AN ANALYSIS OF OPIATE PRESCRIPTION FOR CHRONIC DEGENERATIVE DISEASE AND OTHER PAIN SYNDROMES

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AN ANALYSIS OF OPIATE PRESCRIPTION FOR CHRONIC DEGENERATIVE DISEASE AND OTHER PAIN SYNDROMES

by

Catherine Sawyer

Submitted to Brigham Young University in partial fulfillment of graduation requirements for University Honors

Department of Mathematics
Brigham Young University
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ABSTRACT

AN ANALYSIS OF OPIATE PRESCRIPTION FOR CHRONIC DEGENERATIVE DISEASE AND OTHER PAIN SYNDROMES

Catherine Sawyer

Department of Mathematics

University Honors

Utilizing the National Ambulatory Medical Care Survey (NAMCS) database, this thesis explores patterns of opiate prescribing during time period from 1993 to 2016, which includes the time period when the opiate crisis was recognized in the United States and efforts begun to combat it. We analyze these patterns particularly as they relate to patients who were prescribed opiates and who were simultaneously suffering from various chronic conditions, and interactions between prescription of opiates and diagnosis of chronic conditions. We examine which demographic groups were most likely to receive opiates, and considered opiate prescription trends among patients with any pain diagnosis and with specific pain syndromes. We also attempted to classify which patients were most likely to be prescribed opiates using several machine learning classification techniques.
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Chapter 1. Introduction

The opioid crisis is the widely-recognized, dramatic increase in the number of people using and abusing opiates, particularly prescription opiates, leading to increasing numbers of drug overdose cases and deaths from drug overdose. While abused drugs have traditionally come from the black market and other illicit sources, during this crisis, many people have unfortunately begun their journey of addiction by overusing opiates legally prescribed to them by a healthcare provider, and/or opiates legally prescribed to others [1]. In 2017, the U.S. Department of Health and Human Services (HSS) declared a public health emergency related to the widely discussed opioid crisis [2]. According to the HSS, a rising trend in opiate prescription began to be recognized and to create concern in the late 1990’s [3]. This increase had occurred as the result of several concurrent movements. First, for many years (starting as early as the 1960’s and 1970’s with the hospice movement), experts had begun calling for better assessment of, and more aggressive treatment of, patients suffering from acute injuries and cancer-related pain, and medical providers had begun to re-examine the long-time hesitation to prescribe opiates [4]. Secondly, when guidelines and advocacy efforts failed to change prescription practices sufficiently, some leaders in the medical field started calling for stronger methods to address the problem of under-treatment of pain, particularly among hospitalized patients with acute conditions and end-of-life cancer patients [5]. Thirdly, influenced by these movements, by the mid 1980’s, assessing pain in hospitalized patients became part of the increasingly popular patient satisfaction surveys developed and marketed by Press Ganey Associates [6]. By the year 2000, results of these surveys, including questions about pain treatment, became tied to hospital reimbursement by Medicare [6]. Because of this, hospital administrators began to push physicians to more aggressively treat pain [6]. Although the push from professional organizations was based in the desire to improve treatment of acute and cancer-related pain, doctors increasingly felt pushed to aggressively prescribe opiates to all patients who complained of any type of pain, and to view this as
best practice [6], despite there being little evidence that increased patient satisfaction with
treatment of pain led to improved patient outcomes [6]. Fourth, a movement sponsored
by the The Joint Commission (formerly The Joint Commission on the Accreditation of
Healthcare Organizations or JCAHO) introduced standards that tied the accreditation of
healthcare organizations to their screening for and treatment of both acute and chronic
pain. As with the reimbursement changes, these standards were designed to help health-care
organizations improve their care for patients with pain. Unintentionally, it incentivized
hospitals to prescribe more opiates for any patient who reported pain [7].

Perhaps coincidentally, as hospitals implemented these changes, pharmaceutical companies
developed and marketed patentable types of opiate preparations, particularly long-acting
preparations [8]. By the 1990’s, these companies had developed very aggressive marketing
campaigns that targeted doctors [9]. The campaigns utilized hospital policies that encouraged
doctors to treat pain more often with opiates. They also assured doctors that their new
opiate formulations had little or no addictive effect, and would not be dangerous for patients
[8]. This marketing information was based on two studies–one, a small chart review pilot
study published as a letter to the editor, and one study of patients with acute pain–both of
which suggested that opiate addiction in the acute setting was rare [8], [9]. These marketing
campaigns further encouraged the increase in opiate prescribing.

All these movements (the publicizing of the need to improve treatment of patients
with acute and/or terminal/cancer pain, the tying of patient satisfaction with their pain
treatment to hospital reimbursement, the treatment of pain being tied to hospital/healthcare
accreditation, and the increased and focused marketing of supposedly ‘safe’ opiates by
pharmaceutical companies to medical providers) contributed to a massive increase in opiate
prescriptions, leading to the current opiate crisis.

As the number of opiate prescriptions written in the United States increased, a resultant
increase in opiate abuse (both prescription and non-prescription) developed, and reached
crisis proportions by the early 2000’s [3]. Various methods of combating this crisis have been
gradually developed. For instance, in the mid-2000’s [10], many states began to develop on-line prescription drug monitoring programs (PDMPs) and eventually gave physicians and other health care providers access to those programs. PDMPs are online tracking programs that allow doctors, pharmacists, and others, to monitor patient prescriptions for and receipt of controlled substances such as opiates.

While PDMPs and other tools have helped stem the tide of opiate prescribing, there is still far to go in combating this crisis. Information on trends in opiate prescribing over the past decades, and how those trends may be changing, will be valuable in helping guide formation of government and healthcare policy as the crisis continues. Trend information may also help to inform individual prescribers, thus ultimately helping to decrease opiate over-prescribing.

The National Ambulatory Medical Care Survey (NAMCS) is an invaluable tool in monitoring trends in US medication prescribing. NAMCS is a survey of all patient visits to US physicians in outpatient offices [11]. According to the NAMCS website [11], Each physician [in the survey] is randomly assigned to a 1-week reporting period. During this period, data for a systematic random sample of visits are recorded by U.S. Census interviewers using a computerized Patient Record form. Data are obtained on patient characteristics such as age, gender, race, ethnicity, and visit characteristics such as patient’s reason for visit, physician’s diagnosis, services ordered or provided, and treatments, including medication therapy. In addition, data about the physician and their practice characteristics are collected during a survey induction interview. Patients and doctors are sampled in such a way as to accurately represent all outpatient (non-hospital) visits to all US physicians during each survey year (when used with calculated patient weights for each surveyed visit). The NAMCS survey was conducted intermittently from 1973 to 1981, again in 1985, and annually since 1989, and is therefore an excellent resource for analyzing prescription trends over time. Because formatting has changed over the years, this study utilizes only the data from 1993-2016.

