

# Incidence and Risk Factors for Progression From Short-term to Episodic or Long-term Opioid Prescribing: A Population-Based Study

W. Michael Hooten, MD; Jennifer L. St Sauver, PhD; Michaela E. McGree, BS; Debra J. Jacobson, MS; and David O. Warner, MD

## Abstract

**Objectives:** To determine what proportion of a geographically defined population who receive new opioid prescriptions progresses to episodic or long-term patterns of opioid prescribing and to explore the clinical characteristics associated with patterns of opioid prescribing.

**Patients and Methods:** Population-based drug prescription records for the population of Olmsted County between January 1 and December 31, 2009, were obtained using the Rochester Epidemiology Project medical records linkage system (N=142,377). All medical records were reviewed for a random sample of 293 patients who had a new ("incident") prescription for an opioid analgesic in 2009. Patients were followed through their medical records for 1 year after their initial prescription date, with patterns of opioid prescribing categorized as short-term, episodic, or long-term.

**Results:** Overall, 293 patients received 515 new opioid prescriptions in 2009. Of these, 61 (21%) progressed to an episodic prescribing pattern and 19 (6%) progressed to a long-term prescribing pattern. In multivariable logistic regression analyses, substance abuse was significantly associated ( $P<.001$ ) with a long-term opioid prescribing pattern as compared with an short-term opioid prescribing pattern. Past or current nicotine use ( $P=.03$ ) and substance abuse ( $P=.04$ ) were significantly associated with an episodic or long-term prescribing pattern as compared with a short-term prescribing pattern.

**Conclusion:** Knowledge of the clinical characteristics associated with the progression of a short-term to an episodic or long-term opioid prescribing pattern could aid in the identification of at-risk patients and provide the basis for developing targeted clinical interventions.

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From the Department of Anesthesiology, Mayo Clinic, Rochester, MN (W.M.H., D.O.W.); and Division of Epidemiology (J.L.S.S.) and Division of Biomedical Statistics and Informatics (M.E.M., D.J.J.), Department of Health Sciences Research, the Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN.

Accidental overdose related to the use of long-term opioid therapy for non-cancer pain has emerged as a major threat to US public health.<sup>1,2</sup> As a result, there is an urgent need to better understand patterns of opioid prescribing. Our previous work reported that 12% of the population of Olmsted County, Minnesota, received a new prescription for opioids in 2009; opioids were the third most frequently prescribed drug in this geographically defined population that included both insured and uninsured patients.<sup>3</sup> The Consortium to Study Opioid Risks and Trends (CONSORT), supported by the National Institute of Drug Abuse, was initiated to identify trends and risks associated with long-term opioid therapy for chronic pain.<sup>4</sup> In this work, 3 opioid prescribing patterns were defined: short-term, episodic, and long-term use.<sup>4</sup> Reports from this valuable work

focus on the prevalence and incidence of long-term use as well as on comparing prescribing patterns between those who do and do not have conditions such as depression and substance abuse disorders.<sup>5-8</sup>

With some exceptions, physicians and other health care professionals with prescribing authority generally do not plan that an initial opioid prescription will presage the need for repeated opioid prescriptions. No information is available on characteristics associated with the transition from shorter-term to longer-term opioid use; that is, when opioids are first prescribed, which patients are more likely to eventually receive repeated prescriptions? Indeed, there are no longitudinal studies that follow patients who are initially prescribed opioids. Better understanding of these characteristics would

help guide efforts to optimize the use of opioids and anticipate the potential for episodic or long-term use when the decision is made to initially prescribe opioids.

