I, David Charles Randolph M.D., hereby submit this original work as part of the requirements for the degree of Doctor of Philosophy in Epidemiology (Environmental Health).

It is entitled:
Comparisons of All-Cause Mortality for Chronic Benign Pain Patients Prescribed NSAIDs only, Opiates or Opiates and Adjuvants

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Comparisons of All-Cause Mortality for Chronic Benign Pain Patients Prescribed NSAIDs only, Opiates or Opiates and Adjuvants

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ABSTRACT

Summary of Background Data: Trends of increasing mortality with prescription opiate use have been reported in multiple publications. In populations with CNMP, adjuvant medications are commonly combined with opiates to decrease symptoms and/or side effects. Studies evaluating ACM of these combinations have not been reported in a workers’ compensation population.

Objective: To determine the relative risk and predictors of all-cause mortality (ACM) among workers’ compensation patients prescribed opiates for chronic non-malignant pain (CNMP) alone and in combination with commonly utilized adjuvant medications compared to those taking NSAIDs only.

Methods: A historical cohort study of workers’ compensation population in Ohio from 01/01/2000 to 06/10/2011 was conducted. NSAIDs only patients (controls) are compared to cases who are prescribed short acting opiates only (SA), short and long acting opiates (SLO), short and long acting opiates and/or anxiolytic and/or sedative and/or hypnotic medication (SLO + ASH), and short and long acting opiates and/or any muscle relaxers and/or antidepressants (SLO + MR/AD). Outcome of interest is ACM. Relative risk and adjusted risk factors of ACM are presented for each medication group.

Results: When comparing to NSAIDs only subjects, patients taking SLO + ASH have the highest RR for death, 3.22 (95% CI, 1.60-6.94). Age, sex, dose and duration on medications are not significant predictors of mortality.

Patients who are prescribed SLO + MR/AD also have increased risks of mortality, RR 1.73 (95% CI, 1.15-2.59). Age, sex and the number of emergency room visits are significant predictors of ACM.
SLO and SA opiates only groups have ACM RR of 1.57 (95% CI, 0.92-2.71) and 1.23 (95% CI, 0.89-1.69) respectively. Age and total medications prescribed are significant predictors of ACM in both of these groups.

**Conclusion:** The use of any anxiolytic, sedative, and/or hypnotic medications with short and long acting opiates in combination poses a significant increased risk of ACM. A lesser, but still highly significant risk of death is noted when combining SLO and MR/AD medications. Health care providers should be aware of these risks to provide safe medical care for the injured workers.
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# TABLE OF CONTENTS

ABSTRACT .............................................................................................................................................................................. ii

ACKNOWLEDGEMENTS .................................................................................................................................................................. v

TABLE OF CONTENTS ........................................................................................................................................................................ vi

LIST OF TABLES AND FIGURES ......................................................................................................................................................... viii

CHAPTER ONE: INTRODUCTION .......................................................................................................................................................... 1

INTRODUCTION AND SPECIFIC AIMS .......................................................................................................................................................... 1

Hypothesis: .......................................................................................................................................................................................... 3

Specific Aims: ....................................................................................................................................................................................... 3

Significance: ......................................................................................................................................................................................... 3

Possible mechanisms of cardiac toxicity of opiates: ............................................................................................................................. 4

Prolongation of the QTc interval ............................................................................................................................................................. 4

Blockade of potassium channels ...................................................................................................................................................... 4

Direct cardiac pathology .................................................................................................................................................................. 5

Toxic effects of commonly used opiates: .............................................................................................................................................. 5

Methods of administration of opiates/ opioids ...................................................................................................................................... 7

Long vs. short acting opiates ............................................................................................................................................................... 8

IRB APPROVAL .................................................................................................................................................................................... 9

CHAPTER 2: COMPARISONS OF ALL-CAUSE MORTALITY FOR CHRONIC BENIGN PAIN PATIENTS PRESCRIBED NSAIDS ONLY, OPIATES OR OPIATES AND ADJUVANTS .................................................................................................................. 10

Introduction .................................................................................................................................................................................... 10

Methods ............................................................................................................................................................................................ 12

Study population ................................................................................................................................................................................. 13

Outcome Measured ............................................................................................................................................................................ 13

Statistical Analysis ........................................................................................................................................................................... 13

Results: ................................................................................................................................................................................................ 15

Unadjusted Relative Risks of All-Cause Mortality .............................................................................................................................. 16
Predictors of All-Cause Mortality ................................................................. 16
Discussion: ....................................................................................................... 17

Opiates and anxiolytic/sedative/hypnotics ...................................................... 18
Opiates and muscle relaxants/anti-depressants.............................................. 19
Short and long acting opiates..................................................................... 21
Short acting opiates only ............................................................................. 22
All opiates...................................................................................................... 23
Conclusions .................................................................................................... 23

Table 1. Short and Long Acting Opiates .......................................................... 25
Table 2a. Baseline Characteristics of Patients with Medications of Interest .......... 26
Table 2b. Baseline Characteristics of Patients with Medications of Interest (Cont.).... 27
Table 3a. Univariate Analysis of Predictors for All-Cause Mortality .................. 28
Table 3b. Univariate Analysis of Predictors for All-Cause Mortality (Cont.) ......... 29
Table 4- Unadjusted Relative Risk of All-Cause Mortality.............................. 30
Table 5a. Multivariate Analysis – NSAIDs Only .............................................. 31
Table 5b. Multivariate Analysis – Short and Long Acting Opiates Only ............... 31
Table 5c. Multivariate Analysis – Short and Long Acting Opiates + Anti-Anxiety, Sedatives, & Hypnotics ........................................................................................................... 31
Table 5d. Multivariate Analysis – Short and Long Acting Opiates + Muscle Relaxers and Anti-Depressants ........................................................................................................... 32
Table 5e. Multivariate Analysis – Short Acting Opiates Only............................ 32
Table 5f. Multivariate Analysis – All Opiates ................................................ 32
Figure 1. Selection of Patients with Opiates and NSAIDs Prescriptions ............ 33
BIBLIOGRAPHY ............................................................................................ 34
LIST OF TABLES AND FIGURES

Chapter 2:

Table 1. Short and Long Acting Opiates ..................................................25
Table 2a. Baseline Characteristics of Patients with Medications of Interest ................26
Table 2b. Baseline Characteristics of Patients with Medications of Interest (Cont.) ....27
Table 3a. Univariate Analysis of Predictors for All-Cause Mortality ..........................28
Table 3b. Univariate Analysis of Predictors for All-Cause Mortality (Cont.) ..............29
Table 4. Unadjusted Relative Risk of All-Cause Mortality .........................................30
Table 5a. Multivariate Analysis – NSAIDs Only ....................................................31
Table 5b. Multivariate Analysis – Short and Long Acting Opiates Only .......................31
Table 5c. Multivariate Analysis – Short and Long Acting Opiates + Anti-Anxiety, Sedatives, & Hypnotics ........................................................................................................31
Table 5d. Multivariate Analysis – Short and Long Acting Opiates + Muscle Relaxers and Anti-Depressants ........................................................................................................32
Table 5e. Multivariate Analysis – Short Acting Opiates Only .......................................32
Table 5f. Multivariate Analysis – All Opiates ...............................................................32
Figure 1. Selection of Patients with Opiates and NSAIDs Prescriptions .....................33
CHAPTER ONE: INTRODUCTION

INTRODUCTION AND SPECIFIC AIMS

Non-cancerous pain is non-malignant pain. Opiates remain a primary, but controversial medication in the treatment of chronic non-malignant pain (CNMP). Opiate sales have almost quadrupled over the past ten years. Between 1997 and 2005, the sales of Methadone, Oxycodone, and Hydrocodone increased 934%, 588% and 197% respectively. Deaths in the United States associated with use of narcotic analgesics have increased 91.2% between 1999 and 2002 where the highest death rates occurred in the rural counties of West Virginia, New Mexico, Utah, Louisiana, Oklahoma, Nevada, Kentucky and Tennesse.

A number of chronic medical conditions and complications have been reported in the literature in association with long term opiate use including death, coronary artery disease due to atherosclerosis, hypertension, elevated cholesterol, triglycerides and blood sugar, gastrointestinal problems, falls and fractures.

Since the mid 1990’s, death rates ascribed to prescription opiate use have quadrupled, paralleling the sales of these drugs. Cause of death is not always clear, and frequency of particular opiate use or combination opiate use has been rarely addressed. Methadone, Oxycodone and Fentanyl have all been shown to be associated with Toursades de Pointes, a potentially lethal cardiac arrhythmia.