This thesis analyzes trends in opiate prescribing over time. The analysis examines overall
opiate prescribing trends, as well as trends in prescribing opiates to patients suffering from various chronic conditions. The purpose of this analysis is to take advantage of modern data processing and analysis techniques to examine trends in opiate prescribing, particularly during the recent period of increased abuse of prescription opiates and overdose deaths from opiates. In addition, this analysis will examine whether there are specific characteristics of opiate prescribing which could be targeted in the efforts to reduce over-prescribing of opiates.

While the portion of the NAMCS database used in this study contains in excess of 20 years of data with more than 750,000 data points, these data are not centered specifically on opioid users or recipients. About 30,000 of the visits (representative of hundreds of thousands of visits via weighted samples) recorded across all years involved opiate prescriptions. Other data sets do exist that focus more exclusively on opioids, their prescription and use, but are closed-source and unavailable to us, and are limited in scope. The NAMCS database, because of its breadth and scope, is invaluable in examining these national trends in opiate prescribing.
Chapter 2. Literature Review

The rise in drug abuse and overdose-related deaths elevated the label of opioid crisis to opioid epidemic [3]. This relabeling motivated an increase in the study of opioid prescribing, illuminating many previously unknown facts related to this epidemic. For example, while many drug companies in the early 2000’s advertised that giving a patient with chronic pain an opiate prescription would not lead to opiate misuse, studies showed that this was not the case. For example, a study by Wisniewski et. al. in 2008 demonstrated that those who received legitimate opiate prescriptions were more likely to have Emergency Department visits for opiate misuse than those who did not [1]. In another study, patients receiving prescriptions for hydrocodone and oxycodone (two of the more commonly prescribed oral opiate medications prescribed for pain) were shown to be more likely to visit emergency rooms because of non-medical use of those drugs than patients who did not receive those prescriptions [12]. Deyo’s 2011 study showed that in 2003-2005, of patients with any opioid use, 36% had an emergency visit [13]. Deyo also notes that the incidents of psychological distress, unhealthy lifestyles, and over-utilization seemed to increase with length of time using opiate drugs [13]. These complications are most often associated only with long-term opiate users.

A study by Caudill-Slosberg et. al. [14] showed that the threshold for prescribing NSAIDS and opioids has dropped since 2000. In addition, several studies uncovered other important characteristics of the opiate crisis. One study showed that although prescriptions of opioids for musculoskeletal pain increased from 2% to 9% from 2000 to 2010, there was no increase in visits to physicians for musculoskeletal pain, illustrating that opiates were becoming more and more common for musculoskeletal pain than they had ever been in the past [14]. In fact, from 1996 to 2002, overall use of opiate pain medications increased 309% according to Zerzan et. al. [15]. Another study demonstrated that a significant increase in opioid prescribing was recorded from 2003 to 2009 [16], indicating that this problem has only continued to increase
At this time, in the mid-2000’s, prescription drug monitoring programs (PDMPs) started to become commonplace. A 2016 study shows that the implementation of PDMPs, and their peripheral policies, were directly correlated with a sustained decrease in opioid prescriptions \cite{17}. Unfortunately, a study done by Paulozzi suggested that PDMPs, while an important step forward in curbing the inappropriate prescription of opiates, had no impact on opiate-related mortality rates from 1999-2005 \cite{18}. It also appears that opiate prescription has increased dramatically for patients with a history of substance abuse, in spite of PDMPs being in place to help curb prescribing to patients with opiate-seeking behavior \cite{19}. Indeed, non-verbal and verbal behaviors can have a major effect on whether doctors prescribe opiates to patients from particular demographics; black males exhibiting ‘challenging’ behavior were more likely to receive a stronger opiate prescription than ‘non-challenging’ black males, while less-challenging white males often received stronger opiate prescriptions than white males exhibiting challenging behavior \cite{20}. In addition, rural residents are far more likely to receive opiates than non-rural patients \cite{21}, raising the question of whether training on the proper use of PDMPs and similar tools has propagated out to more rural areas. This finding was backed up by Luo et. al. \cite{22}, who found that geographic location and health insurance status were consistent predictors of opiate prescription 1996 to 1999.

Aside from the issue of containing the problem, patients receiving valid prescriptions for opioids from physicians are far more likely than non-prescription receivers to participate in non-medical use of opiates, and to have Emergency Department visits for over-use of those same opioids \cite{23}. It is a stereotype, whether warranted or not, that patients receiving prescriptions for specific addictive substances will acquire more of that substance than actually prescribed with the intent of non-medical use, hiding behind their prescriptions if caught with the drugs. This is at least part of why it is so concerning that opioid prescriptions have been increasing so much. For instance, although physical therapy is nominally a front-line treatment for lower back pain, patients suffering from this condition are more likely to be
prescribed opiates than to be referred to a physical therapist, especially in lower-income areas [24]. From 1997 to 2008, opioid prescriptions for chronic abdominal pain more than doubled [25], and from 2001 to 2010 opioid prescribing for acute and chronic musculoskeletal pain increased, although one study seemed to show that from 2006 to 2010 prescriptions for chronic pain visits plateaued [26].

For cancer patients, opioid use is especially controversial and concerning. In the UK, over 43.5% of cancer patients were prescribed opiates in the last three months of their lives [27], which many doctors feel is appropriate. However, even in the face of non-terminal cancer, opiate prescribing may be liberal, which may lead to long-term consequences. For instance, according to Sutradhar et. al., among cancer survivors, the rate of opioid prescription is much higher for patients diagnosed with any stage of cancer than for patients who had never been diagnosed with cancer [28].

