



# Utility of accumulated opioid supply days and individual patient factors in predicting probability of transitioning to long-term opioid use: An observational study in the Veterans Health Administration

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## Abstract

Initial supply days dispensed to new users is strongly predictive of future long-term opioid use (LTO). The objective was to examine whether a model integrating additional clinical variables conferred meaningful improvement in predicting LTO, beyond a simple approach using only accumulated supply. Three cohorts were created using Veteran's Health Administration data based on accumulated supply days during the 90 days following opioid initiation: (a) <30 days, (b) ≥30 days, (c) ≥60 days. A base, unadjusted probability of subsequent LTO (days 91-365) was calculated for each cohort, along with an associated risk range based on midpoint values between cohorts. Within each cohort, log-binomial regression modeled the probability of subsequent LTO, using demographic, diagnostic, and medication characteristics. Each patient's LTO probability was determined using their individual characteristic values and model parameter estimates, where values falling outside the cohort's risk range were considered a clinically meaningful change in predictive value. Base probabilities for subsequent LTO and associated risk ranges by cohort were as follows: (a) 3.92% (0%-10.75%), (b) 17.59% (10.76%-28.05%), (c) 38.53% (28.06%-47.55%). The proportion of patients whose individual probability fell outside their cohort's risk range was as follows: 1.5%, 4.6%, and 9.2% for cohorts 1, 2, and 3, respectively. The strong relationship between accumulated supply days and future LTO offers an opportunity to leverage electronic healthcare records for decision support in preventing the initiation of inappropriate LTO through early intervention. More complex models are unlikely to meaningfully guide decision making beyond the single variable of accumulated supply days.

Abbreviation: LTO, long-term opioid use.

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**KEYWORDS**

long-term, medical record data, opioid, Veteran

**1 | INTRODUCTION**

Dramatic increases in the volume of opioids prescribed over the past decades are largely accounted for by expanded long-term opioid use (LTO),<sup>1,2</sup> despite increased awareness of opioid-associated harms and scant evidence that LTO improves functional outcomes.<sup>3</sup> Prior work suggests that duration of opioid exposure at the time of initial prescription is strongly associated with subsequent long-term use,<sup>4-6</sup> defined conceptually as at least 90 days of continuous use.<sup>3,7,8</sup> In addition, there is evidence that once established, LTO generally persists, with more than 80%-90% of patients continuing on opioids for at least 1 year.<sup>9,10</sup> As such, the ability to identify patients at risk of developing LTO early in the process would create an opportunity to intervene, pre-empting unintentional or inappropriate LTO. Such a preventative approach would lessen the need for costly and often challenging efforts to de-prescribe once recipients have developed physiologic dependence or even opioid use disorder.<sup>11</sup> Intervening to circumvent long-term opioid initiation requires a practical and timely way to risk-stratify patients into meaningful categories, which can then empower the health care team to make clinical decisions regarding the timing or intensity of intervention.

While several clinical decision support tools are available to predict individual patient risk for opioid-related harms (eg, death, overdose, abuse),<sup>12-14</sup> none are specifically designed to predict the probability of progression to LTO following incident opioid exposure. The lack of an appropriate prediction approach is an impediment to the goal of designing service interventions to reduce the number of patients who transition to long-term use in the absence of a guideline concordant indication. Building on prior studies,<sup>4-6</sup> we first determined that cumulative opioid supply dispensed in the first 90 days following initiation achieved clinically meaningful stratification in the probability of subsequent long-term use. The objective of this study was to examine the incremental value of combining patient characteristics with information on accumulated opioid exposure to predict future long-term use.

**2 | METHODS****2.1 | Data source**

National administrative data from the VA Corporate Data Warehouse were accessed using the VA Informatics and Computing Infrastructure. Dispensed prescriptions were identified using the outpatient pharmacy domain and diagnosis information was obtained from the outpatient domain based on International Classification of Disease, 9th and 10th revision (ICD-9/10) codes documented with these encounters. All analyses were conducted using SAS Enterprise Guide version 7.1 (Cary, NC). This study was

approved by the University of Iowa Institutional Review Board and the Iowa City Veterans Administration Research and Development Committee.

**2.2 | Patients**

The overall cohort included patients who received an incident opioid prescription during calendar year 2016 (Table 1). Incident use was defined as a first prescription for a noninjectable dosage form of a schedule II opioid or tramadol that was preceded by 365 days with no prescriptions for any of these medications.

**2.3 | Opioid exposure and outcome variables**

Opioid use was ascertained independently for two time frames: (a) the exposure period: within the first 90 days of opioid initiation (Days 1-90); and (b) the outcome period: the remaining year following opioid initiation (Days 91-365). Opioid use during the exposure period was assessed as accumulated supply days dispensed and served as the primary independent variable in the analysis. Opioid use during the outcome period served as the primary outcome variable and was expressed dichotomously as the presence or absence of LTO. LTO is conceptually defined as regular daily opioid use for more than 90 days,<sup>3,7,8</sup> and was determined operationally in this analysis by