Individuals using chronic opiates or COX-2 inhibitors (a type of Non-Steroidal Anti-Inflammatory Drug or NSAIDs) for non-malignant pain were found to have a significant increase in myocardial infarction and/or coronary re-vascularization procedures over a control group not taking medications. This relationship was found to be dose and duration dependent.
in all groups. The adjusted incidence rate ratio (AIRR) for cardiac events among chronic opiate users was 2.66 (95%CI 2.30-3.08). The three COX-2 inhibitors demonstrated AIRR of 1.94 (95%CI 1.65-2.29) for Rofecoxib, 1.79 (95%CI 1.53-2.10) for Celecoxib, and 1.74(95%CI 1.41-2.16) for Valdecoxib. The control “general population” reference comparison group had a crude incidence rate (number events/1000person-years) of 1.58.

A variety of “adjuvant” medications (muscle relaxers, antidepressants, sedative/hypnotics and anxiolytic medications) are commonly utilized with opiates chronic non-malignant pain to control symptoms.\textsuperscript{21-23} The long term impact of such combination of medications on improvement in pain and function is not clear. Benefit from such polypharmacy remains questionable.\textsuperscript{21, 23} The benzodiazepine class of drugs, which include some muscle relaxers, sedative/hypnotic and anxiolytic medications, have been shown to have an elevated hazard ratio (HR) for death, even in low doses (HR for death for any hypnotic use from 0.4-18 tablets/year is 3.91 for males (p<.001, 95% CI 2.91-5.25) and 3.34 for females, (p<.001, CI 2.45-4.56).\textsuperscript{24}

Two commonly used SSRI antidepressant medications have been shown to be cardiotoxic in overdose situations. Paroxetine and citalopram (SSRI antidepressants) both resulted in ventricular conduction delay (Paroxetine OR 1.38, 95%CI 0.69-2.77, citalopram OR 5.11, 95% CI 2.32-11.27).\textsuperscript{25}

The effect of using these multiple adjuvant compounds in combination has not been reported. In summary, current literature has shown: 1) opiate use has increased over the past ten years in terms of daily cumulative dose by 8.3% and number of days supplied increasing 49.9%.\textsuperscript{26, 27, 28} 2) death rate in the United States associated with use of narcotic analgesics in 2008 has increased almost four times since 1999.\textsuperscript{2, 11, 29} 3) Adjuvant medication and NSAIDs
use for management of benign pain has increased. 4) multiple representatives of these differing drug classes have common toxicities when utilized alone.

This study will evaluate all-cause mortality among patients treated for chronic non-malignant pain utilizing opiate medications alone, opiates plus adjuvant medications and NSAIDs alone.

**Hypothesis:**

It is hypothesized that patients who take opiates alone or opiates plus adjuvants have 50% increased risk of all-cause mortality compared to patients who take only NSAIDs.

**Specific Aims:**

To evaluate this hypothesis, the following specific aims will be addressed:

Specific Aim 1: To determine the relative risk of all-cause mortality among patients with prescriptions for NSAIDs alone vs. patients with opiate only or opiate plus adjuvant(s) (muscle relaxer, antidepressant, anxiolytic/sedative/hypnotic) prescriptions.

Specific Aim 2: Identify clinically significant independent predictors associated with all-cause mortality in all medication groups.

**Significance:**

Utilization of opiates in the US has dramatically escalated over the last decade. Along with this escalation is a parallel increase in deaths associated with opioids. The cause of this increased unintentional deaths is not always clear, but there is evidence that cardiac involvement may occur in concert with the use of opiates in a dose response relationship.

Coronary heart disease is the number one killer of men and women. MI is the number one cause of death in women. The prevalence of acute MI in the US population is 3.6% with
first year costs for treatment estimated at $5.5 billion.\textsuperscript{32, 33} Adults who have had a heart attack have a 4 to 6 time’s greater risk of sudden death.\textsuperscript{32} Currently, there is a paucity of literature addressing opiates and cardiovascular disease. This important relationship should be clarified. This information will improve the safety of chronic pain management.

\textbf{Possible mechanisms of cardiac toxicity of opiates}

\textbf{Prolongation of the QTc interval}

There are several pathways of toxicity which could explain sudden cardiac events. The first involves a disruption in the cardiac electrical polarization/repolarization cycle. This process results in a measurable delay in the ventricular electrical cycle known as the QTc interval. This delay has been associated with the sudden occurrence of a potentially life threatening ventricular arrhythmia known as “Toursades des Pointes”. Prolongation of the QTc has been found in association with two commonly prescribed narcotic analgesics, Methadone and Oxycodone.\textsuperscript{34} Methadone users have been found to have cardiac arrhythmias.\textsuperscript{35-39} EKG abnormalities including QT prolongation and ST wave changes have been found in 61\% of the people addicted to opiates.\textsuperscript{40}

\textbf{Blockade of potassium channels}

Another possibly related cardiac toxicity pathway associated with narcotic analgesics involves a blockade of ionic (potassium) channels active in cardiac repolarization. While the mechanism is not entirely clear, functional channel blockade may occur due to an adverse drug interaction, binding of the drug in the channel, or by de-activating the channel pump system.\textsuperscript{41} As the ionic channel system is involved in the repolarization process, an overlap of this blockade with the observed QTc prolongation may occur.
Direct cardiac pathology

In 1989, Dressler and Roberts reported autopsy findings in opiate addicts. They noted 96% of the 168 subjects had cardiac abnormalities and that 58% of the deaths were cardiac in nature. Darke et al. reported autopsy results in a large number of methadone and heroin users. These subjects had a mean age of 48.9 years, but had significant increase in cardiac ventricular hypertrophy (OR 1.61, CI 0.77-3.34), myocardial fibrosis indicative of prior heart attack (OR 2.93, CI 1.50-5.69), perivascular fibrosis indicative of hypertension (OR 2.58, CI 1.18-5.62), severe atherosclerosis (OR 1.11; CI 0.59-2.17), and any cardiac pathology (OR 3.13, CI 2.00-4.90). These findings raise suspicion of an underlying direct cardiac toxic effect from methadone or heroin. Methadone is a schedule II medication.

A recent study showed an increase risk of MI among chronic opiate users for chronic non-malignant pain (adjusted incidence rate ratio (AIRR) 2.66, CI 2.30-3.08). Unfortunately, all opioids were reported as a single group with no differentiation regarding specific opioids or their duration of action.

Oxycodone has also been associated with cardiac pathology in autopsy studies. There was severe coronary artery atherosclerosis in 37%, myocardial fibrosis in 19%, perivascular fibrosis in 13%, ventricular hypertrophy in 15%, and cardiomegaly in 12% of subjects with fatal oxycodone related deaths. The mean age of this group was 49 years old.

Toxic effects of commonly used opiates

Methadone

Methadone is a synthetic, schedule II opioid utilized in the treatment of heroin addicts, in the management of chronic benign pain, maintenance treatment for opioid addiction and in detoxification treatment of opioid addiction.
Normal cardiac function involves a continuous electrical stimulation of cardiac contractility from ion flow channels. Methadone has been found to have a direct inhibitory effect on potassium ion channel function, resulting in delayed electrical conduction. This inhibition in the function of ion channels is reflected in prolonged QT intervals in electrocardiogram recordings and has been associated with the Tournades de Pointes ventricular arrhythmia. This relationship may explain both sudden death and proven cardiac related deaths in individuals involved in Methadone treatment.

Increased cardiac risk factors (hypertension, myocardial fibrosis, ventricular hypertrophy, and atherosclerosis) have also been reported in autopsy studies in association with Methadone use and drug addiction. A chemically similar compound (LAAM or levacetylmethadol marketed as Orlaam) was removed from the market in 2003 in the US due to increased cardiac deaths from ventricular arrhythmias.

These combinations of findings raise serious questions about the relationship of Methadone use and cardiac pathology.

**Oxycodone**

Oxycodone is a semi-synthetic opioid frequently used for pain control. Oxycodone is available in short acting (i.e. Percocet) and long acting (i.e. Oxycontin) preparations. Deaths from Oxycodone have increased 264.6% between 2003-2009. Death rate from Oxycodone have been reported to have substantially increased since the introduction of this long acting preparation.

Methadone and Oxycodone are primarily metabolized by Cytochrome P450 3A4 and 2D6 isozymes. Metabolism is prolonged when there is evidence of renal or hepatic co-morbidity. Prolongation of the QTc interval has also been associated with Oxycodone and
connected to inhibition of ionic channel function. These factors again raise questions regarding association with oxycodone and cardiac events.

The above summary of the current literature indicates despite the increasing sales of prescription opiates in the US to treat chronic non-malignant pain, the long term effects of these medications remain unclear.

