INCIDENCE STUDY TEMPLATE

Title of the study: Opioid prescriptions in the Olmsted County population

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Abstract:
A preliminary examination of prescription data in the Rochester Epidemiology Project (REP) indicates that 12.7% of the 2009 Olmsted County population received a prescription for an opioid analgesic in 2009. Unfortunately, misuse of opioid medications is increasing throughout the US. It is unclear, however, who is at risk of adverse outcomes related to medication use. In this study, we propose to use the Rochester Epidemiology Project (REP) research infrastructure to describe the epidemiology of opioid use in the Olmsted County population through completion of the following specific aims:

Specific Aims

Aim 1. To describe the incidence of opioid prescriptions by age, sex, and indication in the 2009 Olmsted County population.

Aim 2. To estimate the proportion of new opioid users who require dose escalation or prolonged opioid use (prescribed duration of >90 days).

Aim 3. To determine whether age, sex, and indication are associated with an increased risk of dose escalation or prolonged opioid use.

Aim 4. To describe the prevalence of other potential risk factors for adverse opioid events in a subset of new opioid users. These risk factors will include initial pain scores, presence or history of mental illness (including depression and anxiety), presence of concomitant medications that could increase the risk of adverse events due to interactions, and presence or history of substance abuse. We will also perform preliminary analyses to assess associations between these factors and opioid-related adverse events.

This study will provide important data on the epidemiology of opioid use in a community-based setting, and will help us to understand whether specific patients are at an increased risk of adverse opioid-related events. These data may also be useful for health care providers when considering options for prescribing pain medications.

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BACKGROUND AND SIGNIFICANCE

Opioid analgesics are effective pain-relieving medications prescribed for a wide range of indications, including acute pain following surgery, end-of-life palliative care, and chronic, non-malignant pain (CNMP). Opioids are misused and diverted from their intended recipients, and abuse and overdoses have risen alarmingly in the last ten years.(1) Data regarding the basic epidemiology of opioid use are limited, making it difficult to determine how best to use these medications appropriately. Boudreau et al found significant increases in incident opioid prescriptions for CNMP between 1997 and 2005 in the Kaiser Permanente and Group Health populations.(2) Additionally, the proportion of the population receiving long-term therapy nearly doubled in the same time frame. The most common indications for long-term use in this study were chronic back pain, extremity pain, and osteoarthritis. Apart from these data, however, little is known about who receives opioid analgesic prescriptions in an average community. Additionally, few data are available on the risk of opioid-related adverse outcomes, including long-term use, dose-escalation, overdose, and death. Finally, with the exception of a few studies exploring the role of mental illness, depression, or previous patterns of substance abuse,(3-5) patient characteristics that might contribute to these adverse outcomes have not been described.

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PRELIMINARY DATA

We have assembled a database of outpatient prescription data from Olmsted Medical Center and Mayo Clinic for the Olmsted County, MN population as part of Specific Aim 2 of the Rochester Epidemiology Project grant (IRBs: 1945-99 and 015-rep-omc-00). Initial summaries of these data indicate that opioid analgesics are commonly prescribed in the community. Overall, 18,082 (12.7%) people in the 2009 Olmsted County population received an opioid analgesic in the same year. We hypothesize that the majority of these prescriptions are short-term, and associated with a therapeutic or surgical procedure. We also expect that additional prescriptions will be associated with end-of-life treatment of severe pain, while the remaining prescriptions will be associated with treatment of chronic conditions such as back pain. The focus of this study will be to describe these indications, and to characterize the patients receiving opioids in our community.

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RESEARCH DESIGN AND METHODS

Overview

Patient population The patient population for this study will consist of the 18,082 patients who received an opioid prescription in 2009. We will describe the demographic characteristics of this group, type of opioid, dose, and duration of use using electronically available data. The medical records of a random subsample of the population (n=1000) will be abstracted to obtain data on indication, risk factors, and outcomes (described below). Analyses for Aim 4 will be conducted only in the subsample of the population.

Aim 1. Describing incidence of opioid use by age, sex, and indication. An incident opioid prescription will be defined as a prescription between January 1, 2009 and December 31, 2009 with no previous prescription in the prior 6 months.(6) The end date of an opioid prescription episode will be defined as the date of the last prescription plus the number of days the prescription is supplied. For example, a 30-day prescription written on January 1, 2009, would have an end date of January 31, 2009.(2) In order to compare opioids across type prescribed, morphine equivalent doses (MED) will be calculated for each prescribed opioid by multiplying the drug quantity times the milligrams per unit dispensed times the Morphine Equivalent Conversion Factors defined by the CONsortium to Study Opioid Risks and Trends (CONSORT).(7) Total MEDs will be calculated by summing the morphine equivalents for each opioid prescribed during a single episode. The average daily dose will be calculated by dividing the total MED by the number of days in the episode. The average daily dose has been previously used as a way to estimate mean daily consumption of an opioid.(2, 6, 7)

Diagnosis and procedure ICD-9 codes will also be obtained electronically for all residents prescribed a new opioid medication in 2009. Diagnoses and procedures that occur within 3 weeks (+ or – 1.5 weeks) of the opioid prescription date will be assigned to one of the following categories: surgery or other procedure, acute injury, headaches, or chronic pain. Diagnoses or procedures that fall into one of these categories will be considered the indications for the opioid prescription. We will also review a random sample of 1000 medical records to confirm this method of assigning opioid indication (Aim 4).