**TABLE 1** Demographic characteristics among patients initiating opioids in 2016 (N = 444 031)

Characteristic	n (%)
Age	
18-34	43 756 (9.9)
35-49	70 198 (15.8)
50-64	141 248 (31.8)
≥65	188 829 (42.5)
Sex	
Male	401 798 (90.5)
Female	42 233 (9.5)
Race	
White	344 330 (77.5)
Black	75 698 (17.1)
Other/unknown	24 003 (5.4)
Residence	
Urban	384 215 (86.5)
Large rural	31 136 (7.0)
Small rural	16 014 (3.6)
Isolated	12 666 (2.9)

cabinet supply methodology.<sup>15,16</sup> This method estimates the medication supply available to a patient for each day during a defined time period based on the pattern of prescription dates and supply days dispensed, which are used to construct episodes of continuous use. LTO was then defined as the presence of at least one continuous episode with a duration exceeding 90 days. The determination of LTO was based solely on prescriptions dispensed during the outcome period (Days 91-365); prescriptions dispensed during the exposure (Days 1-90) did not contribute to the long-term use status to maintain independence between exposure and outcome variables.

## 2.4 | Risk associated with accumulated supply days

Building on prior work,<sup>4-6</sup> we first determined whether accumulated supply dispensed following opioid initiation was associated with the probability of subsequent long-term use. Four incremental risk categories were created based on the accumulated opioid supply days dispensed during the exposure period (Days 1-90). Categories 1-4 were defined to include patients who received: (a) any incident prescription with a supply <30 days; (b)  $\geq 30$  accumulated days dispensed; (c)  $\geq 60$  accumulated days dispensed; (d)  $\geq 90$  accumulated days dispensed. Accumulated supply could exceed 90 days because it was based on the total supply days of prescriptions dispensed during the exposure period. These risk categories were not mutually exclusive but meant to represent the incremental state of knowledge available to clinicians as patients accumulate supply days from subsequent opioid prescriptions over time. For example, a patient dispensed an incident opioid prescription with 5 supply days, who received subsequent prescriptions during the first 90 days totaling an accumulated dispensed supply of 65 days, would be included in categories 1-3, but not 4. Accumulated supply days during the first 90 days following initiation was associated in an incremental manner with risk for subsequent LTO (Table 2).

**TABLE 2** Incremental risk for long-term use among patients initiating opioids in 2016, based on accumulated supply days dispensed during the first 90 days following initiation (N = 444 031)

Incremental risk categories	Accumulated supply days dispensed <sup>a</sup>	Patients reaching category threshold N	Probability of long-term opioid use <sup>c</sup> n (%)	Risk ranges based on average risk between incremental categories <sup>d</sup>
1	$\geq 1$	312 047 <sup>b</sup>	12 245 (3.92%)	0%-10.75%
2	$\geq 30$	173 967	30 601 (17.59%)	10.76%-28.05%
3	$\geq 60$	65 037	25 061 (38.53%)	28.06%-47.55%
4	$\geq 90$	29 450	16 667 (56.59%)	$\geq 47.56\%$

<sup>a</sup>Incremental risk categories were not mutually exclusive. For example, a patient dispensed an incident opioid prescription with 5 supply days, who received subsequent prescriptions during the first 90 days totaling an accumulated supply of 65 days, were included in cohorts 1-3, but not 4.

<sup>b</sup>Patients dispensed  $\geq 30$  supply days at initiation (N = 131 984) were not included in incremental risk category 1 because they already met the threshold for risk category 2 at initiation.

<sup>c</sup>The determination of long-term opioid use was based solely on prescriptions dispensed during the outcome period (Days 91-365); prescriptions dispensed during the exposure period (Days 1-90) did not contribute to the long-term use status to maintain independence in the ascertainment of exposure and outcome variables.

<sup>d</sup>Risk ranges for subsequent analyses were established for each incremental risk category based on the average risk between categories. For example, the average risk between category 1 (3.92%) and category 2 (17.59%) was 10.75%, which then served as the threshold separating the two risk categories.

## 2.5 | Value of additional patient characteristics

As our intended clinical application is that accumulated risk thresholds could be used to trigger an intervention at a chosen threshold, we examined if inclusion of additional patient characteristics would contribute a meaningful degree of information to predicting risk for progression to long-term opioid use. Our conceptual definition of "meaningful" was how often this additional information would change a patient's risk category relative to only knowing a patient's accumulated opioid supply days. In a clinical decision model based solely on accumulated supply, patients who reached  $\geq 60$  days could be candidates for a hypothetical intervention tied to risk category 3, regardless of other factors. However, it is possible that additional information about protective factors for this patient would reduce their estimated risk such that it was closer to the lower risk category 2. Conversely, additional information about patients with 30 accumulated supply days (risk category 2) may increase their estimated risk closer to patients with 60 accumulated days (risk category 3). In these cases, clinicians would likely make a different decision about whether to initiate an intervention based on the additional information.

To operationalize the concept of being "more like" an adjacent risk category, we chose the average risk between categories (Table 2). For example, the average risk between category 1 (3.92%) and category 2 (17.59%) was 10.75%, which then served as the threshold separating the two risk categories. Similarly, the average risk between category 2 (17.59%) and category 3 (38.53%) was 28.05% yielding a risk range for category 2 as 10.76%-28.05%. Comparable calculations yield the risk ranges for categories 3 and 4, respectively.