Methods of administration of opiates/ opioids

Oral medication is taken by mouth and is intended for swallowing. Buccal (or sublingual) medication is placed under the tongue, for direct absorption in the mouth. Transdermal patch is applied to the skin, generally with an adhesive, for absorption over several days. Intravenous medication is placed into a sterile container, attached to a needle or catheter for direct instillation into a vein. Intrathecal medication is delivered through an implanted pump: a mechanical device surgically implanted under the skin which can be refilled periodically. Suppository drug delivery can involve installation of medication trans-rectally, trans-urethrally or trans-vaginally. It is generally used when the patient is unable to take medications orally (nausea, vomiting, dysphagia) or if, due to patient location (at home in bed) other parenteral mechanisms (IV or IM) are unavailable.

Toxic responses may occur with any form of delivery, alone or in combination. Most published reports address only oral preparations, as these represent the most commonly available preparation. Darke described Oxycodone deaths occurring 78.6% of the time due to oral ingestion, and 21.4% from injected Oxycodone, but 20% of those deaths arose from injected oral preparations.

Additionally, considering only the oral route of administration in calculating total daily
cumulative dose of morphine would reflect an underestimation of the actual dose.

**Long vs. short acting opiates**

Short acting opiate (SAO) medications duration of action is generally 4 to 6 hours. This results in the use of multiple pills per day. It is often used additionally to long acting medication to prevent breakthrough pain. Long acting opiate (LAO) medication duration can vary from 8 hours to days. Transdermal Fentanyl (“Pain Patch”) may last up to 3 days. Some oral preparations (Methadone) have a prolonged half-life (22 hours) with a range of 15-55 hours. This prolonged half-life can contribute to toxicity with prolonged use, due to higher plasma concentrations over time.

Commonly utilized SAO include immediate release (IR) Morphine, Hydromorphone, Oxymorphone, Codeine, Fentanyl, Hydrocodone, and Oxycodone. LAO include Methadone, extended or sustained release Oxycodone, Oxymorphone, Morphine and Fentanyl.

SAO are generally used for acute, chronic or intermittent pain. LAO are prescribed when prolonged analgesia is required. Both forms have shown similar serum concentrations and analgesia. Benefits of LAO include diminished serum level fluctuations, providing a less variable serum level. This could diminish the possibility of variable analgesia seen in SAO which have shorter half-lives. The SAO have more rapid uptake, but less sustained efficacy. SAO may have diminished adverse events.

Fentanyl potency is 50-100 times greater than morphine. It has been reported to induce bradycardia. Long acting Oxycodone is associated with 5 times increased risk of Oxycodone related mortality (p < 0.01) and 41% increase risk of overall opioid related deaths (p = 0.02). More than 70% of these deaths are pronounced as unintentional and/or
As noted earlier, Oxycodone can block the potassium channels and create cardiac arrhythmias. This effect may explain some of these observed outcomes.

Given the significant presence of cardiac disease found in autopsy studies of fatal unintentional overdose, evidence of electrocardiogram abnormalities in opiate addicts and the increased MI and coronary revascularization noted with chronic opiate utilization, it is reasonable to further investigate the risks of all-cause mortality and chronic opiate use with adjuvants.

**IRB APPROVAL**

Institutional Review Board approval from the University of Cincinnati College Of Medicine was obtained prior to data collection (Protocol # 2012-4167).
CHAPTER 2: COMPARISONS OF ALL-CAUSE MORTALITY FOR CHRONIC BENIGN PAIN PATIENTS PRESCRIBED NSAIDS ONLY, OPIATES OR OPIATES AND ADJUVANTS

Introduction

Chronic nonmalignant pain (CNMP) is defined as pain from a non-cancerous origin lasting beyond ninety days. Such complaints are often seen with musculoskeletal conditions and are common in the workers’ compensation population. The World Health Organization and Centers for Disease Control and Prevention have described musculoskeletal complaints as a problem of global proportions. The Global Burden of Disease Study identified musculoskeletal diseases as the second greatest cause of disability in the world.\textsuperscript{62, 64} Treatment for these complaints often involves use of varied pharmaceuticals including non-steroidal anti-inflammatory medications (both non-selective NSAIDs and Cox2 inhibitors) and/or narcotic preparations and adjuvant medications. Adjuvant medications can include muscle relaxers, antidepressants, sedative/hypnotics, anxiolytic medications and neuroleptics. Long term safety and effectiveness of these medication combinations remain unclear.\textsuperscript{2, 3, 4, 10, 65}

NSAIDs are commonly utilized medication for CNMP.\textsuperscript{66} NSAIDs have been reported to produce a number of associated long term cardiovascular, gastrointestinal and renal complications.\textsuperscript{66-80} The risks associated with these NSAIDs can be mitigated to avoid such complications through cautious monitoring of patient comorbidities.\textsuperscript{73}

A wide variety of narcotic preparations are commonly utilized to address CNMP. Narcotics can be classified based on duration of medication effect as short acting (e.g. Hydrocodone, Oxycodone, Codeine) or long acting (i.e. Oxycodone, Methadone, Fentanyl) (Table 1). Health care providers often combine the short and
long acting preparations to address break through pain. Safety of combinations of narcotics remains unclear and questionable.

Randomized clinical trials (RCT) evaluating patients taking opiates for benign pain are scarce and are generally limited to measurements of self-reported pain relief, and/or function. Kalso, et al. described diminished pain with opiate use, but 80% of subjects had at least one adverse event. A systematic review reported limited benefit with a variety of differing opiates (both short and long acting types, but not mixed). A high number of subjects often withdraw from studies due to adverse effect of the opiates. Most of the RCTs do not follow subjects past 16 weeks. This duration is not realistic clinically.

Dunn, et al. reported overdose (OD) incidence among CNMP subjects taking prescribed opiates for at least 90 days. Overdose rates were found to be dose related with a hazard ratio (HR) of 1.44 (95% CI, 0.57-3.62) when daily opiate dose was 20 mg to less than 50 mg morphine equivalents per day (MED). This OD HR increases to 8.87 (95% CI, 3.99-19.72) when daily opiate dose was ≥100mg MED per day. Risks for life threatening events associated with OD were similarly dose related, ranging from HR, 1.19 (95% CI, 0.40-3.60) for 20 mg to less than 50 mg MED to HR, 11.18 (95% CI, 4.80-26.03) for ≥100mg MED per day. Dunn also noted an increase in risk of opioid OD when the study groups received sedative/hypnotic medications.

The HR for opioid OD among those with sedative/hypnotic prescriptions vs. those not receiving such prescriptions varied from HR, 3.40 (95% CI 1.60-7.20) with 1-22 day supply, HR, 0.90 (95% CI 0.20-4.00) with 23-44 day supply, HR, 3.7 (95% CI 1.60-8.90) with 45-71 day supply, and HR, 2.7 (95% CI 1.20-6.00) when a ≥72 day or greater supply was
provided.

Since the mid 1990’s, death rates secondary to prescription opiate use have quadrupled, paralleling the sales of opiates. The percentage increase of retail drug purchases of Oxycodone, Methadone, Fentanyl, Morphine, and Hydrocodone are 588%, 934%, 423%, 154%, and 197% respectively from 1997 to 2005.\textsuperscript{10} From 1999-2005, the number of unintentional deaths due to opioids exceeded the number of deaths due to cocaine and heroin (8,000 deaths vs. 5,000 deaths and 2,000 deaths respectively). Prescription opioids accounts for 38.2% of the unintentional drug overdose deaths in the US in 2005.\textsuperscript{10}

Studies addressing the safety of opiates and adjuvant medication combinations are almost non-existent. Our study evaluates the risks and predictors of all-cause mortality (ACM) among Ohio workers’ compensation patients with CNMP treated with NSAIDs only, opiates only or combinations of opiates and adjuvants.

\textbf{Methods}

Data for this historical cohort study is derived from the Ohio Workers’ Compensation (BWC) de-identified database, from 01/01/2000 to 06/10/2011. Independent variables collected include: date of injury, date of birth, death date, sex, marital status, legal representation, procedures (CPT codes and dates of procedures), diagnoses (ICD-9 codes and descriptions), pharmacy data (dose, route of administration, date and amount medication dispensed), national drug code, national drug code description, therapeutic class code description, strength description, Drug Enforcement Administration code (DEA), morphine conversion factor, and number of pharmacies utilized.
**Study population**

After approval from the University Of Cincinnati College Of Medicine, Institutional Review Board, (study ID number 2012-4167) subjects are sorted based on exclusion criteria, inclusion criteria and medications of interest.

From 01/01/2000- 06/10/2011, the database has 772,136 injured workers. Exclusion criteria include patients with incomplete demographics, no pharmacy data, diagnoses of cancer, pregnancy, HIV, liver disease, respiratory failure, organ transplant, cardiovascular disorder, end stage renal diseases, end stage illnesses, autoimmune or systemic inflammatory disorders, a history of severe trauma or hospitalization within 30 days of injury, hospitalization 30 days prior to date of dispensing medication of interest, and incomplete/inaccurate or inconsistent data (pharmacy or otherwise). Patients aged 18 to 65 years are included. There are 94,364 patients remaining to sort for medications of interest (Figure 1).