In addition, many patients who should, because of their other medical conditions (kidney or liver disease, for instance), receive modified (lower) doses of opiates for their painful conditions, instead often receive typical or even high opiate doses. For example, patients suffering from renal (kidney) disease are less able to filter most substances (including opiates) from their blood stream, and the general consensus is that dosages of medications, including opiates (when indicated), ought to be modified. However, Droney et. al. showed that renal patients were often prescribed unadjusted amounts of morphine [29]. For these patients, although disease variables contributed to pain, psychological symptoms were most strongly associated with pain and opioid use. Since opioids are not prescribed for, nor designed to reduce, psychological distress, this trend in opioid prescription is especially concerning [30]. Interestingly, it seems that more than 50% of opioid prescriptions are for doses higher than the recommended dosing limit of 90 morphine milligram equivalents per day, and for periods of more than 6 months [31]. Further, studies not infrequently show that for patients receiving an opioid-acetaminophen combination drug, about 8% exceeded the recommended maximum daily dose [32]. In this study, of those receiving an opiate prescription for a
higher-than-recommended dose, 23.4% also had a diagnosis of liver dysfunction (meaning that their bodies were even less capable of filtering out the drugs than a patient with a normal liver).

Chou et. al. suggest that the extended prescription of opioids (>8 weeks) for the treatment of chronic pain has questionable benefits for individual patients and presents substantial public health risks [33], as discussed earlier. However, Bajwah somewhat refuted this in a study showing no increase in mortality for patients prescribed high- vs low-dose opiates [34]. While the reason for this inconsistency of mortality rates across increasing opiate dosages is unclear, it may simply be related to the likelihood of abuse not changing based on high- or low-dose opiates being prescribed.
We began by downloading the NAMCS data set from the NAMCS website, maintained by the US Center for Disease Control (CDC) [11]. The CDC readily offers this data set for research purposes, in a generally well-formatted and clean way. Each of the years from 1993-2016 came in its own file, which needed to be read in and processed individually. It is important to recognize that patient anonymity is of paramount importance. Because of this, the CDC only publishes about 10% of the data it collects, and purposefully delays publication for three or more years after the data are collected. Because of this, no data past 2016 are yet available to the public.

After loading the data into Pandas data frames, we began analyzing the information. Data in each year of the survey include patient characteristics such as age, gender, race, and ethnicity; visit characteristics such as patient’s reason for visit, physician’s diagnosis, services ordered or provided; treatments, including medication therapy; and the physician and their practice characteristics. The four categories of data extracted for this study include the following (each listed item included several columns of data):

1. Patient reason for visit (the patient’s explanation of why they were coming to see the doctor, including self diagnosis/diagnoses, reported by the patient at the beginning of the visit)

2. Physician diagnosis/diagnoses (assigned at the end of the visit, just prior to treatments/medications being ordered)

3. Medications prescribed (Including all columns with medication information)

4. Patient demographics (Including race, gender, age, method of payment, etc.)

While far more data were available, these categories best fit our application. Although the number of medications and diagnoses recorded in each survey year tended to fluctuate, varying anywhere from 3 to 5 diagnoses and from 8 to 30 medications, we decided to include
all of the information on diagnoses and medications available to us. This was because even when a patient visits the doctor for something other than a chronic condition, if a chronic condition exists, it is often treated (and therefore is listed as a diagnosis), even though it may not be the primary diagnosis. Similarly, if a patient has a preexisting prescription for opiates, it might be reordered during a visit, but not listed as the first medication, since it might not have been the ‘new’ prescription resulting from the current visit. Demographic information was important for analyzing trends in diagnoses and prescriptions.

From 1993-2015, diagnoses were reported using ninth-revision International Classification of Diseases (ICD-9) codes. These codes describe a diagnosis by a three-digit positive integer, which describes the main category of diagnosis, followed by a decimal point and up to two digits that describe the condition in more detail. For example, a patient with an ICD-9 code of 722.10 would receive the diagnosis of “Displacement of lumbar intervertebral disc without myelopathy,” while 722.1 codes to “Displacement of thoracic or lumbar intervertebral disc without myelopathy,” and 722 codes more generally to “Intervertebral disc disorders.” Because these codes were of variable length between 3 and 5, the NAMCS database generally stored the diagnoses as 5-character strings, where each character could be a number, but any digits of accuracy not coded would be replaced by a ‘-’. For example, 722.10 would be stored as ‘72210’, while 722 would be stored as ‘722-’. This was not true across all years, however. In 1993 and 94, the ICD9 codes were encoded differently for ease of use with statistical software available at the time. For numeric diagnostic codes, a ‘1’ was prefixed to form a 6-digit code, and for ‘V’ codes corresponding with general wellness-visits a ‘20’ was prepended. In addition, in each survey year there are codes that designated blank, illegible, or non-codable diagnoses; these were often unique from year to year.

To compensate for the differences across years, we re-coded the diagnosis codes from 1993 and 1994 to match the other years, recoded (as needed) the codes for blank, illegible, or non-codable diagnoses to all be the same, and combined data from all survey years, and then did each of our analyses on the entire data set as a whole.
To understand and translate the diagnosis code strings into diagnoses, we downloaded the data for all ICD-9 codes, the standard documentation for physician diagnoses, from [35] and [36]. We then built a script to reformat the numerical data strings from the NAMCS format into human-readable strings for when we wanted to know what they meant. This documentation also proved invaluable in helping us to identify specific types of conditions, such as chronic conditions of various types, which we needed to perform our analyses.

In 2016, diagnosis codes for the NAMCS database were updated to the ICD-10 standard, which includes many more diagnoses. While this allows a more accurate understanding of the conditions afflicting the US populace, the ninth- and tenth-revision codes have no one-to-one mapping from one to another. Because of this lack of a straightforward mapping, and because ICD-9 codes were used for so many of the years of data we were observing, we decided to use a general equivalence mapping (GEM) to map all of the ICD-10 codes in the 2016 data to ICD-9 codes, therefore standardizing the format and making analysis possible. We acquired these GEMs from [37].

A potential drawback of this mapping is that many diagnoses that may have been interesting to us were potentially lost in this translation. Because the ICD-10 codes include so many more potential diagnoses than the ICD-9 codes, and because we did not create the GEM ourselves, we can’t be sure that some diagnoses that we should have considered weren’t mapped to codes that we did not include in our list of ICD-10 codes being used. As a result, we found that some of the analyses have confusing results relating to 2016 and suspect that this may be part of the reason. Future research will have us carefully examining the GEM to make sure that we have the right diagnosis mapping.

Among the patient demographics, several obvious categories stood out as important, including age, gender, and race. The importance of some categories, such as the patient weights, were less obvious. Initially, we chose to leave out the patient weights, but then found out that rather than talking about physical weight, this category referred to the sample weight used in the NAMC survey, which is essential in accurate analysis of this data. There were
also some other interesting categories, such as payment type. Several, such as gestation week of pregnancy, applied to so little of the population that we chose to exclude the demographic information given by those columns.