## 2.6 | Individual risk models and statistical analysis

Log-binomial regression was used to model risk for subsequent LTO with an array of independent variables including sociodemographic

characteristics, medical diagnoses, and prescription medications that are potentially associated with long-term use and commonly queryable within electronic medical records.<sup>9,17-22</sup> Diagnoses were identified by ICD-9 and ICD-10 codes from outpatient encounters during the year prior to opioid initiation. Medication use was classified as either concurrent use or prior use, where concurrent use was defined as a prescription occurring prior to opioid initiation and within 1.5 times the supply days dispensed. For example, a prescription for lorazepam of 30 supply days dispensed 35 days prior to opioid initiation would be considered concurrent, as it was within 45 days ( $1.5 \times 30$ ) of initiation. Past medication use was defined by a prescription dispensed in the year prior to opioid initiation that was not classified as concurrent.

Independent statistical models were developed for each patient cohort corresponding to risk categories 1, 2, and 3, where all examined variables were retained in each model. Within these separate cohort models, the probability of subsequent LTO was calculated for each patient using their individual variable values and model parameter estimates. We did not build a model for the risk category 4 cohort because our primary concern was the proportion of patients whose risk was underestimated by only considering accumulated supply days, and less so where risk was overestimated. However, risk category 4 was necessary in the analysis to provide an upper threshold probability for the category 3 risk model.

## 2.7 | Incorporation of individual risk estimates

Individual patient estimates were examined to determine the proportion that fell outside the risk range for that category, indicating that a clinical decision regarding intervention could change based on the additional information contained in the model. For example, in the model for incremental risk category 2, we were interested in the proportion of patients whose individual estimated risk fell outside the category's risk range of 10.76%-28.05% (Table 2). Patients with an individual estimated risk < 10.76% would be deemed more like risk category 1 and may thus be more appropriate for the less intensive intervention (or no intervention) tied to category 1, rather than for category 2. Similarly, patients with personal estimated risk > 28.05% would likely be better candidates for the more intensive intervention tied to the higher risk category 3, than for category 2.

## 2.8 | Sensitivity analyses

Two sensitivity analyses were conducted to examine the robustness of study findings under different modeling assumptions. The first sensitivity analysis used linear regression, rather than log-binomial regression to model risk for LTO. The second sensitivity analysis used log-binomial regression but applied a more stringent threshold for clinical decision making based on reaching the full risk value for the adjacent risk group, rather than the average risk between adjacent groups used in the primary analysis. For example, the primary analysis employed a risk range of 10.76%-20.85% for risk category 2, but

the sensitivity analysis used a risk range of 3.92%-38.53%, meaning that fewer patients would exceed the risk range and be deemed appropriate for a potential change in their intervention approach.

## 3 | RESULTS

### 3.1 | Risk category assignment

A total of 4 991 926 patients received an outpatient VHA prescription in 2016, of which 1 096 843 (22.0%) received at least one prescription for a schedule II opioid or tramadol. Of prevalent opioid recipients, 444 031 (40.5%) were dispensed an incident VHA opioid medication during 2016 and assigned to one or more incremental risk categories based on accumulated supply days in the 90 days following initiation (Table 2). Of these, 312 047 patients received an initial prescription of less than 30 supply days and comprised the incremental risk category 1 cohort. The remaining 131 984 patients were dispensed  $\geq 30$  supply days prescription at initiation and placed directly into the category 2 cohort.

Beyond an initial risk category assignment, patients were also included in higher incremental risk categories if they received subsequent opioid prescriptions and accumulated supplies reaching thresholds of 30, 60, and 90 days. Of the 312 047 patients included in the risk category 1 cohort, 41 983 subsequently accumulated 30 or more supply days and were therefore also included in risk category 2. When added to the 131 984 patients assigned based on  $\geq 30$  supply days dispensed at initiation, a total of 173 967 patients were included in the risk category 2 cohort. Of these, 65 037 individuals further accumulated  $\geq 60$  supply days of opioids and comprised the incremental risk category 3 cohort. Finally, 29 450 received at least 90 opioid supply days, making up the incremental risk category 4 cohort.

The unadjusted risk of observing future long-term use, based on opioid prescriptions dispensed after the 90-day initiation period, increased in a stepwise fashion from 3.92% for incremental risk category 1 to 56.59% for category 4 (Table 2). Risk ranges for subsequent analyses were created based on the average risk between incremental categories.

### 3.2 | Patient characteristics

The relationship between patient characteristics at opioid initiation and risk for subsequent LTO was examined using multivariable log-binomial regression, with separate models for incremental risk category cohorts 1, 2, and 3 (Table 3). In general, the magnitude of relative risk estimates trended toward the null ( $RR = 1$ ) in moving from risk cohorts 1 to 3. For example, the relative risk of concurrent gabapentinoid use decreased from 1.75 (95% CI: 1.65, 1.85) in cohort 1, to 1.38 (1.34, 1.42) in cohort 2, and 1.19 (1.16, 1.22) in cohort 3.