**Outcome Measured**

All-cause mortality is the outcome of interest. Since the Ohio BWC database is de-identified, death certificates or searches for death certificates are not possible. Death date is provided in the database.

**Statistical Analysis**

All nasal, intrathecal, and intravenous route opiates are excluded in the study secondary to lack of reliable conversion to morphine. Patients are selected and grouped by use of medication of interest exclusively of other study groups. For example, patients taking short and long-acting opiates do not take any of the other medications of interest.
such as anti-depressants or anti-anxiety medications.

Daily average morphine equivalent dose (MED) is calculated for each patient. The calculation includes each opiate medication in milligrams (mg) x the number of tablets per day = total mg per day. Equianalgesic dose x total mg per day = mg of morphine equivalents. All daily opiate mg of morphine equivalents is averaged to provide a MED in mg.82

Duration of medications is the sum of days each medication is dispensed. The date dispensed is provided in the database.

The comparison group is NSAIDs only patients. These patients do not take any other medication besides NSAIDs. Relative risk (RR) is used to assess the magnitude of association between the exposed patients prescribed opiates only and opiates plus adjuvant medications and the likelihood of ACM in the exposed groups relative to patients taking only NSAIDs.

Poisson regression is used to determine the adjusted risk factors of ACM for each medication groups. Univariate analyses are performed for all collected independent variables prior to the multivariate analysis. Independent variables with p values of ≤ 0.20 are considered for the multivariate Poisson regression.

Analyses are performed utilizing SAS version 9.4. Analyses are reported with two-sided p values and 95% confidence intervals. Statistical significance is determined at the p < 0.05 level.
Results:

There are five groups of opiates and adjuvant medications compared to NSAIDs only. These combinations are chosen secondary to their common utilization in the treatment of CNMP and the literature reports of known toxicity.

From the 94,364 patients remaining after exclusion, the following patients remained: 11,359 subjects taking short acting opiates only (SA); 743 subjects with short and long acting opiates only (SLO); 182 subjects taking short and long acting opiates combined with anti-anxiety and/or sedative and/or hypnotic drug (SLO + ASH); 1,733 subjects taking short and long acting opiates with muscle relaxants and/or anti-depressants (SLO + MR /AD); and 14,017 all opiates subjects (AO), representing a combination of all the studied opiate groups. There are 2,934 subjects taking only NSAIDs. Among the NSAIDs, there are no patients taking only COX-2 inhibitors. (Figure 1)

Table 2 provides a summary of the characteristics of all 6 groups. There are a few general trends worth noting. The percentage of male subjects is higher in all opiate groups (56.84% - 68.24%) compared to NSAIDs group. Married subjects predominate in all groups. Among those taking opiate combinations (SLO, SLO + ASH, SLO + MR/AD), the majority have legal representation (59.35% to 76.86%). This trend is reversed in those taking SA only and NSAIDs only. In all groups, most patients have had no procedures (37.91% to 87.91%). Spine surgeries represent 2.32% to 24.99% of the opiate subjects and less than one percent of the NSAIDs group. More subjects in the opiate combination groups had any type of surgery than not (57.47% to 62.09%).

Opiate combination groups are more likely to take oral plus other routes of medication (32.84% to 51.47%). Psychiatric drug use is highest among the SLO + ASH (70.33%) and
SLO+ MR / AD (49.97%) groups. The SLO +ASH has the highest percentages of death (4.95%) followed by SLO + MR /AD (2.65%); SLO (2.42%); SA opiates (1.88%) and NSAIDs only (1.53%).

Opiate combination groups have the highest death rates with younger ages (average 39-41 years) at the time of injury, increased utilization of emergency room visits (average 2-3), higher average daily MED (60.55 MED – 77.40 MED), greater total number of medications dispensed (average 6-13 meds) from an average of 3-4 pharmacies and a longer mean duration on medications, 521.72 days – 1895.01 days compared to NSAIDs only (69.70 days) and SA opiates only (185.23 days).

Unadjusted Relative Risks of All-Cause Mortality

When comparing to NSAIDs only group, all opiate groups have greater risks of ACM. The greatest risks is in the SLO + ASH group, RR 3.22 (95% CI, 1.60 – 6.94) and the SLO + MR /AD patients, RR 1.73 (95% CI, 1.15 – 2.59); These 2 groups are statistically significant.

SLO group, RR 1.57 (95% CI, 0.92 – 2.71); SA opiates subjects, RR 1.23 (95% CI, 0.89 – 1.69); and AO group, RR 1.35 (0.99 - 1.84) have increased risks of ACM. However, they are not statistically significant. (Table 4)

Predictors of All-Cause Mortality

Adjusted multivariate Poisson regression for opiate groups show similar trends. Generally, significant predictors of ACM for opiate groups include increasing age at time of injury RR 1.33 (95% CI, 1.26-1.41; P < .01) male gender RR 1.90 (95% CI, 1.47-2.45; P <0.01), increase in the number of total medications RR 1.25 (95% CI, 1.17-1.33; P <0.01),
increase in the number of emergency room visits RR 1.06 (95% CI, 1.02-1.09; P <0.01) increase the risks of ACM. Being married RR 0.47 (95% CI, 0.27-0.82; P <0.01), having had any surgery RR 0.33 (95% CI, 0.12-0.96; P = 0.04), and increasing age at the time of first prescription of interest RR 0.39 (95% CI, 0.21-0.71 P <0.01) is protective. Legal representation increases the risks of ACM, RR 3.07 (95% CI, 0.95-9.89; P = 0.06) (Table 5).

For the NSAIDs group, the only significant predictor of ACM is age at t0, RR 1.06 (95% CI, 1.03-1.09; P <.01) (Table 5a).

**Discussion:**

Opiates and adjuvant medications are frequently provided in the treatment of CNMP. Yet, there is no original research evaluating the safety of opiates and adjuvant medications compared to NSAIDs alone. The results of this study reveal an increased risk of ACM with commonly prescribed *combinations of opiate and adjuvant medications* compared to NSAIDs alone. The most notable group is *SLO+ASH* which has at least 3x increase risks of ACM regardless of age, sex, dose or duration of medication usage, RR 3.22 (95% CI, 1.60-6.49; P <0.01). The most important significant predictor of ACM in this group is the total number of medications prescribed, RR 1.38 (95% CI, 1.07-1.78; P = 0.01). These factors indicate this combination of medications is harmful. Although, any surgery appears to have a protective effect, RR 0.21 (95% CI, 0.06-0.78; P = 0.02), this should be interpreted with caution because this is a generalization regarding all surgeries. This group also has the 2nd to largest number of patients with spine surgery, 8.79% (Tables 4 and 5c).

Similarly, the *SLO + MR /AD group* has 73% increased risk of ACM, RR 1.73 (95% CI, 1.15-2.59; P <0.01). Here the ACM increased risks can be explained partially by age at the time of injury (RR 1.36 (95% CI, 1.17-1.57; P <0.01), gender (RR 2.11 (95% CI, 1.10-
4.02; P = 0.02), and the number of emergency room visits (RR 1.06 (95% CI, 1.02-1.09; P <0.01), but not the duration on opiates (RR 0.99 (95% CI, 0.98 - 1.00; P = 0.07). It should be noted that when all groups of opiates are analyzed together the duration of opiates is statistically significant, RR 0.98 (95% CI, 0.97-0.99; P <0.01), Tables 4 and 5d.

Both of these groups have statistically significant increased risk of ACM. It should be noted the average age of the injured workers in these 2 groups are young, 39-41 years. According to the United States Centers for Disease Control and Prevention, the average numbers of years of life remaining (life expectancy) for persons aged 35 to 40 years are 45years and 40 years respectively. For the total U.S. population in 2009, the life expectancy at birth is 78.5 years. The average age at death for the SLO + ASH, SLO + MR /AD patients are 48.10, 49.55 years respectively. The NSAIDs only group is the oldest at the time of injury (42 years old) and has the lowest death rate, 1.53% with only age at t0 as significant predictor of ACM. Observations regarding the increase in ACM may be explained by known toxicities of these prescribed drugs:

**Opiates and anxiolytic/sedative/hypnotics**

SLO + ASH result in the highest ACM RR, 3.22 (p<0.01). These patients have a mean of 524.73 days on opiates, second to highest duration on all medications, 1,127 days; the highest daily average MED of 77.40 mg, 70% on psychiatric medications and an average of 9-10 medications. This group has the youngest age at death, 48 years (Tables 2, 4 and 5c). Clinically, it is often explained that adjuvants are added to decrease opiate dose and to improve patients’ symptoms. However, the current data do not support these hypotheses.