After reading in the data, we combined and stacked the years based on column headings. We made the names of each column uniform by casting them all to upper-case, and then went through and replaced values that the documentation showed as relating to ‘blank’, ‘unknown’, ‘none’, or something similar with NaNs, 0s, or empty strings, depending on the column type.

In order to control for patients suffering from chronic conditions, we determined a set of diagnoses that seemed of interest to our study. These were diagnoses that generally are associated with some sort of chronic condition. Therefore, there was a greater potential for patients with these diagnoses to be prescribed opiates. These conditions included: patients suffering from malignant cancer, from some form of joint or osteoarthritic pain, heart and lung conditions, kidney, and liver conditions. Lists of diagnosis codes corresponding with each general diagnosis were developed by finding every ICD-9 code that correlated with those conditions (for instance, all of the ICD-9 codes for malignant cancer of any kind, all of the ICD-9 codes for any heart condition, etc.). We then used these lists to assign each patient to a particular category. This one-hot encoding of the chronic conditions suffered by each patient, including if they did not suffer from any chronic condition, helped us in our analyses.

We then examined trends in opiate prescribing over the 20 years of this study, both in general, and in particular to patients with a diagnosis in each of these groups. We performed further in some instances also looked at demographic information within these groups. Our code, along with the lists of opiates and conditions, can be found at https://github.com/crsawyer314/NAMCS-pain-and-chronic-conditions.
Chapter 4. Results

The purpose of this thesis was to examine trends in opiate prescription, specifically to those suffering from chronic degenerative diseases. We hoped to be able to advise prescribing physicians on the demographics who most often receive opiates so that interventions could be put in place to help curb the opiate crisis. What we found relating to opiate prescribing at large was hopeful, as over-all trends seem to show decreasing opiate prescribing. However, prescriptions to those suffering from chronic conditions have increased over time. Since chronic conditions make patients especially vulnerable to the negative side effects of medications taken, this trend is of significant concern. Further compounding the dangers to this group, many patients diagnosed with chronic conditions are also part of an older age group, which increases their risk of complications from taking opiate medications. Throughout this section we examine specific elements of the NAMCS database, and raise specific concerns where they exist. Areas of important future research are identified.

We also ran several machine learning models on the NAMCS database in an attempt to find whether patients could be classified into the group of ‘opiate receivers’ or ‘non-opiate receivers’. While not all methods were suited to this type of classification, we were able to predict whether a patient would receive an opiate with 78.2% accuracy and 79.9% recall. This leads us to believe that there are very real, if non-obvious, trends in patients who receive opiates, and we hope that this model can be used to help physicians overcome any inherent bias they may have in opiate prescribing, and reassess whether patients should actually be given an opiate or whether other interventions are more appropriate.

As can be seen in Figure 4.1, opiate prescriptions to adult patients seen in the outpatient office setting increased dramatically during the first fifteen years of this study. In spite of the recognition of the opiate crisis in the mid 1990’s, and the various public health interventions that attempted to curb the crisis, opiate prescribing continue to increase, with a dramatic rise in the mid-2000’s (about 2004-2010), peaking in approximately 2011. In that year,
approximately 5.3% of all patients seen by a medical provider were given a prescription for opiates. The next year opiate prescribing finally began to decrease, but the decrease has been small. As of 2016, the percentage of patients receiving an opiate prescription at an outpatient visit had only been reduced to 4.15%.

Although the rate of opiate prescription remains high, the overall trend seems to be one of gradual decrease. This indicates that the many interventions that have been put in place in the recent years are taking effect and helping to resolve the issue of opiate over-prescription. For our purposes, we focus on patients who received opiate prescriptions and who were also diagnosed with a chronic condition (e.g., chronic back pain, diabetes, etc.), and examine if, among the patients who receive opiate prescriptions, these diagnoses of chronic conditions are becoming more or less common. It is presumed that there has not been a dramatic increase in acute problems (such as a broken leg, etc.) that would justify an opiate prescription. It is therefore presumed that medical providers have begun to justify opiate prescriptions more and more for chronic conditions instead. To examine this concern, we further analyzed the data.
We first examined the trends over-all in the diagnosis of chronic conditions. Figure 4.2 shows the percentage of all patients at outpatient US office visits who were diagnosed with a chronic condition. In the early 1990s relatively few patients treated by physicians in the outpatient setting were diagnosed with chronic conditions, but as time passed, an increasing percentage of patients were diagnosed with a chronic condition. While the rate of increase was fairly steady through the 1990’s and early 2000’s at around a 42% increase each year, starting in 2010 the rate grew to a 148% yearly increase in chronic condition diagnoses.

This increase in the diagnosis of chronic conditions could be happening for several reasons. First, this may be a reflection of an aging population in the US, as increased age is highly correlated with increased chronic conditions, and the increase seen starting in 2010 would correlate with the majority of the baby boomer generation entering their sixties and early seventies. Second, this increase in chronic condition diagnoses could be due to the increase in obesity in the United States, as nearly all of the conditions examined are worsened by obesity.

It is especially interesting to note that this sudden increase in chronic condition diagnoses
came just at the time when overall opiate prescriptions started its major decline. As shown in Figure 4.3a chronic condition patients have not followed the overall trend of receiving fewer opiates, but have instead been prescribed opiates more often.

Figure 4.3: These charts show the percentage of all patients who received an opiate prescription were diagnosed with a chronic condition (4.3a) or who were diagnosed with a non-chronic condition (4.3b). As shown by the regression lines, prescriptions of opiates to patients diagnosed with a chronic condition have increased at 120.3% yearly, while opiate prescriptions to patients not suffering from chronic conditions have decreased at about 120.3% yearly.

Figure 4.3a shows that most patients in the early years of this study did not have a chronic condition, so likely were suffering from acute conditions (for example a broken bone or other recent injury). As can be seen in Figure 4.3a however, over the past 20 years, the percentage of patients who received an opiate prescription and who were also diagnosed with a chronic condition has increased fairly steadily. Of note, the abrupt increase in 2016 may not be a true reflection of the situation, since the change from ICD-9 to ICD-10 diagnosis codes may have caused some discrepancies in the data due to incomplete translation maps. In spite of the potential discrepancy in 2016, there is a clear growth pattern of around 120.3% annually.