Among demographic variables, age, sex, and rural residence were found to have the most consistent associations with risk for long-term use across the three cohort models. Risk for long-term

**TABLE 3** Patient characteristics as predictors for long-term opioid use across three incremental risk categories based on accumulated supply days dispensed in the 90 days following initiation

Patient characteristic	Relative risk (95% Confidence Interval) <sup>a</sup>		
	Incremental risk categories <sup>b</sup>		
	Risk category 1	Risk category 2	Risk category 3
<b>Demographics</b>			
Age, years			
18-34	0.61 (0.57, 0.66)	0.79 (0.75, 0.82)	0.91 (0.88, 0.95)
35-49	0.74 (0.70, 0.78)	0.87 (0.84, 0.90)	0.94 (0.91, 0.97)
50-64	[Reference]	[Reference]	[Reference]
≥65	0.74 (0.71, 0.77)	0.77 (0.75, 0.79)	0.85 (0.83, 0.86)
Female sex	0.74 (0.70, 0.79)	0.81 (0.78, 0.84)	0.89 (0.86, 0.93)
Race			
White	[Reference]	[Reference]	[Reference]
Black	0.96 (0.92, 1.01)	0.95 (0.93, 0.98)	0.97 (0.94, 1.00)
Other	1.00 (0.92, 1.09)	0.96 (0.91, 1.01)	0.97 (0.93, 1.02)
Unknown	0.88 (0.72, 1.07)	0.87 (0.78, 0.97)	0.94 (0.84, 1.04)
Residence			
Urban	[Reference]	[Reference]	[Reference]
Large rural	1.49 (1.40, 1.58)	1.21 (1.17, 1.26)	1.11 (1.08, 1.15)
Small rural	1.44 (1.33, 1.56)	1.18 (1.13, 1.24)	1.12 (1.07, 1.17)
Isolated	1.35 (1.23, 1.48)	1.21 (1.15, 1.28)	1.13 (1.08, 1.19)
Unknown	1.00 (0.83, 1.20)	0.85 (0.78, 0.92)	0.72 (0.66, 0.79)
<b>Service connection<sup>c</sup></b>			
100%	[Reference]	[Reference]	[Reference]
50%-90%	0.95 (0.90, 0.99)	1.00 (0.97, 1.02)	1.02 (0.99, 1.04)
0%-40%	0.95 (0.89, 1.02)	0.96 (0.92, 1.00)	1.02 (0.98, 1.06)
Unknown	0.99 (0.94, 1.06)	1.05 (1.01, 1.08)	1.05 (1.02, 1.08)
<b>Body mass index, kg/m<sup>2</sup></b>			
Underweight (<18.5)	1.82 (1.56, 2.12)	1.23 (1.11, 1.35)	1.05 (0.96, 1.15)
Normal (18.5-24.9)	1.16 (1.10, 1.22)	1.09 (1.06, 1.12)	1.03 (1.00, 1.06)
Overweight (25.0-29.9)	[Reference]	[Reference]	[Reference]
Obese, class I (30.0-34.9)	0.98 (0.93, 1.03)	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)
Obese, class II (35.0-39.9)	0.96 (0.91, 1.02)	1.03 (1.00, 1.07)	1.02 (0.99, 1.05)
Obese, class III-VI (≥40)	1.21 (1.12, 1.30)	1.19 (1.14, 1.24)	1.09 (1.05, 1.14)
Unknown	1.15 (1.05, 1.26)	1.06 (1.00, 1.12)	1.02 (0.96, 1.07)
<b>Diagnoses</b>			
Chronic pain	1.20 (1.16, 1.25)	0.97 (0.95, 0.99)	0.96 (0.94, 0.98)
Drug use disorder, non-opioid	0.95 (0.88, 1.02)	1.03 (0.98, 1.08)	0.99 (0.95, 1.04)
Drug use disorder, opioid	1.70 (1.52, 1.89)	1.42 (1.33, 1.52)	1.21 (1.14, 1.29)
Alcohol abuse	1.02 (0.96, 1.08)	1.01 (0.97, 1.05)	0.97 (0.94, 1.01)
Diabetes	0.92 (0.89, 0.97)	0.98 (0.96, 1.01)	0.97 (0.95, 1.00)
Cardiovascular disease	0.99 (0.94, 1.04)	0.93 (0.90, 0.96)	0.93 (0.90, 0.95)
Chronic pulmonary disease	1.23 (1.17, 1.29)	1.11 (1.08, 1.14)	1.04 (1.01, 1.06)
HIV/AIDS	0.74 (0.60, 0.93)	0.71 (0.60, 0.83)	0.77 (0.66, 0.90)
Depression or anxiety	1.09 (1.04, 1.13)	1.06 (1.04, 1.09)	1.02 (0.99, 1.04)
Posttraumatic stress disorder	0.91 (0.86, 0.95)	0.97 (0.94, 1.00)	0.97 (0.94, 1.00)

(Continues)

TABLE 3 (Continued)