In separate analysis (not included), comparing to NSAIDs, the combination of
Hydrocodone + Alprazolam had an OR for death of 6.11 (95% CI, 2.54 – 14.85; p < 0.01). The combination of SLO + Alprazolam had an RR, 5.66 (95% CI, 2.92 – 10.96; p < 0.01). The SLO + benzodiazepine group is noted to have at least 2 opiates in addition to the benzodiazepine. (i.e., at least one short acting and one long acting opiate).

Alprazolam is a benzodiazepine often prescribed for anxiety and panic attacks. Long term use, especially when co-prescribed with psychoactive medications, has been associated with dependence, abuse and toxicity. Alprazolam has been found to be rarely a cause of death when utilized alone, but fatal overdoses can occur when co-prescribed with other drugs, especially opiates. An average of three drugs has been detected among Alprazolam decedents. Opiate preparations have been found to be the most common medication associated with Alprazolam related deaths.\textsuperscript{84} Involvement of Alprazolam in drug related deaths has escalated 233.8\% between 2003-2009 and was associated with hydrocodone in 26.8\% of drug related deaths in West Virginia between 2005-2007.\textsuperscript{84, 85, 86} Both low and high doses of benzodiazepines and high doses of opioids have been reported to increase death hazard ratios, 1.68 (1.17-2.42) and 1.49 (1.10 – 2.01) respectively.\textsuperscript{86}

**Opiates and muscle relaxants/anti-depressants**

Another common practice in the management of CNMP involves combining SLO with different muscle relaxants and anti-depressants.

In this study, subjects taking SLO + MR/AD show an ACM RR, 1.73 (95% CI, 1.15 – 2.59; p < 0.01). This group has the longest duration on opiates and all medications, largest percentages of legal representation, the most emergency room visits, number of pharmacies used, and total types of medications prescribed.
Dose and duration on opiates are not significant predictors of ACM in this group. Age at time of injury, number of emergency room visits and age at time of injury are statistically significant predictors of ACM (Tables 2, 4 and 5d). In a separate analyses (not included), SLO + antidepressants has an OR of ACM of 1.90 (95% CI, 1.30 – 2.78; p < 0.01) and SLO + muscle relaxers RR, 1.42 (95% CI, 1.02 – 1.98; p = 0.04). These data do not support the hypotheses that adding these adjuvants with opiates improve patient safety.

Muscle relaxants are prescribed to diminish spasms. There are a number of commercially available muscle relaxants, but Carisoprodol is one of the most commonly used. Carisoprodol has neurologic side effects of somnolence, sedation, respiratory depression and is subject to abuse, dependence and withdrawal. It can interact with many opiates resulting in increased sedation. Increased deaths have been reported among individuals simultaneously taking Hydrocodone, Carisoprodol and Alprazolam. Forrester described this combination as recreational or suicidal substance abuse. Adverse effects were noted to be neurological, cardiovascular and respiratory in nature, consisting of drowsiness, slurred speech, coma, tachycardia, hypertension, hypotension, and respiratory depression.

Tricyclic antidepressants are commonly used to address neuropathic pain (pain due to nerve tissue damage) with conflicting published data pertaining to effectiveness. The mechanism of tricyclic antidepressant toxicity has been reported as possible fatal cardiac arrhythmias and neurologic effects. The cardiac toxicity occurs due to sodium channel blockade in the heart, producing delayed conduction and possible arrhythmias. This effect is not dependent on dose.

Two commonly used SSRI antidepressant medications have been shown to be cardiotoxic in overdose situations. Paroxetine and citalopram (SSRI antidepressants) both
resulted in ventricular conduction delay (Paroxetine OR 1.38, 95%CI 0.69-2.77, citalopram OR 5.11, 95% CI 2.32-11.27).  

Short and long acting opiates

Long acting opiate preparations are designed to provide prolonged analgesia in the range of 8-12 hours, and a second opiate to provide coverage for break-through pain. This combination has not been studied for safety and effectiveness through an RCT. The ACM for this group is RR, 1.57 (95% CI, 0.92 – 2.71; p = 0.11) compared to NSAIDs. Patients taking combination opiates have longer duration on opiates and all medications, more legal representation, more emergency room visits, total pharmacies used, and total types of medication prescribed compared to NSAIDs and short acting opiates only. Significant protective predictors include age at t0 (the older the patient is at the time of the first prescription of opiates, the less likely the patient is to die) and having any surgery. On the contrary, increasing age at time of injury and total medications prescribed are significant predictors of increasing mortality (Table 2, 4, and 5b).

In a different analysis from this data, Oxycodone users have an increased ACM OR, 1.67 (95% CI, 1.05 – 2.65; p = 0.03) compare to NSAIDs. Solomon, et al., reported a RR of ACM with oxycodone vs. hydrocodone of 2.43 (95% CI 1.47-4.00).  

Paulozzi showed a progressive increase in adjusted OR for death with more potent opiates in a population of unintentional overdose deaths in New Mexico.  

Overlapping opiate prescriptions resulted in an increase of the crude OR to 11.7 (95% CI 8.8-15.7). A recent study showed an increase in risk of myocardial infarction (MI) among chronic opiate users treated for CNMP with an increase in adjusted incidence rate ratio for MI 2.66, (95% CI 2.30-3.08).
Potential mechanisms of cardiac toxicity of opiates include prolongation of the QTc interval due to blockade of potassium repolarization channels and direct cardiac pathology. There are several pathways of toxicity which could explain sudden cardiac events. The first involves a disruption in the cardiac electrical polarization/repolarization cycle. This process results in a measurable delay in the ventricular electrical cycle known as the QTc interval. This delay has been associated with the sudden occurrence of a potentially life threatening ventricular arrhythmia known as Toursades de Pointes (TDP). TDP has been reported in the long acting opioid preparations Oxycodone and Methadone. EKG abnormalities including QT prolongation and ST wave changes have been found in 61% of the people addicted to opiates.

Oxycodone is primarily metabolized by Cytochrome P450 3A4 and 2D6 isozymes. Metabolism can be altered when there is evidence of renal or hepatic co-morbidity or with use of substances known to interfere with P450 metabolism.

**Short acting opiates only**

This group of opiates does not have statistically significant increase risks of ACM compared to NSAIDs alone, RR 1.23, p= 0.22. There are a few factors which may explain this effect. These patients have less surgery, lower average MED, much shorter average duration on opiates and all medications, less legal representation, less psychiatric medications, less spine surgery, less emergency room visit, less pharmacies and total medications prescribed compared to the combination opiates groups. Increasing age at t0, male gender, and total medications prescribed are significant predictors of increased ACM in this group (Tables 2, 4, 5e).
All opiates

Combining all opiates increases the sample size to n = 14,017 patients. Significant predictors of increased ACM include increasing age at time of injury, male gender, duration on opiates, and total medication prescribed. Although, the RR of ACM for all opiates was not statistically significant compared to NSAIDs alone, RR 1.35 (95% CI 0.99 – 1.84), this should be interpreted with caution. Subgroup analyses of SLO combined with specific adjuvants do have high statistically significant increased risks of ACM (Tables 2, 4, and 5f).

It should be noted that average daily MED was not a statistically significant predictor of ACM in any of the opiate groups. However, it is known that opiates have different potency and toxicity. Current classification of the data by therapeutic class description and duration of opiate action could minimize the true effects of the more potent opiates. Future studies will require additional analyses of specific opiates with dose and duration.

Conclusions

Treatment of CNMP often includes combination of analgesics with addition of “adjuvant” medications. As can be seen in this study, NSAIDs remain safest among the workers’ compensation population. Opiates combining with specific adjuvants can be harmful.

Patients with prescribed opiate combinations, show a longer duration on medications, more types of medications prescribed, increase utilization of emergency room visits and pharmacies, higher average MED and increased risks of ACM. The trends noted herein are consistent with a pattern of drug toxicity associated with increased drug duration of use and combinations of medications (Table 5). Specifically, when opiates are prescribed with
muscle relaxants and/or antidepressants the RR of ACM increased 73% and adding anxiolytic, sedative, and/or hypnotic drugs increased the RR of ACM 222%.

It is most concerning to note the average age of all opiates patients to be 40 years at time of injury. The patients with severe trauma and/or severe medical conditions were excluded from this study. These combination prescription patterns appear to be having a significant deleterious impact on this young employed population.

