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Incidence and Risk Factors for Progression From Acute to Longer-term Opioid Prescribing: A Population-based Study

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Abstract

Objective—To determine what proportion of a geographically-defined population who receive new opioid prescriptions progress to episodic or chronic patterns of opioid prescribing, and to explore the clinical characteristics associated with patterns of opioid prescribing.

Methods—Population-based drug prescription records for the Olmsted County population 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 following their initial prescription date, with patterns of opioid prescribing categorized as acute, episodic, or chronic.

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 chronic prescribing pattern. In multivariable logistic regression analyses, substance abuse was significantly associated with a chronic opioid prescribing pattern compared to an acute prescribing pattern. Past or current nicotine use and substance abuse were significantly associated with episodic or chronic prescribing patterns compared to an acute prescribing pattern.

Conclusion—Knowledge of the clinical characteristics associated with the progression of an acute to an episodic or chronic prescribing pattern of opioid use could aid in the identification of at-risk patients and provide the basis for developing targeted clinical interventions.

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INTRODUCTION

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. [1, 2] As a result, there is an urgent need to better understand patterns of opioid prescribing. Our prior work demonstrated that 12% of the population of Olmsted County, MN received a new prescription for opioids in 2009; opioids were the third-most frequently prescribed drug in this geographically-defined population which included both insured and uninsured patients. [3] 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. [4] In this work, three opioid prescribing patterns were defined: acute, episodic, and long-term use. [4] Reports from this valuable work focus on the prevalence and incidence of long-term use, as well as comparing prescribing patterns among those who do and do not have conditions such as depression and substance abuse disorders. [5–8]

With some exceptions, providers generally do not plan that an initial opioid prescription will presage the need for repeated opioid prescriptions. There is no information available regarding characteristics associated with the transition from acute to longer-term opioid use; i.e., 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 chronic use when the decision is made to initially prescribe opioids.

The aims of this study were, in a geographically-defined population, 1) to determine what proportion of patients receiving new (incident) opioid prescriptions progress to episodic or chronic opioid prescribing patterns, and 2) to determine the associations between patient characteristics and the transition from acute to episodic or chronic prescribing patterns, as defined by the CONSORT classification. To accomplish these aims, we utilized 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 residents of Olmsted County, Minnesota. [9–11]

METHODS

Study Population

All individuals residing in Olmsted County on April 1, 2009 were identified using the REP census (n = 142,377). [9] 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 United States Census, and the age and sex distributions were virtually identical to those of the US Census estimates. [10] Additional details about the population of Olmsted County and about the REP have been published elsewhere. [9, 11, 12]

Outpatient drug prescriptions written for these individuals between January 1 and December 31, 2009 were obtained from Mayo Clinic and the Olmsted Medical Center (both in Rochester, Minnesota). These two institutions provide the majority of medical care for

Olmsted County residents. [9–12] Since 2002, both institutions have used proprietary electronic prescription systems in their outpatient settings (i.e., office and hospital outpatient settings). Electronic prescriptions in 2009 were retrieved from the proprietary systems and were converted into RxNorm codes retrospectively. [13] The prescriptions were then grouped using the National Drug File-Reference Terminology classification system. [13, 14] 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 prior 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, current), current or past diagnosis of depression, anxiety, other psychiatric disorders or substance abuse. The presence of comorbid medical problems were identified including cardiovascular disease (e.g., myocardial infarction, congestive heart failure, peripheral vascular disease), neurological disorders (e.g., cerebrovascular disease, hemiplegia, dementia), chronic pulmonary disease (e.g. chronic obstructive pulmonary disease, asthma), diabetes mellitus, renal disease, liver disease, peptic ulcer disease, connective tissue or rheumatologic disease (e.g., rheumatoid arthritis), HIV/AIDS, and neoplastic disease. Utilizing diagnosis codes from 2005–2009, the Charlson Comorbidity Index (CCI) was calculated including weighted scores for 1) disease severity, and 2) disease severity and age. [15, 16]

Categorization of Opioid Prescribing Patterns

Opioid prescribing patterns were classified into three groups using categories defined by the CONSORT study. The CONSORT study was conducted in two large integrated health plans (Kaiser Permanente Northern California and Group Health Cooperative Washington State) to study trends in long-term opioid therapy for non-cancer chronic pain from 1997 to 2005. [4] Patients were followed for at least one year past their initial prescription date to identify all subsequent opioid prescriptions. Episodes of opioid prescribing that lasted less than or equal to 90 days were classified as acute. Periods of opioid prescribing lasting longer than 90 days were classified as episodic if the total days supply was less than 120, and the total number of prescriptions was less than 10. Episodes of prescribing lasting longer than 90 days and 120 or more total days supply, or 10 or more prescriptions were defined as chronic.