The objectives of this study were (1) to determine what proportion of a geographically defined population receiving new (“incident”) opioid prescriptions progress to episodic or long-term opioid prescribing patterns and (2) to determine the associations between patient characteristics and the transition from short-term to episodic or long-term prescribing patterns, as defined by the CONSORT classification. To accomplish these objectives, we used a cohort of patients receiving opioids previously identified using the Rochester Epidemiology Project (REP), a medical records linkage system that captures all health care information for the residents of Olmsted County.<sup>9-11</sup>

## PATIENTS AND METHODS

All individuals residing in Olmsted County on April 1, 2009, were identified using the REP census (N=142,377).<sup>9</sup> Past work shows that the total number of people identified by the REP for the study period represented 98.7% of the population predicted to reside in Olmsted County by the US Census, and the age and sex distributions were virtually identical to those of the US Census estimates.<sup>10</sup> Additional details about the population of Olmsted County and about the REP have been published elsewhere.<sup>9,11,12</sup>

Outpatient drug prescriptions written for these individuals from January 1 through December 31, 2009, were obtained from Mayo Clinic and the Olmsted Medical Center (both in Rochester, Minnesota). These 2 institutions provide most of the medical care for Olmsted County residents.<sup>9-12</sup> Since 2002, both institutions have used proprietary electronic prescription systems in their outpatient settings (ie, office and hospital outpatient settings). Electronic prescriptions in 2009 were retrieved from the proprietary systems and were converted into RxNorm codes retrospectively.<sup>13</sup> The prescriptions were then grouped using the National Drug File—Reference Terminology classification system.<sup>13,14</sup> We included all prescriptions in the opioid analgesic drug class. These medications included all formulations of oxycodone, morphine, hydromorphone, oxymorphone, hydrocodone, fentanyl, meperidine, codeine, and methadone.

Patients eligible to be sampled for this analysis included all individuals who received a new prescription (no opioid prescriptions in the previous 6 months) for an opioid analgesic (n=14,869) and patient authorization for use of their medical records for research purposes. Full chart reviews by nurse abstractors were conducted on the random sample of 299 patients. Of these, 293 (98%) had a confirmed new (incident) prescription for an opioid analgesic.

## Demographic and Clinical Characteristics

Data abstracted from the medical records included indication for first prescription, age, sex, race, years of education, tobacco use status (never, past, and current), current or past diagnosis of depression, anxiety, other psychiatric disorders, or substance abuse. The presence of comorbid medical problems was identified including cardiovascular diseases (eg, myocardial infarction, congestive heart failure, and peripheral vascular disease), neurological disorders (eg, cerebrovascular disease, hemiplegia, and dementia), chronic pulmonary disease (eg, chronic obstructive pulmonary disease, and asthma), diabetes mellitus, renal disease, liver disease, peptic ulcer disease, connective tissue or rheumatic diseases (eg, rheumatoid arthritis), human immunodeficiency virus/acquired immunodeficiency syndrome, and neoplastic disease. Using diagnosis codes from 2005 to 2009, the Charlson Comorbidity Index (CCI) was calculated, including weighted scores for (1) disease severity and (2) disease severity and age.<sup>15,16</sup>

## Categorization of Opioid Prescribing Patterns

Opioid prescribing patterns were classified into 3 groups based on categories defined by the CONSORT study. The CONSORT study was conducted in 2 large integrated health plans (Kaiser Permanente Northern California and Group Health Cooperative Washington State) to study trends in long-term opioid therapy for noncancer chronic pain from 1997 to 2005.<sup>4</sup> Patients were followed for at least 1 year past their initial prescription date to identify all subsequent opioid prescriptions. Episodes of opioid prescribing that lasted 90 days or less were classified as *short-term*. Episodes of opioid prescribing lasting longer than 90 days were classified as *episodic* if the total days supply was less than 120 and the total

**TABLE 1. Baseline Characteristics of Short-term, Episodic, and Long-term Prescribing Patterns of Opioid Use<sup>a</sup>**