Treatment safety and effectiveness should be the goals for all healthcare interventions. The results of this study and a steadily increasing literature should provide serious cautions for medical practitioners to re-evaluate the common practice of utilizing chronic opiates and adjuvant prescriptions for CNMP.
Table 1. Short and Long Acting Opiates*

<table>
<thead>
<tr>
<th>Short-Acting Opiate</th>
<th>Dosage</th>
<th>Long-Acting Opiate</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CODEINE</td>
<td>32-713-60</td>
<td>BUPRENOPHINE</td>
<td>2, 8 MG</td>
</tr>
<tr>
<td>DIHYDROCODEINE</td>
<td>32-713-60</td>
<td>BUTORPHANOL</td>
<td>5,10,20 MCG/HR</td>
</tr>
<tr>
<td>FENTANYYL</td>
<td>100,200,400,600,800,1200,1600 MCG</td>
<td>FENTANYYL</td>
<td>12,25,50,75,100 MCG/HR</td>
</tr>
<tr>
<td>HYDROCODONE</td>
<td>2.5-500MG</td>
<td>HYDROMORPHONE</td>
<td>8,12,16,24,32 MG</td>
</tr>
<tr>
<td>HYDROCODONE</td>
<td>5MG-200,300,325,400,500 MG</td>
<td>METHADONE</td>
<td>5 MG/5 ML</td>
</tr>
<tr>
<td>HYDROCODONE</td>
<td>7.5-200,300,325,400,500,650,750 MG</td>
<td>METHADONE</td>
<td>10 MG/5 ML</td>
</tr>
<tr>
<td>HYDROCODONE</td>
<td>7.5-325/15</td>
<td>METHADONE</td>
<td>5,10,40 MG</td>
</tr>
<tr>
<td>HYDROCODONE</td>
<td>7.5-500/15</td>
<td>MORPHINE</td>
<td>10,15,20,30,45,50,60,75,80,90,100,120,200 MG</td>
</tr>
<tr>
<td>HYDROCODONE</td>
<td>10MG-200,300,325,400,500,650,660,750 MG</td>
<td>MORPHINE</td>
<td>20MG-0.8MG</td>
</tr>
<tr>
<td>HYDROMORPHONE</td>
<td>1 MG/ML</td>
<td>MORPHINE</td>
<td>30MG-1.2MG</td>
</tr>
<tr>
<td>HYDROMORPHONE</td>
<td>2,3,4,8 MG</td>
<td>MORPHINE</td>
<td>50 MG-2 MG</td>
</tr>
<tr>
<td>HYDROMORPHONE</td>
<td>4 MG/ML</td>
<td>MORPHINE</td>
<td>60MG-2.4MG</td>
</tr>
<tr>
<td>MORPHINE</td>
<td>10,15,30,60,100,200 MG</td>
<td>MORPHINE</td>
<td>80MG-3.2MG</td>
</tr>
<tr>
<td>MORPHINE</td>
<td>10,20,100 MG/5 ML</td>
<td>MORPHINE</td>
<td>100MG-4MG</td>
</tr>
<tr>
<td>OXYCODONE</td>
<td>5,10,15,20,30,40,80 MG</td>
<td>OXYCODONE</td>
<td>10,15,20,30,40,60,80,160 MG</td>
</tr>
<tr>
<td>OXYCODONE</td>
<td>2.5-325MG</td>
<td>OXYMORPHONE</td>
<td>5,7.5,10,15,20,30,40 MG</td>
</tr>
<tr>
<td>OXYCODONE</td>
<td>4.5-325MG</td>
<td>PROPOXYPHENE</td>
<td>100-325MG</td>
</tr>
<tr>
<td>OXYCODONE</td>
<td>5 MG/5 ML</td>
<td>TRAMADOL</td>
<td>100,200,300 MG</td>
</tr>
<tr>
<td>OXYCODONE</td>
<td>5 MG-325,500MG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OXYCODONE</td>
<td>7.5-325,500MG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OXYCODONE</td>
<td>10MG-325,650MG</td>
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</tr>
<tr>
<td>OXYCODONE</td>
<td>20 MG/ML</td>
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<td></td>
</tr>
<tr>
<td>OXYCODONE</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>OXYMORPHONE</td>
<td>5,10 MG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAPENTADOL</td>
<td>50,75,100 MG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRAMADOL</td>
<td>50,100,200 MG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRAMADOL</td>
<td>37.5-325MG</td>
<td></td>
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</tr>
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</table>

*Medication list provided by the Ohio Bureau of Workers’ Compensation.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NSAIDs Only (%)</th>
<th>Short-Acting Opiates (SA)</th>
<th>Short and Long-Acting Opiates (SLO)</th>
<th>SLO and/or Anti-anxiety, and/or Sedatives, and/or Hypnotics (SLO+ASH)</th>
<th>SLO and/or Muscle Relaxers and/or Anti-Depressants (SLO+MR/AD)</th>
<th>All Opiates</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>2,934</td>
<td>11,359</td>
<td>743</td>
<td>182</td>
<td>1,733</td>
<td>14,017</td>
</tr>
<tr>
<td>*Age at t0 (years) (mean ± SD)</td>
<td>41.51 +/- 12.22</td>
<td>40.21 +/- 12.34</td>
<td>41.82 +/- 12.00</td>
<td>43.16 +/- 11.08</td>
<td>42.27 +/- 11.01</td>
<td>40.59 +/- 12.18</td>
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<tr>
<td>Age at Death</td>
<td>53.93 +/- 10.86</td>
<td>50.78 +/- 11.62</td>
<td>53.20 +/- 9.85</td>
<td>48.10 +/- 7.29</td>
<td>49.55 +/- 11.10</td>
<td>50.65 +/- 11.32</td>
</tr>
<tr>
<td>Age at time of injury</td>
<td>42.10 +/- 12.12</td>
<td>39.97 +/- 12.10</td>
<td>40.60 +/- 11.76</td>
<td>40.89 +/- 10.72</td>
<td>39.40 +/- 10.65</td>
<td>39.94 +/- 11.9</td>
</tr>
<tr>
<td>Sex – No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1,609 (54.84%)</td>
<td>4,527 (39.85%)</td>
<td>236 (31.76%)</td>
<td>62 (34.07%)</td>
<td>748 (43.16%)</td>
<td>5,573 (39.76%)</td>
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<tr>
<td>Male</td>
<td>1,325 (45.16%)</td>
<td>6,832 (60.15%)</td>
<td>507 (68.24%)</td>
<td>120 (65.93%)</td>
<td>985 (56.84%)</td>
<td>8,444 (60.24%)</td>
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<td>Any Surgery - No. (%)</td>
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<td></td>
<td></td>
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<tr>
<td>No</td>
<td>2,573 (87.91%)</td>
<td>6,691 (58.95%)</td>
<td>304 (40.92%)</td>
<td>69 (37.91%)</td>
<td>737 (42.53%)</td>
<td>7,801 (55.69%)</td>
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<tr>
<td>Yes</td>
<td>354 (12.09%)</td>
<td>4,659 (41.05%)</td>
<td>439 (59.08%)</td>
<td>113 (62.09%)</td>
<td>996 (57.47%)</td>
<td>6,207 (44.31%)</td>
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<tr>
<td>Average Daily Morphin Equivalent (mg) (MED)</td>
<td>0.00</td>
<td>53.1 +/- 42.62</td>
<td>62.74 +/- 51.17</td>
<td>77.4 +/- 67.96</td>
<td>60.55 +/- 38.46</td>
<td>54.84 +/- 43.24</td>
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<td>MED max</td>
<td>0.00</td>
<td>1,322.08</td>
<td>803.33</td>
<td>579.47</td>
<td>331.53</td>
<td>1,322.08</td>
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<td>MED min</td>
<td>0.00</td>
<td>1.49</td>
<td>10.33</td>
<td>10.83</td>
<td>7.50</td>
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<td></td>
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<tr>
<td>No</td>
<td>2,889 (98.47%)</td>
<td>11,145 (98.12%)</td>
<td>725 (97.58%)</td>
<td>173 (95.05%)</td>
<td>1,687 (97.35%)</td>
<td>13,730 (97.95%)</td>
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<tr>
<td>Yes</td>
<td>45 (1.53%)</td>
<td>214 (1.88%)</td>
<td>18 (2.42%)</td>
<td>9 (4.95%)</td>
<td>46 (2.65%)</td>
<td>287 (2.05%)</td>
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<td>Drug Route - No. (%)</td>
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<tr>
<td>Oral</td>
<td>2,885 (98.33%)</td>
<td>9,512 (83.74%)</td>
<td>499 (67.16%)</td>
<td>102 (56.04%)</td>
<td>841 (48.53%)</td>
<td>10,954 (78.15%)</td>
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<td>Oral+Combinations</td>
<td>49 (1.67%)</td>
<td>1,847 (16.26%)</td>
<td>244 (32.84%)</td>
<td>80 (43.96%)</td>
<td>892 (51.47%)</td>
<td>3,063 (21.85%)</td>
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<td>Duration on Opiates (days) (Mean ± SD)</td>
<td>0.00</td>
<td>65.55 +/- 170.87</td>
<td>213.36 +/- 406.08</td>
<td>524.73 +/- 673.14</td>
<td>631.19 +/- 809.06</td>
<td>170.68 +/- 431.08</td>
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<tr>
<td>Duration on All Medications (days) (Mean ± SD)</td>
<td>69.70 +/- 121.78</td>
<td>185.23 +/- 380.54</td>
<td>521.72 +/- 922.30</td>
<td>1,127.19 +/- 1,253.52</td>
<td>1,895.01 +/- 2,181.36</td>
<td>426.68 +/- 1,044.68</td>
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<td>Legal Representation(%)</td>
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<tr>
<td>No</td>
<td>2,229 (75.97%)</td>
<td>6,446 (56.75%)</td>
<td>302 (40.65%)</td>
<td>49 (26.92%)</td>
<td>401 (23.14%)</td>
<td>7,198 (51.35%)</td>
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<tr>
<td>Yes</td>
<td>705 (24.03%)</td>
<td>4,913 (43.25%)</td>
<td>441 (59.35%)</td>
<td>133 (73.08%)</td>
<td>1,332 (76.86%)</td>
<td>6,819 (48.65%)</td>
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</table>

