorders, is based on diagnoses recorded in the EHR as part of routine care; thus, individuals with more visits may have more opportunity to receive a diagnosis. Also, there can be truncation of episodes that began prior to 2008 or continued post 2014 and, therefore, possible underestimation of long-term episode duration. These limitations are similar to those of other EHR-data-based studies. Finally, generalizability to other systems may be limited, although study algorithms can be adapted.

## CONCLUSIONS

This study established a population-based opioid registry that is flexible, and can be used to address important questions of prescription opioid use. Future analyses will leverage the prescription opioid registry and its algorithms to examine prescription opioid misuse, fatal and nonfatal overdose, and health service utilization and cost. Thus, with this same registry, we will be able to address a broad range of critical public health issues relating to prescription opioid use. ■

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## eAppendix

**eAppendix Table 1.** Opioid-Related Drugs on Kaiser Permanente Northern California Formulary Included in Protocol<sup>a</sup>

<b>Generic drug name</b>	<b>Opioid type</b>	<b>Action<sup>d</sup></b>	<b>Route/form</b>	<b>Morphine equivalent conversion factor<sup>b</sup></b>
Acetaminophen/codeine	Schedule III	Short	Tablets	0.15
Butalbital/acetaminophen/ caffeine/codeine phosphate	Schedule III	Short	Capsule	0.15
Codeine phosphate/carisoprodol	Schedule II	Short	Tablet	0.15
Codeine phosphate	Schedule II	Short	Tablet	0.15
Codeine phosphate/aspirin	Schedule II	Short	Tablet	0.15
Codeine sulfate	Schedule II	Short	Tablet	0.15
Codeine phosphate/butalbital/acetaminophen/caffeine	Schedule II	Short	Capsule	0.15
Codeine/butalbital/aspirin/caffeine	Schedule II	Short	Capsule	0.15
Dihydrocodeine/butalbital/aspirin/caffeine	Schedule III	Short	Capsule	0.25
Dihydrocodeine/acetaminophen/caffeine	Schedule III	Short	Capsule	0.25
Dihydrocodeine/aspirin/caffeine	Schedule III	Short	Capsule	0.25
Fentanyl (patch) <sup>c</sup>	Schedule II	Long	Patch	7.20
Fentanyl (spray)	Schedule II	Short	Spray	0.125
Fentanyl citrate	Schedule II	Short	Lozenge	0.125
Hydrocodone bitartrate/acetaminophen	Schedule III	Short	Liquid, tablet	1.00
Hydrocodone/acetaminophen	Schedule III	Short	Liquid, tablet	1.00
Hydrocodone/acetaminophen/caffeine	Schedule III	Short	Tablet	1.00
Hydrocodone/ibuprofen	Schedule III	Short	Tablet	1.00
Hydromorphone	Schedule II	Short	Liquid	4.00
Hydromorphone HCL	Schedule II	Short	Capsule, liquid, tablet	4.00
Hydromorphone HCL (suppository)	Schedule II	Short	Suppository	6.67
Levorphanol tartrate	Schedule II	Long	Tablet	11.00
Meperidine	Schedule II	Short	Syrup	0.10
Meperidine HCL	Schedule II	Short	Tablet	0.10
Meperidine/acetaminophen	Schedule II	Short	Tablet	0.10
Meperidine/promethazine	Schedule II	Short	Tablet	0.10
Methadone	Schedule II	Long	Capsule, suppository	3.00