Since the group described in Figure 4.3a is the percentage of opiate-prescribed patients who were diagnosed with a chronic condition, it may be useful to recall both the trends both in over-all opiate prescription (seen in Figure 4.1) and trends over-all in the diagnosis of chronic conditions (seen in Figure 4.2). Although opiate prescribing has increased and decreased over the time period of this study, the diagnosis of chronic conditions has only increased...
during that same time. In fact, the rate of greatest decline in opiate prescription correlates with the rate of greatest growth in the diagnosis of chronic conditions. This means that the steady growth of chronic condition patients among those patients receiving opiates may simply reflect the increasing numbers of patients over-all who are diagnosed with a chronic condition. As such, this trend may also simply be a reflection of the general population growing older and having more chronic conditions.

However, of concern is that these results may instead reflect a shift in prescribing patterns. As shown in Figure 4.3b, whereas in the early 1990’s, most opiates were prescribed only for patients with non-chronic, acute conditions (such as a broken bone), it could be that over the time period of this study, doctors shifted their practice more and more towards prescribing opiates to patients with chronic conditions instead. If this is an accurate representation of what has happened, it maybe that pharmaceutical companies advertising and pushing opiates for treatment of ‘pain’ led doctors to respond by prescribing opiates more and more often to patients who have chronic pain from various chronic conditions.

As Figure 4.3a shows, the patients receiving opiates are increasingly patients that have diagnoses of chronic conditions, so we next examined this trend to see if, among the patients receiving opiates, there were demographic groups that were being diagnosed more often with chronic conditions than others.

![Figure 4.4](image)

(a) Race of opiate-prescribed chronic patients  
(b) Gender of opiate-prescribed chronic patients

Figure 4.4: Percent of opiate-prescribed patients diagnosed with chronic conditions, by race and gender. The data for both figures were grouped by 2-year increments to provide smoother trends and to ensure sufficient data for each point analyzed.
In Figure 4.4a, we looked at the diagnosis of chronic conditions among patients who received opiates by race (black versus white). (Other race designations were not included since in many of the years there were insufficient data on other races/ethnicities.) While there was some variability across the years, in general the trends were the same among these two groups. Both groups show a relatively similar increase over time in the percentage of patients diagnosed with a chronic condition among opiate-receiving patients.

In a like manner, Figure 4.4b looked at patients who received opiates, by gender. The overall trend of upward growth that exists across all opiate prescriptions can be observed across both genders as well. No significant difference exists in chronic condition diagnoses to male and female among patients receiving opiate prescriptions.

The steady increase in the percent of patients diagnosed with a chronic condition among all patients prescribed an opiate could be explained in two ways. The first is that there is a simple increase in opiate prescribing to patients with chronic conditions. Or, it could be that patients who are already receiving opiates are being diagnosed with a chronic condition as justification for the opiate prescription. To help clarify this, we next looked at all patients with chronic conditions to see if, among this population, there has been an increase in the percentage who receive opiate prescriptions.

Although there is some discussion about the appropriate use of ‘gender’ versus ‘sex’ based on self-identification or label assigned at birth, we use the term ‘gender’ in this thesis. While some patients were assigned an imputed gender, most survey participants self-identified to the surveyor as either male or female, leading us to believe that gender is an appropriate label for this setting.
Figure 4.5: Percentage of patients with a chronic condition who receive an opiate prescription. Trend lines show the rate of increase or decline in opiate prescriptions over time. Data was combined into two year increments to assure sufficient data for analysis.

In Figure 4.5 it can be seen that among all patients who have a chronic condition, the percentage who received an opiate prescription was relatively stagnant through 2003, with prescriptions increasing around 2.0% per year. Then, from 2003 to 2009, the percent of patients with chronic conditions who were prescribed an opiate skyrocketed at a rate of 96.8% increase each year until 2009. From 2009 onward, opiate prescriptions to this group of patients has decreased at a rate of about 41.3% per year.

Examining trends in the demographics of those patients with chronic conditions who are receiving opiate prescriptions could shed light on who among patients suffering from chronic conditions received opiates. We looked at some of the demographics of this group of opiate-receiving patients.
(a) Race of chronic patients prescribed opiates   (b) Gender of chronic patients prescribed opiates

Figure 4.6: Patients diagnosed with chronic conditions that were also prescribed opiates, by race and gender. Figure 4.6a shows that blacks who had been diagnosed with a chronic condition received opiates about 3% more often than whites in many years of this study. Figure 4.6b shows that females diagnosed with a chronic condition receive opiate prescriptions more often than males, although the difference in this trend is much less extreme. Statistical significance of these differences could not be calculated.

Figure 4.6 examines demographic differences in the percentage of patients diagnosed with a chronic condition who were also prescribed opiates. While Figure 4.4 shows that neither race nor gender made a significant difference for opiate-prescribed patients diagnosed with chronic conditions, Figure 4.6 shows that for patients suffering from a chronic condition, there was a significant difference in opiate prescriptions to particular races and genders.

While the NAMCS database does allow accurate calculation of confidence intervals around trend lines, due to hidden variables that can be manipulated by methods only available in specialized statistical software not used in this thesis, these calculations can not be made currently. Because of this, we are unable to determine if there is a statistical significance in the apparent difference between the races and genders seen in Figure 4.6. However, if these differences are shown to be statistically significant, it could indicate that, at least among patients with chronic conditions, the stereotype of black patients receiving opiate prescriptions more commonly than white patients, and the stereotype of (at least middle-aged) females

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2 The differences between Figures 4.4 and 4.6, while subtle, are important. Figure 4.4 looks at percentages of opiate-receiving patients who are diagnosed with a chronic condition (opiate receiving + Chronic condition / opiate receiving), while Figure 4.6 looks at percentages of patients with a chronic condition who are prescribed opiates (chronic condition + opiate receiving / chronic condition.)
receiving opiate prescriptions more often than males may, in fact, to be justified. However, as previously explained, no statistical significance was able to be calculated around these perceived differences.

As can be seen, for patients with chronic conditions, whether examined as a group or by demographic factors, the pattern of opiate prescribing, while not directly mirroring the general trend in over-all opiate prescribing (seen in Figure 4.1), is nevertheless very similar to overall opiate prescription rates. These rates started to increase dramatically starting about 2004, peaked in about 2011, then began to gradually decrease. In contrast, among patients who receive opiates there is a steady and continuing pattern of increasingly being diagnosed with a chronic illness (Figure 4.3a).