Characteristic	Short-term (N=213)	Episodic (N=61)	Long-term (N=19)	P value <sup>b</sup>
Sex				.50
Men	84 (39.4)	25 (41.0)	5 (26.3)	
Women	129 (60.6)	36 (59.0)	14 (73.7)	
Age (y)				.50
0-18	23 (10.8)	4 (6.6)	0 (0)	
19-29	31 (14.6)	10 (16.4)	1 (5.3)	
30-49	45 (21.1)	14 (23.0)	3 (15.8)	
50-64	45 (21.1)	16 (26.2)	6 (31.6)	
>65	69 (32.4)	17 (27.9)	9 (47.4)	
Race				.93
Other/unknown	34 (16.0)	11 (18.0)	3 (15.8)	
White	179 (84.0)	50 (82.0)	16 (84.2)	
Education <sup>c</sup>				.004
High school graduate or less	59 (31.1)	19 (33.3)	12 (63.2)	
Some college or greater	125 (65.8)	38 (66.7)	5 (26.3)	
Unknown/not reported	6 (3.2)	0 (0)	2 (10.5)	
Indication for first prescription				.58
Surgery/painful procedure	92 (43.2)	26 (42.6)	5 (26.3)	
Musculoskeletal pain	43 (20.2)	15 (24.6)	7 (36.8)	
Trauma	26 (12.2)	5 (8.2)	3 (15.8)	
Other <sup>d</sup>	52 (24.4)	15 (24.6)	4 (21.1)	
Depression or anxiety				.049
Never	148 (69.5)	35 (57.4)	9 (47.4)	
Past/current	65 (30.5)	26 (42.6)	10 (52.6)	
Other psychiatric diagnosis				.03
Never	203 (95.3)	54 (88.5)	16 (84.2)	
Past/current	10 (4.7)	7 (11.5)	3 (15.8)	
Substance abuse <sup>e</sup>				<.001
Never	196 (92.0)	53 (86.9)	9 (47.4)	
Past/current	17 (8.0)	8 (13.1)	10 (52.6)	
Nicotine use				.002
Never	132 (62.0)	28 (45.9)	5 (26.3)	
Past/current	81 (38.0)	33 (54.1)	14 (73.7)	
Charlson Comorbidity Index <sup>f</sup>	2.9±3.7	3.2±3.9	5.3±4.7	.01

<sup>a</sup>Values are presented as mean ± SD or as No. (percentage).

<sup>b</sup>Fisher exact P value reported for education, indication, and other psychiatric diagnosis, chi-square P value reported for all other categorical variables, and Kruskal-Wallis P value reported for the Charlson Comorbidity Index.

<sup>c</sup>Based on patients older than 18 y.

<sup>d</sup>Includes other, dental/mouth pain, visceral pain, cancer pain/palliative care, birth-related, viral/bacterial infection/headache/migraine, and neuropathic/psychogenic pain.

<sup>e</sup>Alcohol, marijuana, methamphetamine, benzodiazepine, or cocaine.

<sup>f</sup>Severity and age weighted sum of diseases.

number of prescriptions was fewer than 10. Episodes of opioid prescribing lasting longer than 90 days and 120 or more total days supply or 10 or more prescriptions were classified as *long term*.

### Statistical Analyses

Patient characteristics were described overall and compared by opioid prescribing pattern (short-term, episodic, and long-term) using chi-square

or Fisher exact tests for categorical variables and *t* tests or rank sum tests for continuous variables. A Firth bias correction was applied to account for missing values of education level. Logistic regression models were used to identify characteristics associated with episodic opioid use vs short-term opioid use and with long-term opioid use vs short-term opioid use; associations were summarized as odds ratios (ORs) and 95% CIs. Additional logistic regression models were used to identify characteristics associated with episodic or long-term use vs short-term use. Variables that were consistently associated with episodic or long-term prescribing patterns in univariate models (other psychiatric diagnoses, substance abuse, and nicotine use) were considered in multivariable models adjusted for all univariately significant factors ( $P<.05$ ). Models included only those patients who were older than 18 years.