Patient characteristic	Relative risk (95% Confidence Interval) <sup>a</sup>		
	Incremental risk categories <sup>b</sup>		
	Risk category 1	Risk category 2	Risk category 3
Bipolar affective disorder	0.97 (0.89, 1.07)	1.07 (1.01, 1.14)	1.01 (0.95, 1.06)
Psychotic disorders	0.95 (0.86, 1.05)	1.00 (0.94, 1.06)	1.01 (0.96, 1.07)
Medication use <sup>d</sup>			
NSAID, concurrent use	0.93 (0.88, 0.97)	0.97 (0.95, 1.00)	0.94 (0.91, 0.96)
NSAID, prior use	0.84 (0.80, 0.88)	0.89 (0.87, 0.92)	0.88 (0.86, 0.91)
Gabapentinoid, concurrent use	1.75 (1.66, 1.85)	1.38 (1.34, 1.42)	1.19 (1.16, 1.22)
Gabapentinoid, prior use	1.35 (1.27, 1.43)	1.22 (1.18, 1.26)	1.09 (1.06, 1.13)
Muscle relaxant, concurrent use	1.46 (1.38, 1.55)	1.15 (1.12, 1.19)	1.08 (1.05, 1.12)
Muscle relaxant, prior use	1.18 (1.12, 1.25)	1.07 (1.04, 1.11)	1.03 (0.99, 1.06)
Benzodiazepine, concurrent use	1.48 (1.37, 1.60)	1.22 (1.17, 1.28)	1.11 (1.06, 1.15)
Benzodiazepine, prior use	1.15 (1.08, 1.23)	1.05 (1.01, 1.10)	1.02 (0.98, 1.06)
Hypnotic, concurrent use	1.55 (1.40, 1.71)	1.25 (1.18, 1.32)	1.12 (1.06, 1.18)
Hypnotic, prior use	1.17 (1.07, 1.28)	1.11 (1.05, 1.17)	1.04 (0.98, 1.09)
TCA, concurrent use	1.37 (1.23, 1.53)	1.25 (1.17, 1.32)	1.14 (1.08, 1.21)
TCA, prior use	1.11 (1.00, 1.23)	1.12 (1.05, 1.19)	1.05 (0.99, 1.12)
SNRI, concurrent use	1.19 (1.09, 1.29)	1.15 (1.10, 1.21)	1.09 (1.04, 1.14)
SNRI, prior use	1.23 (1.13, 1.34)	1.17 (1.12, 1.23)	1.07 (1.02, 1.12)

<sup>a</sup>Relative risk from multivariable log-binomial regression, with separate models for each incremental risk category.

<sup>b</sup>Incremental risk categories as described in Table 1, corresponding to categories of accumulated opioid supply days dispensed in the 90 days following initiation.

<sup>c</sup>Service connection refers to degree of rated disability related to military service.

<sup>d</sup>Concurrent medication use defined as a prescription occurring prior to opioid initiation and within 1.5 times the supply days dispensed; whereas prior medication defined by a prescription dispensed in the year prior to opioid initiation that was not classified as concurrent.

use was significantly lower for women, highest among patients aged 50-64 years relative to other age groups, and higher for all rural residence categories relative to urban residents. Higher risk for LTO was also observed for patients with very low (<18.5 kg/m<sup>2</sup>) and very high body mass index (≥ 40 kg/m<sup>2</sup>). Medical diagnoses associated with increased risk for long-term use included chronic pulmonary disease and a prior history of opioid use disorder; HIV/AIDS was associated with lower risk. Concurrent medication use at the time of opioid initiation was associated with increased risk for LTO for gabapentinoids, muscle relaxants, benzodiazepines, other hypnotics, and SSRI and TCA antidepressants. In general, historical use of these medications in the year prior to opioid initiation was also associated with increased risk for long-term use, but with lower risk estimates relative to concurrent use.

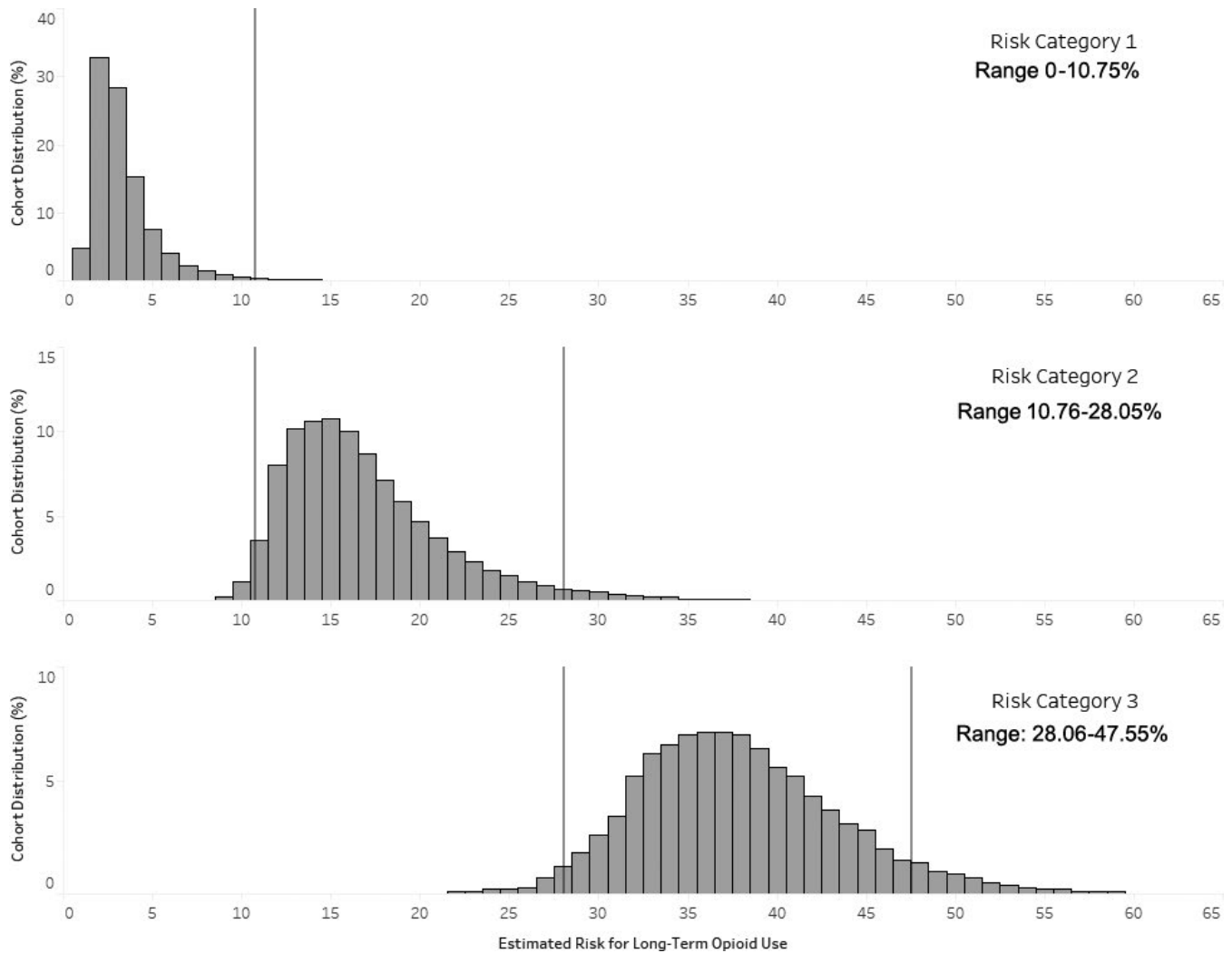
### 3.3 | Added value of patient characteristics to medical decision making