Table 2a. Baseline Characteristics of Patients with Medications of Interest
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NSAIDs Only</th>
<th>(SA)</th>
<th>SLO</th>
<th>SLO+ASH</th>
<th>SLO+MR/AD</th>
<th>All Opiates</th>
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<tr>
<td>Marital Status-</td>
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<td></td>
<td></td>
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<td>No. (%</td>
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<td></td>
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</tr>
<tr>
<td>Divorced</td>
<td>328 (11.18%)</td>
<td>1,231 (10.84%)</td>
<td>72 (9.69%)</td>
<td>23 (12.64%)</td>
<td>16 (9.22%)</td>
<td>2,007 (5.38%)</td>
</tr>
<tr>
<td>Married</td>
<td>1,597 (54.43%)</td>
<td>5,313 (46.77%)</td>
<td>382 (51.41%)</td>
<td>95 (52.2%)</td>
<td>773 (44.6%)</td>
<td>6,563 (46.82%)</td>
</tr>
<tr>
<td>Separated</td>
<td>106 (3.61%)</td>
<td>332 (2.92%)</td>
<td>15 (2.02%)</td>
<td>3 (1.65%)</td>
<td>79 (4.56%)</td>
<td>429 (3.06%)</td>
</tr>
<tr>
<td>Single</td>
<td>855 (29.14%)</td>
<td>4,349 (38.29%)</td>
<td>269 (36.20%)</td>
<td>60 (32.97%)</td>
<td>649 (37.45%)</td>
<td>156 (1.11%)</td>
</tr>
<tr>
<td>Widowed</td>
<td>48 (1.64%)</td>
<td>134 (1.18%)</td>
<td>5 (0.67%)</td>
<td>1 (0.55%)</td>
<td>16 (0.92%)</td>
<td>1,542 (11%)</td>
</tr>
<tr>
<td>¥Procedures (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Extremity</td>
<td>10 (0.61%)</td>
<td>202 (1.83%)</td>
<td>14 (7.69%)</td>
<td>374 (21.58%)</td>
<td>3,016 (21.53%)</td>
<td></td>
</tr>
<tr>
<td>Lumbar</td>
<td>2 (0.07%)</td>
<td>61 (0.54%)</td>
<td>10 (1.35%)</td>
<td>2 (1.10%)</td>
<td>59 (3.40%)</td>
<td>7,801 (55.69%)</td>
</tr>
<tr>
<td>Lower Extremity</td>
<td>136 (4.65%)</td>
<td>1,529 (13.47%)</td>
<td>154 (20.73%)</td>
<td>32 (17.58%)</td>
<td>147 (8.48%)</td>
<td>132 (0.94%)</td>
</tr>
<tr>
<td>Cervical/Thoracic</td>
<td>2 (0.07%)</td>
<td>61 (0.54%)</td>
<td>10 (1.35%)</td>
<td>2 (1.10%)</td>
<td>59 (3.40%)</td>
<td>7,801 (55.69%)</td>
</tr>
<tr>
<td>¥Psychiatric Drug Use (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2,934 (100.00%)</td>
<td>11,341 (99.84%)</td>
<td>738 (99.33%)</td>
<td>54 (29.67%)</td>
<td>867 (50.03%)</td>
<td>13,000 (92.74%)</td>
</tr>
<tr>
<td>Yes</td>
<td>0.00%</td>
<td>18 (0.16%)</td>
<td>5 (0.67%)</td>
<td>128 (70.33%)</td>
<td>866 (49.97%)</td>
<td>1,017 (7.26%)</td>
</tr>
<tr>
<td>Spine Surgery -</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>2,907 (99.32%)</td>
<td>11,087 (97.68%)</td>
<td>712 (95.83%)</td>
<td>166 (91.21%)</td>
<td>1,300 (75.01%)</td>
<td>13,265 (94.7%)</td>
</tr>
<tr>
<td>Yes</td>
<td>20 (0.68%)</td>
<td>263 (2.32%)</td>
<td>31 (4.17%)</td>
<td>16 (8.79%)</td>
<td>433 (24.99%)</td>
<td>743 (5.3%)</td>
</tr>
<tr>
<td>Total ER Visits (Mean ± SD)</td>
<td>0.75 +/- 1.01</td>
<td>1.31 +/- 1.44</td>
<td>1.56 +/- 2.64</td>
<td>1.40 +/- 1.56</td>
<td>2.30 +/- 3.26</td>
<td>1.45 +/- 1.87</td>
</tr>
<tr>
<td>Total Hospital Visits (Mean ± SD)</td>
<td>0.02 +/- 0.27</td>
<td>0.16 +/- 0.58</td>
<td>0.41 +/- 0.99</td>
<td>0.57 +/- 1.14</td>
<td>0.36 +/- 0.99</td>
<td>0.2 +/- 0.69</td>
</tr>
<tr>
<td>Total Pharmacies used (Mean ± SD)</td>
<td>0.00</td>
<td>1.53 +/- 0.99</td>
<td>2.44 +/- 2.04</td>
<td>3.09 +/- 2.60</td>
<td>3.44 +/- 2.87</td>
<td>1.84 +/- 1.60</td>
</tr>
<tr>
<td>†Total Types of Meds Prescribed (Mean ± SD)</td>
<td>1.2 +/- 0.49</td>
<td>4.00 +/- 2.23</td>
<td>6.64 +/- 3.90</td>
<td>9.43 +/- 4.27</td>
<td>13.12 +/- 6.62</td>
<td>2.45 +/- 1.77</td>
</tr>
</tbody>
</table>

*Patient’s age at first prescription of interest.
¥Procedures and/or surgeries related to listed categories.
†Drug use with therapeutic class code description of: Anti-anxiety, Anti-psychotic, Anti-mania, Anti-depressant, Selective Serotonin Reuptake Inhibitors, Benzodiazepine, or Phenothazine.
‡Total number of medications per therapeutic class code description.
<table>
<thead>
<tr>
<th>Variable</th>
<th>NSAIDs Only</th>
<th>Short-Acting Opiates</th>
<th>SLO Only</th>
<th>SLO+ ASH</th>
<th>SLO+ MR/AD</th>
<th>ALL OPIATES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>p</td>
<td>RR</td>
<td>p</td>
<td>RR</td>
<td>p</td>
</tr>
<tr>
<td>Age at t0</td>
<td>1.35</td>
<td>&lt;.0001</td>
<td>1.27</td>
<td>&lt;.0001</td>
<td>1.38</td>
<td>0.0041</td>
</tr>
<tr>
<td>Age at Injury Date</td>
<td>1.35</td>
<td>&lt;.0001</td>
<td>1.28</td>
<td>&lt;.0001</td>
<td>1.43</td>
<td>0.0018</td>
</tr>
<tr>
<td>Sex</td>
<td>1.06</td>
<td>0.85</td>
<td>1.53</td>
<td>0.0037</td>
<td>0.93</td>
<td>0.89</td>
</tr>
<tr>
<td>Any Surgery</td>
<td>0.91</td>
<td>0.86</td>
<td>1.12</td>
<td>0.40</td>
<td>0.34</td>
<td>0.03</td>
</tr>
<tr>
<td>Average M.E.D.</td>
<td>.</td>
<td>.</td>
<td>1.001</td>
<td>0.37</td>
<td>1.002</td>
<td>0.50</td>
</tr>
<tr>
<td>Drug Route Category</td>
<td>&lt;.0001</td>
<td>1.00</td>
<td>0.57</td>
<td>0.87</td>
<td>0.51</td>
<td>1.02</td>
</tr>
<tr>
<td>Duration on Opiates</td>
<td>1.03</td>
<td>0.03</td>
<td>1.01</td>
<td>0.69</td>
<td>1.01</td>
<td>0.67</td>
</tr>
<tr>
<td>ER Total Visits</td>
<td>1.03</td>
<td>0.86</td>
<td>0.94</td>
<td>0.25</td>
<td>1.01</td>
<td>0.86</td>
</tr>
<tr>
<td>Hospital Total Visits</td>
<td>1.16</td>
<td>0.62</td>
<td>1.07</td>
<td>0.50</td>
<td>1.04</td>
<td>0.87</td>
</tr>
<tr>
<td>Legal Representation</td>
<td>1.15</td>
<td>0.67</td>
<td>1.18</td>
<td>0.20</td>
<td>2.44</td>
<td>0.11</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Married vs Single</td>
<td>1.34</td>
<td>0.43</td>
<td>1.07</td>
<td>0.66</td>
<td>1.96</td>
<td>0.25</td>
</tr>
<tr>
<td>-Separated vs Single</td>
<td>1.63</td>
<td>0.53</td>
<td>1.87</td>
<td>0.07</td>
<td>&lt;.0001</td>
<td>0.99</td>
</tr>
<tr>
<td>-Widowed vs Single</td>
<td>&lt;.0001</td>
<td>1.00</td>
<td>2.82</td>
<td>0.02</td>
<td>16.56</td>
<td>0.02</td>
</tr>
<tr>
<td>-Divorced vs Single</td>
<td>2.11</td>
<td>0.12</td>
<td>1.71</td>
<td>0.01</td>
<td>1.89</td>
<td>0.47</td>
</tr>
<tr>
<td>Maximum M.E.D.</td>
<td>.</td>
<td>.</td>
<td>1.00</td>
<td>0.24</td>
<td>1.00</td>
<td>0.08</td>
</tr>
</tbody>
</table>
Table 3b. Univariate Analysis of Predictors for All-Cause Mortality (Cont.)