This steady increase in chronic diagnoses among opiate-receiving patients does not follow the over-all trends of opiate prescriptions, nor does it follow the percentage of patients diagnosed with a chronic conditions who were then given an opiate prescription (see Figure 4.5). One possible explanation for this is that the same general group of patients could be receiving opiate prescriptions across the years, and that the physicians prescribing the opiates are simply shifting from using acute diagnoses to chronic diagnoses as justification for an opiate prescription.

Because many patients with chronic conditions are older patients, we thought it prudent to look at age distribution of patients with chronic conditions who received opiate prescriptions.
Figure 4.7: Average age distribution of opiate-receiving patients over time. Blue represents the age distribution of patients prescribed an opiate who were diagnosed with a chronic condition, whereas orange represents opiate-prescribed patients who were specifically diagnosed with a pain condition.

Unfortunately, Figure 4.7 shows that the average age of a patient who is receiving an opiate prescription and is diagnosed with chronic pain is centered around the late 50s, and is concentrated between 40 and 80 years of age. The same holds true for patients receiving an opiate prescription diagnosed with chronic pain.

This is an unfortunate situation. Opiates are known to be effective at treating certain types of pain, but for chronic pain, generally other interventions such as physical therapy have been shown to be more effective and less risky for long-term treatment. Thus an average age over all years that is centered around the older part of the population is cause for concern. This age group represents patients that are at the highest risk for poor outcomes when treated with opiates. This represents an important public health issue that should be addressed immediately if confirmed by future research.
Figure 4.8: The average age of opiate-receiving patients over time. Although the variance is higher among patients diagnosed with chronic conditions, the same trend of increasing average age is observed among both the group of all patients receiving opiates, as well as among those suffering from chronic conditions who are prescribed an opiate medication. In both instances, ordinary least square regression shows an average yearly growth rate close to 32%.

Figures 4.8a and 4.8b show trends in the average age of patients who were prescribed opiates over the course of this study. It is clear from the superimposed trend lines that both among all opiate-receiving patients, as well as specifically among those diagnosed with a chronic condition and prescribed and opiate, that the average age of these patients is increasing. While there is wider variance in the data points in Figure 4.8b, the average yearly growth as calculated by ordinary least squares regression in the two groups is nearly identical.

While overall opiate prescribing may be decreasing, the patients who are continuing to receive opiate prescriptions are of increasing age. This represents a significant public health issue that has not been previously reported and is of utmost concern. Future research should consider the validation of this trend a priority. The rising age of the opiate-receiving population, both generally and more specifically among chronic condition patients, is of considerable concern particularly because it tends to be the elderly who suffer the most from untoward side effects of opiate medications. It is well-known that as a person ages, opiates and their side effects become more problematic, and increasingly dangerous.

In an effort to further clarify this trend, we next created a concentration map showing the ages of all patients who have received opiate prescriptions over the years of the study.
Figure 4.9: The concentration of opiate prescription by age over time. More red indicates a higher concentration, while blue is less. A clear trend is visible among all opiate-receiving patients; the age at which the highest concentration of patients has been receiving opiates has been going up over the years. The same trend is observable, though less obvious, among patients suffering from chronic conditions who receive opiates.

Figure 4.9a shows the ages of all patients who received outpatient opiate prescriptions during the years of the study. This mapping shows that in the earliest year of the study (1993), the largest group of patients who received opiate prescriptions were in approximately the 35-45 year age range. Ten years later, in the mid 2000’s (about 2005), the largest group of patients who received opiates were in the 45-55 year age range. Ten years later, around 2015, prescriptions of opiates were concentrated in the 55-65 year age group. In other words, it is highly likely that most opiate prescriptions are being given to the same group of patients—patients who were in their late 30’s to early 40’s in the 1990’s, and who were, by the end of the study, in their late 50’s to early 60’s.

This same pattern is seen in Figure 4.9b, albeit not quite as clearly, when looking at patients who received opiate prescriptions who had been diagnosed with a chronic condition. It appears that here as well, in the early years of the study the highest concentration of opiate prescriptions to these patients was given to patients who were in their early to mid 40s. Ten to fifteen years later the highest concentration of opiate prescriptions were given to patients in their mid 50s. Another 10 years later, around 2015, the highest concentration centers around patients in their 60s.

These two figures raise strong suspicion that the same cohort of patients is receiving most
of the opiate prescriptions across the years of this study. In other words, a group of patients appear to have been started on opiates 20 years ago when they were in their 30s and 40s, and that same group of patients continues to receive opiate prescriptions across time, and were in their 50s and 60s at the end of this study.

While NAMCS data cannot show trends for individual patients, these charts raise strong concerns of a trend of continued opiate prescribing to a specific group of patients that is not only aging, but is increasingly being diagnosed with chronic conditions that complicate opiate prescribing and significantly increase individual patient risk of bad outcomes.

While additional research will have to be done to confirm this pattern, it represents an urgent public health issue that needs to be addressed. If this trend is indeed true rather than an artifact of the data, it is essential that extensive efforts be developed to help these older patients wean off of opiates, and to warn prescribers of the increased risk they are giving to their patients who continue to receive these medications as they age.

We next turned our attention to opiate prescribing to patients with specific chronic conditions. Figure 4.10 considers all patients prescribed an opiate who were diagnosed with various conditions that were likely to represent chronic pain syndromes of one type or another.

In Figure 4.10 we examine trends in the percentage of opiate-prescribed patients diagnosed with various conditions that likely represent chronically painful conditions. Figure 4.10a, which represents all patients diagnosed with any painful condition, is similar to Figure 4.3a, which represents opiate receivers who had a diagnosis of any chronic condition (whether directly pain-producing or not). Patients who received opiates and were diagnosed with a chronic condition tended to be diagnosed with a chronically painful condition far more than they tended to be diagnosed with other chronic conditions such as heart disease. In fact, the rates of opiate prescription to patients suffering from such conditions as heart disease, chronic lung disease, or malignant or benign cancer were so low as to preclude including any trend data in this paper. The number of data points representing patients suffering from these conditions and receiving an opiate prescription was so low that we couldn’t draw any
meaningful conclusions about opiate prescriptions to patients with these non-painful chronic conditions.