Statistical Analyses

Patient characteristics were described overall and compared by opioid prescribing pattern (acute, episodic and chronic) using χ^2 or Fisher's exact tests for categorical variables and *t* tests or rank-sum tests for continuous variables. A Firth's 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. acute opioid use and chronic opioid use vs. acute opioid use; associations were summarized as odds ratios (OR) and 95% confidence intervals (CI). Additional logistic regression models were used to identify characteristics associated with episodic/chronic use vs. acute use. Variables which were consistently associated with episodic or chronic prescribing patterns in univariate models (other psychiatric diagnoses, substance abuse, and nicotine use) were considered in multivariable models adjusted for all univariately significant factors. Models were based only on those who were >18 years of age.

RESULTS

The 293 patients received 515 opioid prescriptions in 2009. The majority of 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). The majority of patients received one prescription, but 47 (16%) received two prescriptions and 46 (16%) received three or more prescriptions. Overall, 61 (21%) patients progressed to an episodic prescribing pattern and 19 (6%) progressed to a chronic prescribing pattern of opioid use. Across the three categories of prescribing patterns, patient characteristics that differed included education, the presence of depression or anxiety, other psychiatric illness, substance abuse, nicotine use, and CCI (severity and age weighted sum of diseases) (Table 1).

In univariate models, patients in the group that received the episodic prescribing pattern (n=61) were more likely to be past or current nicotine users compared to patients in the group that received the acute prescribing pattern (Table 2). Patients in the group with the chronic prescribing pattern (n=19) 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) compared to patients in the group that received the acute prescribing pattern (Table 2). When those in the episodic and chronic groups (i.e., who received >90 days of prescriptions) were considered together (n=80) and compared with those in the acute 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 use compared to acute users. Similarly, in multivariable models, only history of substance abuse remained significantly associated with the chronic group compared to the acute group (history of substance abuse: OR=8.72, 95% CI=2.76, 27.55). In the model where the episodic and chronic groups were combined and compared to the acute group, associations with nicotine use and a past or current history of substance abuse were attenuated, but remained significantly associated with chronic/episodic use (nicotine: OR=1.85; 95% CI: 1.05–3.26 and substance abuse: OR=2.26, 95% CI = 1.02, 5.02).

DISCUSSION

Although the clinical characteristics associated with the progression of acute to episodic or chronic prescribing patterns of opioid use have not been characterized in longitudinal studies, the clinical factors associated with prevalence longer-term opioid use have been described for various groups of patients in cross-sectional study designs. For example, in nonsurgical hospitalized veterans, long-term opioid use prior to hospital admission was associated with a diagnosis of pulmonary disease, “complicated” diabetes, post-traumatic stress disorder (PTSD), and a mental health disorder other than PTSD compared to non-opioid users and patients who used opioids “occasionally”. [17] Among 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. [18–20] In ambulatory care patients, longer-term opioid use was associated with a history of substance abuse, older age, being female, and depression [5, 6, 8]. More specifically, among disabled Medicare beneficiaries, long-term and intermittent opioid use was associated with female sex, increased likelihood of having musculoskeletal disease, and depression compared to patients not using opioids. [21]

We confirmed some but not all of these associations in this longitudinal analysis of incident opioid prescriptions occurring over a one-year period. Although specific associations depended upon the specific analyses, patients with a history of substance abuse or nicotine use were more likely to have an episodic or chronic prescribing pattern. For nicotine, smokers with chronic pain are more likely to use opioids and consume greater quantities of opioids compared to nonsmokers with chronic pain independent of pain severity and depression. [22–24] 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. [25–27] Preclinical studies suggest the antinociceptive effects of nicotine and morphine are linked, and that morphine-related antinociception is influenced by activation of supraspinal nicotinic acetylcholine receptors. [28–30] Collectively, these studies suggest 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 the medial prefrontal cortex (mPFC) and the amygdala are involved in processing of pain stimuli in adults with chronic pain, and connectivity between the mPFC and the nucleus accumbens may potentiate development of chronic pain. [31, 32] The mPFC and nucleus accumbens are key structures comprising the mesocorticolimbic circuitry, which is the principal reward system of the brain, and plays a central role in the neurobiology of substance abuse. [33, 34] In addition to the neural circuits shared by chronic pain and substance abuse, preclinical studies also suggest that the transition from acute to chronic pain, and development of opioid tolerance share common cellular mechanisms via a protein kinase C-epsilon dependent process involving afferent nociceptors. [35] 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 chronic opioid prescribing pattern.

Increased burden of illness was the other factor found in multivariable analysis to be associated with a chronic prescribing pattern, consistent with some of the prior cross-sectional studies. Only two 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 univariable analysis, these did not prove to be independent predictors in multivariable analyses, as these conditions are themselves associated with substance abuse.