### RESULTS

The 293 patients received 515 opioid prescriptions in 2009. Most of the patients receiving prescriptions were women ( $n=179$  [61%]). The most common indication for the first prescription was surgery or other painful procedure, followed by musculoskeletal pain and trauma (Table 1). Most of the patients received 1 prescription, but 47 (16%) received 2 prescriptions and 46 (16%) received 3 or more prescriptions. Overall, 61 patients (21%) progressed to an episodic opioid prescribing pattern and 19 (6%) progressed to a long-term opioid prescribing pattern. Across the 3 categories of prescribing patterns, patient characteristics that differed included education, presence of depression or anxiety, other psychiatric illness, substance abuse, nicotine use, and CCI (severity and age weighted sum of diseases) (see Table 1).

In univariate models, patients in the group who received the episodic prescribing pattern were more likely to be past or current nicotine users than were patients in the group who received the short-term prescribing pattern (Table 2). Patients in the group with the long-term prescribing pattern were more likely to have lower education levels, a past or current history of nicotine use, a past or current history of substance abuse, and a higher CCI (severity and age weighted sum of diseases) than were patients in the group who received the short-term prescribing pattern (see Table 2). When those

**TABLE 2. Univariate Analyses Comparing the Characteristics of Short-term Patterns of Opioid Prescribing With Those of Episodic and Long-term Patterns of Opioid Prescribing<sup>a</sup>**

Characteristic	Short-term vs episodic or long-term		Short-term vs episodic		Short-term vs long-term	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex		.87		.74		.32
Men	Referent		Referent		Referent	
Women	1.05 (0.60-1.81)		0.90 (0.49-1.65)		1.71 (0.59-4.94)	
Age (y)		.85		.82		.46
19-29	Referent		Referent		Referent	
30-49	1.07 (0.44-2.58)		0.96 (0.38-2.45)		2.07 (0.21-20.80)	
50-64	1.38 (0.59-3.24)		1.10 (0.44-2.75)		4.13 (0.47-36.05)	
>65	1.06 (0.47-2.42)		0.76 (0.31-1.86)		4.04 (0.49-33.32)	
Race		.66		.69		.80
Other/unknown	Referent		Referent		Referent	
White	0.85 (0.40-1.78)		0.85 (0.37-1.93)		0.85 (0.23-3.10)	
Education		.14		.84		.003
High school graduate or less	Referent		Referent		Referent	
Some college or greater	0.66 (0.38-1.14)		0.94 (0.50-1.76) <sup>b</sup>		0.20 (0.07-0.58)	
Depression or anxiety		.06		.16		.11
Never	Referent		Referent		Referent	
Past/current	1.68 (0.98-2.89)		1.54 (0.84-2.81)		2.19 (0.85-5.65)	
Other psychiatric diagnosis		.04		.12		.06
Never	Referent		Referent		Referent	
Past/current	2.70 (1.03-7.09)		2.37 (0.81-6.96)		3.77 (0.93-15.34)	
Substance abuse <sup>c</sup>		.002		.27		<.001
Never	Referent		Referent		Referent	
Past/current	3.16 (1.53-6.53)		1.66 (0.68-4.08)		11.31 (4.04-31.65)	
Nicotine use		.005		.04		.01
Never	Referent		Referent		Referent	
Past/current	2.18 (1.27-3.76)		1.85 (1.02-3.37)		3.77 (1.30-10.88)	
Charlson Comorbidity Index <sup>d</sup>	1.04 (0.98-1.11)	.20	1.01 (0.94-1.09)	.72	1.12 (1.01-1.24)	.03

<sup>a</sup>OR = odds ratio.  
<sup>b</sup>Firth bias correction applied owing to zero cell issue.  
<sup>c</sup>Alcohol, marijuana, methamphetamine, benzodiazepine, or cocaine.  
<sup>d</sup>Severity and age weighted sum of diseases.

in the episodic and long-term groups (ie, who received >90 days of prescriptions) were considered together (n=80 [27%]) and compared with those in the short-term group, the former were more likely to have a past or current history of nicotine use, other psychiatric diagnosis, and a past or current history of substance abuse.