Figure 4.10: Percentage of opiate-prescribed patients diagnosed with various pain conditions. While the rate of prescription rose about 120.3% each year over all pain conditions for patients prescribed opiates, it rose only 90.2% each year for the group of patients suffering from any form of joint pain or osteoarthritis, and for neck and back pain patients the prescription rate grew about 64.1% each year. Meanwhile, the prescription rate for patients suffering from headache conditions actually decreased by about 10.7% each year.

Figure 4.10b looks specifically at pain of the neck back, and knee (traditionally areas of chronic pain), along with osteoarthritis and rheumatism. Osteoarthritis was included in this grouping because in the US in particular, it is the primary cause of chronic joint pain. In this figure we can see that these painful joint and osteoarthritis-related diagnoses constitute a large percentage of the painful conditions diagnosed among opiate receivers.

While NAMCS records do not distinguish between acute pain back or neck pain and chronic back or neck pain, it is unlikely that the majority of the patients with neck or back
pain had acute issues. Rather, it is far more likely that they had chronic neck or back pain problems. Traditionally, neck and back pain have been considered to be some of the more common diagnoses among patients who receive opiate prescriptions. However, Figure 4.10c shows that only a very small percentage of patients receiving opiates have had one of these two diagnoses. This trend appears to have dramatically changed in the last two years of the study, when there was a dramatic increase in these diagnoses among opiate-receiving patients. The reason for this sudden increase is not clear. Overall, this increase in the diagnosis of neck and back pain among patients receiving opiates is unsettling. Opiates have been repeatedly shown in the literature to be very poor treatment for chronic neck or back pain.

Another set of diagnoses often considered common among opiate-receiving patients are migraines and other headaches. However, as can be seen in Figure 4.10d, not only do these diagnoses represent only a small fraction of the diagnoses given to patients who receive opiates, but in a somewhat surprising trend, they have become less and less common among opiate-receiving patients over the course of this study. Perhaps this represents one area where anti-opiate initiatives were effective. If so, future research that focuses on this area might be able to determine why the efforts to decrease opiate prescribing were effective for headache syndromes, and perhaps lessons learned could be applied to help decrease opiate prescribing to patients with diagnoses of other chronic conditions. Alternatively, perhaps this study simply captured a time period when alternative therapies were being developed and were found to be very effective in treating chronic headache conditions that were not available just before this study began.

Looking at the 4 charts above in 4.10, we can see that while overall, the diagnosis of chronic pain conditions as justification for an opiate prescription have increased dramatically (regression shows 120.3% growth), each of the categories contributes in specific ways. Headache, in particular, has decreased as a diagnosis for those receiving opiates, showing a 10.7% decrease. All joint pains and osteoarthritic conditions together show a 90.1% increase, with just neck and back pain contributing a 64.1% increase. Again, while a higher proportion of opiate
receivers are diagnosed with chronic pain today than twenty years ago, headaches as a justification for an opiate prescription has decreased.

It is worth noting that, as has been previously mentioned, the 2016 diagnosis data was coded differently than all other years used in this thesis. As such, some doubt has been cast on whether the trends reflected in the 2016 data present an accurate picture. Although the accuracy of the 2016 data cannot, at present, be verified completely, the trends observed and commented on previously still hold when the 2016 data is ignored. Average trends were different, however. All chronic pain conditions increased from 1993 to 2015 at an average rate of 93.4% each year, all joint pain grew 72.1% on average, and neck and back pain grew at 34.0%, while headache conditions decreased 9.4% each year on average.

4.0.1 Machine Learning. Attempting to classify opiate receivers in the NAMCS database using machine learning is a perfect example of imbalanced classification. Of the records available to us, 18,024 had received an opiate prescription, while 454,706 had not. This meant that only 3.81% of all data points reflected an opiate prescription, making any guess of ‘patient did not receive opiates’ correct 96.19% of the time. Using various methods, including XGBoost, random forest, and logistic regression\(^3\) the result was the same; the method might get slightly better accuracy than always guessing ‘no’ some of the time, but generally performed the same or worse over several different test-train splits.

There are a few different ways of getting around the imbalanced classes in imbalanced classification; upsampling, downsampling \[39\], and a method specifically designed for imbalanced classification called SMOTE \[40\]. In the case of upsampling, data points from the smaller class are copied at random until they match the size of the larger class. With downsampling, similarly, data points from the larger class are randomly deleted until the two classes are of equal size. With SMOTE, random perturbations are made along linear interpolations between data points in the smaller class, and data points are randomly generated from the resulting perturbations.

\(^3\)For a more detailed explanation of what these algorithms are and how they work, see \[38\].
In the case of this thesis, each method was attempted in turn with differing results. In the case of a random forest classifier on the unaltered data, accuracy was 96.8%, but recall was a mere 18.8%. Accuracy is how often the classifier guesses correctly, while recall is how often the classifier correctly guesses a true positive [41], in this case correctly guessing when a patient was prescribed opiates. When the same random forest classifier was run on downsampled data, its accuracy was 78.2%, while recall was 79.9%. On upsampled data, accuracy was 96.7%, while recall was 21.7%. For each of the sampling techniques, the data was split into a testing and a training set, then the training set was sampled in the indicated way, following which the test set was used to gauge accuracy and recall. Especially in the case of upsampling, if the data was upsampled and then split, the accuracy and recall are bound to be unfairly imbalanced towards perfect accuracy and recall, simply because the data points would have been replicated.

While we had high hopes that the SMOTE method would perform well, we discovered that it actually performed about the same with a random forest as guessing all ‘no’, both in accuracy and recall. Its accuracy was 96.1%, while recall was 25.9%. We believe this is at least partially because the samples in the NAMCS database have patient weights associated with them, and perturbations based on linear interpolations between data points would fail to accurately reflect the correct weighting of patient data.

After observing how the different sampling techniques performed on random forests, and why they performed in that way, we decided to focus primarily on downsampled data for the other techniques we tried. When we used logistic regression to classify opiate receivers or not, there was some interesting behavior observed; when we did not include any of the engineered features, accuracy was 51.3% and recall was 67.3%. When we included the ‘chronic condition’ column, accuracy reduced to 36.4% but recall increased to 77.6%, and upon including the ‘pain’ column as well, accuracy again went down to 17.0% while recall increased to 91.7%.

We also attempted to use an XGBoost classifier on the data. The data without any engineered columns achieved an accuracy of 74.3% and a recall of 74.4%, while the inclusion
of the ‘chronic condition’ column increased accuracy to 75.0% while decreasing the recall to 74.1%. Including the ‘pain condition’ column resulted in an accuracy of 74.6% and a recall of 73.7%.