Aim 2. To estimate the proportion of new opioid users who require dose escalation or prolonged opioid use (>90 days). Dose escalation will be defined as an increase in opioid dose within 90 days of the initial prescription. Prolonged opioid use will be defined as longer than 90 days, with either a total days supply of 120 or with 10 or more opioid prescriptions of any type. Van Korff and colleagues found that individuals who met these criteria for prolonged use were highly likely to continue this level of use one year later.(7) We will also note those cases who received at least one refill of their prescription. We anticipate that this may have utility in analyzing opioid use for procedural indications, as typically the duration of prescriptions for post-procedural pain reflect the anticipated duration of need (i.e., it is not anticipated that patients will require a refill of these prescriptions).

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Aim 3. To determine whether age, sex, and indication are associated with an increased risk of dose escalation or prolonged opioid use. We will estimate associations between age, sex, and indication and dose escalation and prolonged use using Cox proportional hazard models (described in the analysis section).

Aim 4. Describe the prevalence of other potential risk factors for adverse opioid events. A number of risk factors may contribute to dose escalation and prolonged opioid use, and many of these risk factors cannot be obtained electronically. We are unable to abstract these types of information for all patients in the study, and the distribution of these factors among those prescribed opioids is unknown. Therefore, we will abstract information on these risk factors for a random sample of 1000 patients, and will estimate the prevalence of these risk factors among our population of incident opioid users. These data will be used for future studies designed to evaluate the contribution of such potential risk factors to adverse opioid events.

First, we will validate the electronic method of assigning opioid indication through chart review of the sample of 1000 patients. Second, pain intensity and duration are likely to be important risk factors for continued opioid use. Pain scores using the numeric pain intensity score and/or the faces pain scale are routinely collected at many local hospitals, and we expect these data to be widely available for inpatient indications. The last pain score prior to hospital dismissal will be collected for all inpatient events associated with an opioid prescription. However, we are not certain if pain scores are routinely collected at all outpatient sites. These data will be abstracted from the medical records for outpatient indications when available. We will also collect data on history and presence of co-morbid mental health issues (including depression and anxiety) within 5 years prior to the date of the opioid prescription. We will collect data on the presence of concomitant prescriptions that could increase the risk of adverse outcomes due to risk of interactions (particularly the CYP3A4 inhibitors).(8) We will also collect data on history of substance abuse (nicotine, alcohol, other drug) within 5 years prior to the opioid prescription date. In addition, there are several other potential adverse outcomes associated with opioid use in addition to dose escalation and prolonged opioid use (both of which suggest that the opioids are not achieving their therapeutic intent). We will abstract these outcomes, including overdose (diagnosed using ICD-9 codes according to the method of Dunn et al(9)), gastrointestinal symptoms (nausea and constipation), pruritis, and CNS symptoms (dizziness or somnolence).

Statistical Analysis

Age- and sex-specific incidence rates of opioid use will be estimated by dividing the number of individuals with an incident opioid use (defined above) by the corresponding age- and sex- Olmsted County population stratum. Age-adjusted and overall age- and sex-adjusted prevalence rates will be obtained by direct standardization to the US population. Descriptive statistics will be used to summarize the number of days prescribed, total MED, average daily dose and indication for opioid use**.** Multivariable Cox proportional hazards models will be used to estimate differences in the time to

adverse opioid event (dose escalation or prolonged opioid use) by age, sex and indication for opioid use. Follow-up will be from the time of the incident diagnosis until the first occurrence of an adverse opioid event or 12/31/2011. Interaction terms will be included to determine whether there are differences in the association of adverse opioid event and age, sex or indication which vary by the level of the other variables. Descriptive statistics will be used to summarize the potential risk factors for adverse opioid events in the random subsample of incident opioid users**.**

Power depends on the frequency of adverse opioid events and the proportion of subjects in each group. Table 1 display the smallest detectable hazard ratio (for example for males relative to females), assuming 80% power and a two-sided, alpha=.05 test for the total population of opioid users. For an event rate of only 5%, the smallest detectable hazard ratio ranges from 1.22 to 1.36. In general, the total cohort has adequate power to detect small effects. Table 2 displays the smallest detectable hazard ratio, assuming 80% power and a two-sided, alpha=.05 test for the subset of 1000 opioid users. For an event rate of 10%, the smallest detectable hazard ratio ranges from 1.8 to 2.5.

Table 1. Detectable Hazards ratio (total population)

	Minimally detectable hazard ratio (α=.05, 80% power)		
	Expected number of adverse opioid events)		
Proportion	5% (904)	10% (1808)	20% (3616)
0.10	1.36	1.25	1.16
0.20	1.26	1.18	1.12
0.30	1.22	1.15	1.11

Table 2. Detectable Hazards Ratio (subsample of 1000 opioid users)

	Minimally detectable hazard ratio (α=.05, 80% power)		
	Expected number of adverse opioid events)		
Proportion	5% (50)	10% (100)	20% (200)
0.10	3.7	2.5	1.9
0.20	2.7	2.0	1.6
0.30	2.4	1.8	1.5
0.40	2.2	1.8	1.5
0.50	2.2	1.8	1.5

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HUMAN SUBJECTS

This project does not involve experimentation on human subjects. It is limited to a retrospective review of electronically available prescription data, medical and surgical procedure codes, demographic data, and medical record information on a subset of the study population. No patients will be contacted during this study. The data will be analyzed anonymously and the usual policies and safeguards enforced by the Department of Health Sciences Research will be used to protect the confidentiality of the patient records. Data on the individual patients will not be released outside of Mayo Clinic and results will only be published in aggregate. Additionally, we will not include anyone in the study who has refused MN research authorization. Finally, we will not compare any results across the participating REP institutions.

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