Methadone HCL	Schedule II	Long	Liquid, tablet	3.00
Morphine	Schedule II	Short	Liquid, gel Capsule, gel, liquid tablet,	1.00
Morphine sulfate	Schedule II	Short	suppository Capsule, tablet	1.00
Morphine sulfate sustained release	Schedule II	Long	tablet	
Morphine/naltrexone HCL	Schedule II	Long	Capsule	1.00
Oxycodone HCL	Schedule II	Short	Liquid, tablet	1.50
Oxycodone HCL, controlled release	Schedule II	Long	Tablet	
Oxycodone HCL/acetaminophen	Schedule II	Short	Tablet	1.50
Oxycodone HCL/aspirin	Schedule II	Short	Tablet	1.50
Oxycodone/acetaminophen	Schedule II	Short	Tablet	1.50
Oxycodone/aspirin	Schedule II	Short	Tablet	1.50
Oxycodone/ibuprofen	Schedule II	Short	Tablet	1.50
Oxycodone HCL terephthalate/aspirin	Schedule II	Short	Tablet	1.50
Oxymorphone HCL	Schedule II	Short	Tablet	3.00
Oxymorphone HCL extended release	Schedule II	Long	Tablet	3.00
Oxymorphone HCL (suppository)	Schedule II	Short	Suppository	10.00
Pentazocine/acetaminophen	Schedule III	Short	Tablet	0.37
Pentazocine/naloxone	Schedule III	Short	Tablet	0.37
Propoxyphene HCL	Schedule III	Short	Capsule	0.23
Propoxyphene HCL/acetaminophen	Schedule III	Short	Tablet	0.23
Propoxyphene HCL/aspirin	Schedule III	Short	Pulvule	0.23
Propoxyphene HCL/napsylate	Schedule III	Short	Tablet	0.23
Propoxyphene/acetaminophen	Schedule III	Short	Tablet	0.23
Propoxyphene/aspirin	Schedule III	Short	Tablet	0.23
Propoxyphene/aspirin/caffeine	Schedule III	Short	Tablet	0.23
Tramadol HCL	Schedule III	Short	Tablet	0.10
Tramadol HCL extended release	Schedule III	Long	Tablet	0.10
Tramadol HCL/acetaminophen	Schedule III	Short	Tablet	0.10

<sup>a</sup>Not all medications were necessarily used with the registry cohort during 2008 to 2014 period. Some opioids (such as tapentadol) were not used at KPNC during the study period and therefore are not included on the list.

<sup>b</sup>The daily morphine-equivalent dose associated with an opioid fill was generally calculated by multiplying the milligrams of drug dispensed in the fill by the conversion factor, then dividing by the days' supply in the fill.

<sup>c</sup>Morphine-equivalent factor for the fentanyl transdermal patch refers to the morphine-equivalent delivered over the entire 3 days that the patch is assumed to be in place. Thus, a fill for 10 25-

mcg patches (a 30-day supply) is assumed to include a total of 1800 morphine-equivalent milligrams (10 x 25 x 7.2).

<sup>d</sup>Opioids that are short-acting, but which are in a long-acting formulation such as fentanyl patches or extended or sustained-release formulations, are considered long-acting.

HCL indicates hydrochloride; KPNC, Kaiser Permanente Northern California.

**eAppendix Table 2.** Sedative/Hypnotics on Kaiser Permanente Northern California Formulary Included in Protocol<sup>a</sup>

<b>Generic Drug Name</b>	<b>Generic Drug Name</b>
Alprozolam	Hydroxyzine HCl
Amobarbital	Hydroxyzine pamoate
Amobarbital sodium	Lorazepam
	Mephobarbital
Amobarbital/secobarbital	Meprobamate/aspirin
Aprobarbital	
Buspirone HCl	Meprobamate
Butobarbital sodium	Metaxalone
Carisoprodol	Metharbital
Carisoprodol/aspirin	Methocarbamol
Chlordiazepoxide/clidinium bromide	Methocarbamol/aspirin
Chloral hydrate	Methyprylon
Chlordiazepoxide	Oxazepam
Chlordiazepoxide HCl	Pentobarbital
Chlormezanone	Pentobarbital sodium
	Phenazopyridine HCl/hyoscyamine/ butobarbital
Chlorphenesin carbamate	Phenobarbital
Chlorzoxazone	Phenopharbital/belladonna alkaloids
Clonazepam	Phenytoin sodium/phenobarbital
Clorazepate dipotassium	Prazepam
Codeine phosphate/carisprodol/aspirin	Primidone
Cyclobenzaprine HCl	Quazepam
Diazepam	Ramelteon
Ergotamine/belladonna alkaloids/phenobarbital	
Ergotamine/belladonna alkaloids/ caffeine/phenobarbital	Secobarbital sodium
Estazolam	Talbutal
Eszopiclone	Tasimelteon
Ethchlorvynol	Temazepam
Ethinamate	Tizanidine HCl
Flurazepam HCl	Triazolam
Glutethimide	Zaleplon
Halazepam	Zolpidem tartrate

<sup>a</sup>Not all medications were necessarily used by the registry cohort during 2008 to 2014 period. Only drugs with oral routes of administration were included.