In using the XGBoost algorithm, one benefit is that the parameters can be tuned to achieve better results. While parameter tuning is available for many machine learning algorithms, the tuning for XGBoost can be largely performed by hand without needing to run an exhaustive grid search. In the case of this thesis, the parameters that we experimented with most were the maximal tree depth, the learning rate, and the number of estimators. While certain values did give us better models than others, what we found was that no particular set of parameters gave us much worse or much better accuracy than any others; at worst, we got about 73% accuracy or recall, and at best they were around 75%.

An additional benefit of using the XGBoost algorithm is that we were able to determine the importance of each feature in the model. What we found consistently across each model was that the first, or primary, diagnosis was most important and informative for the model, closely followed by the primary reason for visit, or patient self-diagnosis. This indicates that most health care providers are primarily concerned with prescribing opiates based on the conditions that patients either exhibit or describe. However, after these comes age in importance. As mentioned earlier in this thesis, older patients receive opiates far more often than younger patients. Using age as a deciding factor in prescribing opiates is probably causing patients more complications than necessary. We hope that getting these models into the hands of health care providers can help them to reassess their prescription practices in healthy ways, leading to patients getting the care that they need.

Although we attempted to run a neural network classifier on the data, we quickly ran into several complications. The main complication was that, although the majority of the data was represented numerically, each of those numbers in fact represented a category. With some categorical columns having upwards of 900,000 different potential entries, one-hot encoding was infeasible, and other encoding schemes that would allow the neural network to
understand the categorical data were impractical at best. In the end, we decided that neural networks were unsuited to this particular problem, though with more processing they may be an interesting potential application.
Our original intent in conducting this research was to predict and/or identify which factors were most associated with opiate abuse. However, the data we have are not sufficient to answer this question. Rather, it is able to help predict which patients are most likely to receive an opiate prescription, based on trends over time. It could be easy to confuse the situation and say that a patient who was prescribed opiates will abuse them, but this misconstrues the information we have and could be harmful to patients in the future who actually ought to receive opiates for medicinal purposes.

In addition, our analysis revealed some demographic trends in opiate prescriptions. For example, patients from the older population, especially with pain syndrome diagnoses, are more likely than others to receive opiate prescriptions. These trends should be considered correlative and not causal—useful for approaching and trying to solve the important issue of opiate over-prescription. This data is not useful for definitive conclusions when deciding whether or not to prescribe an opiate.

While our machine learning models, as of now, do not actively harm anyone, using the models could be potentially both dangerous and helpful to future patients. The results of this project may help alert doctors of problematic prescription trends, and help them avoid prescribing opiates based on inherent group biases. However, this model should not be used to prevent anyone from receiving necessary health care.
Chapter 6. Future Research

In the future, we hope to continue this project in meaningful ways. Opiate prescription continues to be a major issue in most areas of healthcare at present. As this study illustrates, while the percent of patients diagnosed with pain has not increased in major ways over the last decades, the level of opiate prescriptions for pain-diagnosed patients has gone up dramatically. This is one symptom of a multi-faceted problem, which is further exposed in this study. As we continue to do research in this area, we hope to discover more trends around opiate prescription, especially trends showing over-prescription for certain conditions, leading to development of helpful public and private policy changes.

In particular, we plan on further examining trends in opiate prescription as they relate to particular chronic conditions over time, such as osteoarthritis. We also want to examine how opiate prescriptions have been affected by the existence of PDMPs and other mitigating legislation. While the NAMCS database does not differentiate every state, data from the most populous states can be pulled out, and major regions of the US can be controlled for. This would allow examination of whether particular regions or groups of states are more likely to prescribe opiates for particular conditions, etc. Examinations of trends over time would also assist in helping to illustrate whether or not programs such as PDMPs had an influence in the areas where they were first established as compared to other areas.

We would also like to examine more thoroughly the apparent trend of a particular cohort of patients receiving more opiates over time than other groups at similar times.
This research illuminates trends in opiate prescribing to US patients seen in non-hospital settings. It considers patients diagnosed with a variety of chronic conditions.

As we conducted this study, we found various trends and patterns in opiate prescription. Important findings include the following.

First, patients in their fifties and sixties, appear to be the patients who have typically received the highest number of opiate prescriptions. This is very concerning, given that patients who receive legitimate opiate prescriptions are the patients most likely to over-use opiates (including non-prescribed opiates). If patients in their fifties and sixties suffering from chronic conditions are being prescribed opiates in large numbers, it follows that we are putting a large number of our future elderly patients at increased risk of opiate misuse.

Secondly, as these patients age, the side effects of opiates become more and more significant. If these patients actually continue to receive opiate prescriptions, as seems likely from other research, they are at increased risk of serious complications, including death, from opiate use.

Third, our study shows that when looked at in the aggregate of all patients receiving opiate prescriptions, there is a clear trend that seems to support the concern that once opiates are prescribed, they will continue to be prescribed. This is most clearly illustrated in Figure 4.9a which shows that in the early 1990’s, patients in their 30’s and 40’s received the most opiates. In the early 2000’s, patients in their 40’s and 50’s were receiving the most opiate prescriptions. In the early 2010’s to 2015, this number had again shifted so that most opiate prescriptions were being written for patients in their 50’s and 60’s (and by 2015 seems to be shifting towards patients in their 70’s).

While this database is unable to connect individual patients with prescribing over time, the ages that many patients are being started on opiates is a cause for concern. Once prescribed opiates, most patients will likely continue on opiates as they age—and may even start receiving ever-increasing doses of opiates. This is a very concerning trend and warrants
immediate further research. It would also be reasonable to develop rapid public health interventions alerting providers to this concerning trend, and perhaps even pushing providers to focus on rapidly de-escalating opiate prescriptions to their most vulnerable elderly patients.

One positive finding of this study is an overall decrease in outpatient opiate prescribing that began in about 2011, which may actually represent a downward trend (data is insufficient to confirm this at this point). This may indicate that the programs put into place in the early 2000’s are finally taking some effect. It does seem to correlate with changes in policies by the various health care accrediting agencies, as well as government payment systems (such as Medicare) that de-emphasized the treatment of all pain with opiates and shifted to a more balanced approach. This gives hope for further positive improvement in this area.
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Bibliography