Parameter estimates from the multivariable log binomial regression models for incremental risk category cohorts 1, 2, and 3 were used to estimate individual patient-level level risks for developing LTO. The distributions of these risks are presented in Figure 1, along with vertical bars indicating the risk range for each category. Category 1 included

all patients dispensed an incident opioid prescription with less than 30 supply days. The baseline risk for LTO for these individuals, determined solely from supply days dispensed at initiation, was 3.92%. However, by incorporating patient characteristics in the decision-making process, 1.5% of patients in this cohort had an estimated risk exceeding the upper threshold of 10.75%, indicating their risk was more similar to patients in risk category 2, and thus may benefit from additional intervention (Table 4). Incremental risk category 2 included all patients who accumulated at least 30 supply days of opioids during the 90 days following initiation. Overall, 95.4% of patients had an estimated risk for subsequent long-term use that fell within this group's risk range (10.76%-28.05%). Of the remaining 4.6%, the majority (3.8%) of patients fell above the range, indicating an individualized risk more in line with risk category 3 and that these individuals should instead receive a more intensive intervention; whereas 0.8% fell below the range and may be more appropriate for a less intensive intervention. Finally, 90.8% of patients in incremental risk category 3 had an individual risk score within range (28.06%-47.55%), whereas 7.2% of patients fell above range and 2.1% below range.

Two sensitivity analyses were included to examine the stability of primary analysis findings under alternative assumptions (Table 4). The first analysis used linear regression as an alternative to log-binomial regression. While findings were generally similar to the primary





**FIGURE 1** Distribution of patient-level risk estimates for future long-term opioid use and risk ranges associated with incremental risk category

analysis, a greater proportion of patients fell outside the assigned risk range for categories 2 (7.3% vs 4.6%) and 3 (10.2% vs 9.2%). However, this difference was explained by more patients falling below the risk range when applying linear regression and would result in a greater proportion of patients qualifying for less intensive interventions. The second sensitivity analysis used the same regression models as the primary analysis but imposed more restrictive thresholds for altering clinical decision-making. Where the primary analysis used the midpoint between unadjusted risk between adjacent categories, this sensitivity analysis used the full risk value for adjacent categories. In applying this standard, fewer than 1.0% of patients would qualify for a different treatment intervention in any of the incremental risk category cohorts.

## 4 | DISCUSSION

Our study is the first to test the incremental value of patient-level characteristics, beyond early opioid exposure, in predicting the

probability for LTO. We demonstrate that accumulated opioid supply alone provides clinically relevant stratification in risk, producing actionable information on which patients may be appropriate for stepped interventions to pre-empt inappropriate LTO. Incorporating patient characteristics available through the electronic medical record offered modest additional discrimination, shifting some patients into higher-risk categories, and fewer into lower-risk categories. This is consistent with prior studies indicating that patient-level factors are not the strongest predictors of subsequent LTO.<sup>23</sup> These results could have practical implications for informing the selection of targeted interventions to prevent guideline-discordant initiation of LTO based on individualized patient-level risk.