In multivariable models, the associations between other psychiatric diagnosis and nicotine use were slightly attenuated and no longer significant for episodic users as compared with short-term users (Table 3). Similarly, in multivariable models, only history of substance abuse remained significantly associated with a long-term opioid prescribing pattern as compared with an short-term opioid prescribing pattern (history of substance abuse: OR, 8.72; 95% CI, 2.76-27.55). In the model in which the

episodic and long-term groups were combined and compared with the short-term group, associations with nicotine use and a past or current history of substance abuse were attenuated, but remained significantly associated with a long-term or episodic opioid prescribing pattern (nicotine: OR, 1.85; 95% CI, 1.05-3.26; substance abuse: OR, 2.26; 95% CI, 1.02-5.02).

## DISCUSSION

Although the clinical characteristics associated with the progression of short-term to episodic or long-term opioid prescribing patterns have not been characterized in longitudinal studies, the clinical factors associated with the prevalence of longer-term opioid use have been described for various groups of patients in cross-sectional study designs. For example, in

**TABLE 3. Adjusted Analyses<sup>a</sup> Comparing the Characteristics of Short-term Patterns of Opioid Prescribing With Those of Episodic and Long-term Patterns of Opioid Prescribing<sup>b</sup>**

Characteristic	Short-term vs episodic or long-term		Short-term vs episodic		Short-term vs long-term	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Other psychiatric diagnosis		.33		.22		.99
Never	Referent		Referent		Referent	
Past/current	1.70 (0.59-4.93)		2.11 (0.64-6.95)		0.99 (0.19-5.19)	
Substance abuse <sup>c</sup>		.04		.87		<.001
Never	Referent		Referent		Referent	
Past/current	2.26 (1.02-5.02)		1.09 (0.39-3.03)		8.72 (2.76-27.55)	
Nicotine use		.03		.06		.21
Never	Referent		Referent		Referent	
Past/current	1.85 (1.05-3.26)		1.78 (0.97-3.30)		2.12 (0.66-6.80)	

<sup>a</sup>Models adjusted for all variables in the table.  
<sup>b</sup>OR = odds ratio.  
<sup>c</sup>Alcohol, marijuana, methamphetamine, benzodiazepine, or cocaine.

nonsurgical hospitalized veterans, long-term opioid use before hospital admission was associated with a diagnosis of pulmonary disease, “complicated” diabetes, posttraumatic stress disorder (PTSD), and a mental health disorder other than PTSD as compared with nonopioid users and patients who used opioids “occasionally.”<sup>17</sup> In surgical patients, long-term postoperative opioid use was associated with younger age, lower household income, diabetes, heart failure, pulmonary disease, PTSD, preoperative pain, and preoperative opioid use.<sup>18-20</sup> In ambulatory care patients, longer-term opioid use was associated with a history of substance abuse, older age, being female, and depression.<sup>5,6,8</sup> More specifically, in Medicare beneficiaries with disabilities, long-term and intermittent opioid use was associated with female sex, increased likelihood of having musculoskeletal disease, and depression as compared with patients not using opioids.<sup>21</sup>

We confirmed some but not all of these associations in this longitudinal analysis of incident opioid prescriptions occurring over a 1-year period. Although specific associations depended on the specific analyses, patients with a history of substance abuse or nicotine use were more likely to have an episodic or long-term prescribing pattern. For nicotine, smokers with chronic pain are more likely to use opioids and consume greater quantities of opioids than are nonsmokers with chronic pain independent of pain severity and depression.<sup>22-24</sup> Furthermore, a reciprocal relationship has

been observed between opioid and nicotine consumption: increases in opioid use have been associated with increases in nicotine use, and increases in nicotine use have been associated with increases in opioid consumption.<sup>25-27</sup> Preclinical studies suggest that the antinociceptive effects of nicotine and morphine are linked and that morphine-related antinociception is influenced by activation of supraspinal nicotinic acetylcholine receptors.<sup>28-30</sup> Collectively, these studies suggest that an interaction exists between the pharmacology of nicotine and opioids and provides support for the observed associations.