The observations from this study have important clinical and research implications. First, prior to 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 prior to actually receiving the initial prescription. Second, the study observations need to be replicated in prospective studies that also incorporate pharmacologic 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 compliance with 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 [3], opioid prescriptions from one smaller outpatient practice in Olmsted County were not included because this group does not utilize an electronic drug prescription system. [9, 12] 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 acute, episodic, and chronic groups were comparable to other studies that used a similar classification scheme [4]. Finally, this was designed as a relatively small study to generate hypotheses for larger future investigations, and the relatively small numbers of especially chronic users limits that statistical power to determine associations.

CONCLUSION

In this study, approximately a quarter of patients in a geographically-defined population who received a new opioid prescription progressed to an episodic or chronic opioid prescribing pattern. Although specific associations depend upon 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.

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Abbreviations

CONSORT	Consortium to Study Opioid Risks and Trends
REP	Rochester Epidemiology Project
CCI	Charlson Comorbidity Index
CI	confidence interval
PTSD	post-traumatic stress disorder
mPFC	medial prefrontal cortex

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Table 1

Baseline characteristics of acute, episodic, and chronic prescribing patterns of opioid use.

Characteristics	Acute (N=213)		Episodic (N=61)		Chronic (N=19)		*P* value[†]
	N	%	N	%	N	%	
Sex							0.50
Men	84	39.4	25	41.0	5	26.3	
Women	129	60.6	36	59.0	14	73.7	
Age (years)							0.50
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							0.93
Other/unknown	34	16.0	11	18.0	3	15.8	
White	179	84.0	50	82.0	16	84.2	
Education[a]							0.004
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							0.58
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[d]	52	24.4	15	24.6	4	21.1	
Depression or anxiety							0.049
Never	148	69.5	35	57.4	9	47.4	
Past/current	65	30.5	26	42.6	10	52.6	
Other psychiatric diagnosis							0.03
Never	203	95.3	54	88.5	16	84.2	

Characteristics	Acute (N=213)		Episodic (N=61)		Chronic (N=19)		*P* value†
	N	%	N	%	N	%	
Past/current	10	4.7	7	11.5	3	15.8	
Substance abuse[b]							<0.001
Never	196	92.0	53	86.9	9	47.4	
Past/current	17	8.0	8	13.1	10	52.6	
Nicotine use							0.002
Never	132	62.0	28	45.9	5	26.3	
Past/current	81	38.0	33	54.1	14	73.7	
	Mean	SD	Mean	SD	Mean	SD	
Charlson Comorbidity Index[c]	2.9	3.7	3.2	3.9	5.3	4.7	0.01

[a] Based on patients >18 years old

[b] Alcohol, marijuana, methamphetamine, benzodiazepine, or cocaine

[c] Severity and age weighted sum of diseases

[d] Includes other, dental/mouth pain, visceral pain, cancer pain/palliative care, birth-related, viral/bacterial infection/headache/migraine and neuropathic/psychogenic pain

† Fisher's 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 Charlson Comorbidity Index.

Table 2

Univariate analyses comparing the characteristics of acute to episodic and chronic patterns of opioid use.

	Acute vs Episodic or Chronic		Acute vs Episodic		Acute vs Chronic	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Sex		0.87		0.74		0.32
Men	Referent		Referent		Referent	
Women	1.05 (0.60, 1.81)		0.90 (0.49, 1.65)		1.71 (0.59, 4.94)	
Age (years)		0.85		0.82		0.46
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		0.66		0.69		0.80
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		0.14		0.84		0.003
High school graduate or less	Referent		Referent		Referent	
Some college or greater	0.66 (0.38, 1.14)		0.94 (0.50, 1.76)[c]		0.20 (0.07, 0.58)	
Depression or anxiety		0.06		0.16		0.11
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		0.04		0.12		0.06
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[a]		0.002		0.27		<0.001
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		0.005		0.04		0.01
Never	Referent		Referent		Referent	
Past/current	2.18 (1.27, 3.76)		1.85 (1.02, 3.37)		3.77 (1.30, 10.88)	

	Acute vs Episodic or Chronic		Acute vs Episodic		Acute vs Chronic	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Charlson Comorbidity Index[b]	1.04 (0.98, 1.11)	0.20	1.01 (0.94, 1.09)	0.72	1.12 (1.01, 1.24)	0.03

[a] Alcohol, marijuana, methamphetamine, benzodiazepine, or cocaine

[b] Severity and age weighted sum of diseases

[c] Firth's bias correction applied due to zero cell issue

Table 3

Adjusted analyses[a] comparing the characteristics of acute to episodic and chronic patterns of opioid use.

	Acute vs Episodic or Chronic		Acute vs Episodic		Acute vs Chronic	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Other psychiatric diagnosis		0.33		0.22		0.99
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[b]		0.04		0.87		<0.001
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		0.03		0.06		0.21
Never	Referent		Referent		Referent	
Past/current	1.85 (1.05, 3.26)		1.78 (0.97, 3.30)		2.12 (0.66, 6.80)	

[a] Models adjusted for all variables in table.

[b] Alcohol, marijuana, methamphetamine, benzodiazepine, or cocaine