This personalized approach could involve the initiation of a single intervention at a fixed level of risk (eg, risk category 2). Alternately, it could involve progressively more intensive interventions at escalating levels of risk, since the highest risk patients would progress temporally through the levels of risk, triggering more intensive levels of intervention at each stage (or risk category). A tiered approach could involve both patient-focused and provider-focused components to

	Sensitivity analyses		
	Primary analysis	1: Linear regression <sup>a</sup>	2: Alternative risk <sup>b</sup>
<b>Incremental risk category 1</b>			
Sample size	312 047	312 047	312 047
Range of estimated risk	0%-10.75%	0%-10.75%	0%-17.58%
<b>Estimated patient-level risk</b>			
Below lower threshold, n (%)	N/A	N/A	N/A
Within risk range, n (%)	307 516 (98.5)	309 900 (99.3)	311 463 (99.8)
Above upper threshold, n (%)	4531 (1.5)	2147 (0.7)	584 (0.2)
Total out of risk range, n (%)	4531 (1.5)	2147 (0.7)	584 (0.2)
<b>Incremental risk category 2</b>			
Sample size	173 967	173 967	173 967
Range of estimated risk	10.76%-28.05%	10.76%-28.05%	3.92%-38.52%
<b>Estimated patient-level risk</b>			
Below lower threshold, n (%)	1330 (0.8)	6635 (3.8)	0 (0)
Within risk range, n (%)	166 023 (95.4)	161 198 (92.7)	173 165 (99.5)
Above upper threshold, n (%)	6605 (3.8)	6134 (3.5)	802 (0.5)
Total out of risk range, n (%)	7935 (4.6)	12 769 (7.3)	802 (0.5)
<b>Incremental risk category 3</b>			
Sample size	65 037	65 037	65 037
Range of estimated risk	28.06%-47.55%	28.06%-47.55%	17.59%-56.58%
<b>Estimated patient-level risk</b>			
Below lower threshold, n (%)	1345 (2.1)	1935 (3.0)	0 (0)
Within risk range, n (%)	59 029 (90.8)	58 431 (89.8)	64 424 (99.0)
Above upper threshold, n (%)	4663 (7.2)	4671 (7.2)	613 (0.9)
Total out of risk range, n (%)	6008 (9.2)	6606 (10.2)	613 (0.9)

<sup>a</sup>The first sensitivity analysis used linear regression rather than log-binomial regression.

<sup>b</sup>The second sensitivity analysis used log-binomial regression but applied a more stringent threshold for clinical decision making based on reaching the full risk value for the adjacent risk group, rather than the average risk between adjacent groups used in the primary analysis.

ensure LTO is being prescribed in a safe and effective manner when indicated, and conversion to alternative pharmacological and non-pharmacological pain management strategies when not indicated. For example, a patient reaching risk category 2 ( $\geq 30$  supply days or  $\geq 10.75\%$  individualized risk) could trigger an automated notification to the prescriber containing reminders about guideline-concordant indications and risks of LTO, along with suggestions for alternative treatment strategies. Once that patient reaches risk category 3, this could initiate an independent case review by a clinical pharmacist to assess the appropriateness of on-going opioid therapy and offer recommendations concerning monitoring parameters or conversion strategies to non-opioid alternatives (eg, NSAIDs, gabapentinoids, etc<sup>3,24</sup>). This patient then reaching risk category 4 could precipitate a recommendation for referral to specialty pain medicine services which include more intensive approaches such as management by a pain medicine physician and behavioral therapies such as physical therapy or pain psychology.<sup>25,26</sup>

**TABLE 4** Proportion of patients with individual estimates of risk for future long-term opioid use falling above and below risk ranges for each incremental risk category: summary of primary and sensitivity analyses

While opioid prescribing practices and policies are currently evolving,<sup>3,7,27-31</sup> the magnitude of the relationship between initial exposure and the probability of subsequent long-term use may not be stable over time. However, data comparing opioid prescribing practices across time suggest that while overall opioid prescribing has decreased since 2012, the relationship between initial opioid exposure and risk for long-term use has remained.<sup>6</sup> As such, we expect the fundamental relationship between accumulated supply days and LTO to prove durable even as overall rates of prescribing (ie, absolute numbers of patients, days supplied in initial prescription) decrease. An additional limitation concerns inability to identify illicit opioids or prescription use from non-VA sources. Also, it is possible that the patients included in this study were not entirely opioid naive, since we looked back only 1 year (ie, they could have taken opioids prior to 1 year ago). Finally, it is not known whether findings from this study would directly apply to different healthcare systems, other than the United States Veteran's Healthcare system.



## 5 | CONCLUSION

This study demonstrates an approach for defining risk for progression to LTO using medical record data. Specifically, adding over 30 individual patient characteristics would change clinical decision making in less than 10% of patients compared to using accumulated supply days alone using this approach. The risk stratification approach we describe informs future research to develop and evaluate an intervention or set of interventions to prevent inappropriate LTO by monitoring accumulated opioid supply days. Further personalization of risk estimates based on the incorporation of additional patient characteristics could be considered but would likely yield modest incremental improvements to LTO prediction and associated clinical decision making.

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### DISCLOSURE

The authors have no conflicts of interest to report.

### AUTHOR CONTRIBUTIONS

KH, HM, and BL are responsible for study concept and design. BL, AO, and KM are responsible for data analysis. KH, HM, BL, and MV are responsible for manuscript drafting and study design refinement. All authors provided input into the final manuscript, and critically revised and approved the final version.