Potential mechanisms linking substance abuse to longer-term opioid use may be related, in part, to neural circuits mediating chronic pain and substance abuse. Functional imaging studies in humans suggest that the medial prefrontal cortex (mPFC) and the amygdala are involved in the processing of pain stimuli in adults with chronic pain and connectivity between the mPFC and the nucleus accumbens may potentiate the development of chronic pain.<sup>31,32</sup> The mPFC and nucleus accumbens are key structures comprising the mesocortico-limbic circuitry, which is the principal reward system of the brain, and plays a central role in the neurobiology of substance abuse.<sup>33,34</sup> In addition to the neural circuits shared by chronic pain and substance abuse, preclinical studies suggest that the transition from acute to chronic pain and the development of opioid tolerance share common cellular mechanisms via a protein kinase C-epsilon—dependent process involving

afferent nociceptors.<sup>35</sup> Thus, the shared neural circuitry between chronic pain and substance abuse and common cellular mechanisms between chronic pain and opioid tolerance provide a potential explanation for the observed association between substance abuse and the progression to an episodic or long-term opioid prescribing pattern.

Increased burden of illness was the other factor found in multivariable analysis to be associated with a long-term prescribing pattern, which is consistent with some of the previous cross-sectional studies. Only 2 patients had long-term prescriptions for cancer pain/palliative care; thus, cancer-related pain was not a significant explanatory factor. Although depression, anxiety, and other psychiatric diagnoses were also associated with longer-term use in univariate analysis, these did not prove to be independent predictors in multivariable analyses because these conditions are themselves associated with substance abuse.

The observations from this study have important clinical and research implications. First, before initiating a new opioid prescription, patients should be screened for past or current tobacco use and past or current substance abuse. This would allow the clinician to assess the risk of longer-term prescribing and would provide the opportunity to counsel the patient about these potential risk factors before actually receiving the initial prescription. Second, the study observations need to be replicated in prospective studies that also incorporate pharmacological and behavioral interventions aimed at mitigating the identified risk factors for longer-term prescribing.

This study has several limitations. First, it was not possible to determine patient adherence to the prescribed opioid; therefore, the identified patterns of prescribed opioids may not be representative of actual patient use. Second, as previously described in our work in this area,<sup>3</sup> opioid prescriptions from 1 smaller outpatient practice in Olmsted County were not included because this group does not use an electronic drug prescription system.<sup>9,12</sup> This may have resulted in an underestimation of the actual number of opioid prescriptions. Third, the pattern of opioid prescribing we observed in Olmsted County may not be representative of the prescribing practices in other geographical regions. However, the proportions of patients in the

short-term, episodic, and long-term groups were comparable to those in other studies that used a similar classification scheme.<sup>4</sup> Finally, this study was designed as a relatively small study to generate hypotheses for larger future investigations, and the relatively small numbers of especially long-term users limit that statistical power to determine associations.

## CONCLUSION

In this study, approximately a quarter of the patients in a geographically defined population who received a new opioid prescription progressed to an episodic or long-term opioid prescribing pattern. Although specific associations depend on the specific analyses, patients with a history of substance abuse, nicotine use, and a greater burden of illness were more likely to progress to longer-term use. Knowledge of the clinical characteristics and potential underlying mechanisms associated with this progression could aid in the identification of at-risk patients and provide the basis for developing targeted clinical interventions.

**Abbreviations and Acronyms:** CCI = Charlson Comorbidity Index; CONSORT = Consortium to Study Opioid Risks and Trends; mPFC = medial prefrontal cortex; OR = odds ratio; PTSD = posttraumatic stress disorder; REP = Rochester Epidemiology Project

**Grant Support:** This study was made possible by the Rochester Epidemiology Project (grant number R01-AG034676; Principal Investigator: Walter A. Rocca, MD, MPH, and Barbara P. Yawn, MD, MSc).

**Correspondence:** Address to W. Michael Hooten, MD, Department of Anesthesiology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (hooten.william@mayo.edu).

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