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### REFERENCES

- Tehrani AB, Henke RM, Ali MM, Mutter R, Mark TL. Trends in average days' supply of opioid medications in Medicaid and commercial insurance. *Addict Behav.* 2018;76:218-222.
- Mosher HJ, Krebs EE, Carrel M, Kaboli PJ, Weg MW, Lund BC. Trends in prevalent and incident opioid receipt: an observational study in Veterans Health Administration 2004–2012. *J Gen Intern Med.* 2015;30:597-604.
- Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. *MMWR Recomm Rep.* 2016;65:1–49.
- Shah A, Hayes CJ, Martin BC. Characteristics of initial prescription episodes and likelihood of long-term opioid use - United States, 2006–2015. *Morb Mortal Wkly Rep.* 2017;66:265-269.
- Deyo RA, Hallvik SE, Hildebran C, et al. Association between initial opioid prescribing patterns and subsequent long-term use among opioid-naïve patients: a statewide retrospective cohort study. *J Gen Intern Med.* 2017;32:21-27.
- Hadlandsmyth K, Lund BC, Mosher H. Associations between initial opioid exposure and the likelihood for long-term use. *J Am Pharm Assoc.* 2019;59(1):17-22.
- Affairs DoV, Defense Do. VA/DoD clinical practice guideline for opioid therapy for chronic pain, Version 3.0. 2017.
- Taxonomy IAftSoPSo. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. *Pain Suppl.* 1986;S1-S226.
- Vanderlip ER, Sullivan MD, Edlund MJ, et al. National study of discontinuation of long-term opioid therapy among veterans. *Pain.* 2014;155:2673-2679.
- Martin BC, Fan MY, Edlund MJ, Devries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. *J Gen Intern Med.* 2011;26:1450-1457.
- Kolodny A, Frieden TR. Ten steps the federal government should take now to reverse the opioid addiction epidemic. *JAMA.* 2017;318:1537-1538.
- Oliva EM, Bowe T, Tavakoli S, et al. Development and applications of the Veterans Health Administration's Stratification Tool for Opioid Risk Mitigation (STORM) to improve opioid safety and prevent overdose and suicide. *Psychol Serv.* 2017;14:34-49.
- Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med.* 2005;6:432-442.
- Cheatle MD, Compton PA, Dhingra L, Wasser TE, O'Brien CP. Development of the revised opioid risk tool to predict opioid use disorder in patients with chronic nonmalignant pain. *J Pain.* 2019;20:842–851.
- Mosher HJ, Richardson KK, Lund BC. The 1-year treatment course of new opioid recipients in Veterans health administration. *Pain Med.* 2016;17:1282–1291.
- Becker WC. Rigorous epidemiologic work shows positive impact of VHA's efforts to rein in opioid prescribing. *Pain Med.* 2016;17:1209–1210.
- Tonelli M, Wiebe N, Fortin M, et al. Methods for identifying 30 chronic conditions: application to administrative data. *BMC Med Inform Decis Mak.* 2015;15:31.
- Tian TY, Zlateva I, Anderson DR. Using electronic health records data to identify patients with chronic pain in a primary care setting. *J Am Med Inform Assoc.* 2013;20(e2):e275–e280.
- Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol.* 2011;173:676–682.
- Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005;43:1130–1139.
- Hadlandsmyth K, Vander Weg MW, McCoy KD, Mosher HJ, Vaughan-Sarrazin MS, Lund BC. Risk for prolonged opioid use following total knee arthroplasty in Veterans. *J Arthroplasty.* 2018;33:119–123.
- Calcaterra SL, Scarbro S, Hull ML, Forber AD, Binswanger IA, Colborn KL. Prediction of future chronic opioid use among hospitalized patients. *J Gen Intern Med.* 2018;33:898–905.
- Thielke SM, Shortreed SM, Saunders K, Turner JA, LeResche L, Von Korff M. A prospective study of predictors of long-term opioid use among patients with chronic noncancer pain. *Clin J Pain.* 2017;33:198–204.
- Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain.* 2007;132:237–251.
- Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. *Am Psychol.* 2014;69:153–166.
- Oliveira CB, Maher CG, Pinto RZ, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. *Eur Spine J.* 2018;27:2791–2803.
- Hadlandsmyth K, Mosher H, Vander Weg MW, Lund BC. Decline in prescription opioids attributable to decreases in long-term use: a retrospective study in the Veterans health administration 2010–2016. *J Gen Intern Med.* 2018;33:818–824.

28. Lin LA, Bohnert ASB, Kerns RD, Clay MA, Ganoczy D, Ilgen MA. Impact of the Opioid Safety Initiative on opioid-related prescribing in veterans. *Pain*. 2017;158:833-839.
29. Huff C. States aim to limit opioid prescriptions. *ACP Internist*. 2016; <https://acpinternist.org/archives/2016/10/laws.htm>
30. Gellad WF, Good CB, Shulkin DJ. Addressing the opioid epidemic in the United States: lessons from the department of Veterans Affairs. *JAMA Intern Med*. 2017;177:611-612.
31. Guy GP Jr, Zhang K, Bohm MK, et al. Vital signs: changes in opioid prescribing in the United States, 2006–2015. *Morb Mortal Wkly Rep*. 2017;66:697-704.

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