<table>
<thead>
<tr>
<th>Procedure Category</th>
<th>NSAIDs Only</th>
<th>Short-Acting Opiates</th>
<th>SLO Only</th>
<th>SLO+ ASH</th>
<th>SLO+ MR/AD</th>
<th>ALL OPIATES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>p</td>
<td>RR</td>
<td>p</td>
<td>RR</td>
<td>p</td>
</tr>
<tr>
<td>- Lumbar vs None</td>
<td>&lt;0.001 0.99</td>
<td>1.39 0.48</td>
<td>1.22 0.85</td>
<td>&lt;0.001 0.97</td>
<td>1.15 0.72</td>
<td>1.39 1.64</td>
</tr>
<tr>
<td>- Cervical /Thoracic vs None</td>
<td>&lt;0.001 0.99</td>
<td>&lt;0.001 0.98</td>
<td>&lt;0.001 0.99</td>
<td>&lt;0.001 0.99</td>
<td>2.02 0.27</td>
<td>1.13 0.04</td>
</tr>
<tr>
<td>- Upper Extremity vs None</td>
<td>0.35 0.30</td>
<td>1.15 0.40</td>
<td>&lt;0.001 0.95</td>
<td>0.46 0.35</td>
<td>1.42 0.43</td>
<td>1.02 0.02</td>
</tr>
<tr>
<td>- Lower Extremity vs None</td>
<td>1.43 0.56</td>
<td>1.06 0.79</td>
<td>0.65 0.46</td>
<td>0.34 0.33</td>
<td>0.26 0.19</td>
<td>0.93 0.14</td>
</tr>
<tr>
<td>- Combination</td>
<td>4.87 0.13</td>
<td>1.15 0.75</td>
<td>0.47 0.47</td>
<td>&lt;0.001 0.97</td>
<td>0.87 0.78</td>
<td>1.02 0.003</td>
</tr>
<tr>
<td>Psychiatric Drug use</td>
<td>.</td>
<td>.</td>
<td>3.07 0.25</td>
<td>&lt;.0001 0.72</td>
<td>0.84 0.81</td>
<td>1.20 0.55</td>
</tr>
<tr>
<td>Spine Surgery</td>
<td>&lt;.001 0.57</td>
<td>1.01 0.97</td>
<td>1.36 0.77</td>
<td>&lt;.001 0.34</td>
<td>1.32 0.39</td>
<td>1.35 0.19</td>
</tr>
<tr>
<td>Total Medication Use</td>
<td>0.99 0.96</td>
<td>1.31 &lt;.0001</td>
<td>1.21 0.04</td>
<td>1.32 0.04</td>
<td>1.01 0.93</td>
<td>1.15 &lt;.0001</td>
</tr>
<tr>
<td>Total Pharmacies</td>
<td>.</td>
<td>.</td>
<td>1.05 0.38</td>
<td>1.04 0.72</td>
<td>1.07 0.50</td>
<td>0.99 0.78</td>
</tr>
<tr>
<td>Medication</td>
<td>Subjects (%)*</td>
<td>Deaths (%) **</td>
<td>Relative Risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs only</td>
<td>2,934 (3.11%)</td>
<td>45 (1.53%)</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-Acting Opiates (SA)</td>
<td>11,359 (12.04%)</td>
<td>214 (1.88%)</td>
<td>1.23 (0.89, 1.69)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short and Long- Acting Opiates (SLO)</td>
<td>743 (0.79%)</td>
<td>18 (2.42%)</td>
<td>1.57 (0.92, 2.71)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLO and/or Anti- anxiety and/or Sedatives, and/or Hypnotics (SLO + ASH)</td>
<td>182 (0.19%)</td>
<td>9 (4.95%)</td>
<td>3.22 (1.60, 6.49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLO and/or Muscle Relaxers and/or Anti- Depressants (SLO + MR/AD)</td>
<td>1,733 (1.84%)</td>
<td>46 (2.65%)</td>
<td>1.73 (1.15, 2.59)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Opiates</td>
<td>14,002 (14.84%)</td>
<td>285 (2.04%)</td>
<td>1.35 (0.99, 1.84)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Percentage based on 94,364 subjects with medication data.
**Percentage based on total subjects with medication of interest
### Table 5a. Multivariate Analysis – NSAIDs Only

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at t0 (per 5 years)</td>
<td>1.06</td>
<td>(1.03, 1.09)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

### Table 5b. Multivariate Analysis – Short and Long Acting Opiates Only

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at t0 (per 5 years)</td>
<td>0.39</td>
<td>(0.21, 0.71)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age at Injury Date (per 5 years)</td>
<td>3.55</td>
<td>(1.87, 6.76)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Any Surgery</td>
<td>0.33</td>
<td>(0.12, 0.96)</td>
<td>0.04</td>
</tr>
<tr>
<td>Legal Representation</td>
<td>3.07</td>
<td>(0.95, 9.89)</td>
<td>0.06</td>
</tr>
<tr>
<td>Total Medication Prescribed</td>
<td>1.45</td>
<td>(1.19, 1.76)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

### Table 5c. Multivariate Analysis – Short and Long Acting Opiates + Anti-Anxiety, Sedatives, & Hypnotics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Surgery</td>
<td>0.21</td>
<td>(0.06, 0.78)</td>
<td>0.02</td>
</tr>
<tr>
<td>Total Medication Prescribed</td>
<td>1.38</td>
<td>(1.07, 1.78)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
### Table 5d. Multivariate Analysis – Short and Long Acting Opiates + Muscle Relaxers and Anti-Depressants

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Injury Date</td>
<td>1.36</td>
<td>(1.17, 1.57)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(per 5 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration on Opiates</td>
<td>0.99</td>
<td>(0.98, 1.001)</td>
<td>0.07</td>
</tr>
<tr>
<td>(per 30 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER Total Visits</td>
<td>1.06</td>
<td>(1.02, 1.09)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex</td>
<td>2.11</td>
<td>(1.10, 4.02)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### Table 5e. Multivariate Analysis – Short Acting Opiates Only

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at t0 (per 5 years)</td>
<td>1.32</td>
<td>(1.24, 1.40)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration on Opiates</td>
<td>0.98</td>
<td>(0.96, 1.004)</td>
<td>0.10</td>
</tr>
<tr>
<td>(per 30 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital Status</td>
<td>0.49</td>
<td>(0.26, 0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex</td>
<td>1.91</td>
<td>(1.43, 2.58)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total Medication Prescribed</td>
<td>1.32</td>
<td>(1.19, 1.46)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

### Table 5f. Multivariate Analysis – All Opiates

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Date of Injury</td>
<td>1.33</td>
<td>(1.26, 1.41)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(per 5 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration on Opiates</td>
<td>0.98</td>
<td>(0.97, 0.99)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(per 30 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital Status</td>
<td>0.47</td>
<td>(0.27, 0.82)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex</td>
<td>1.90</td>
<td>(1.47, 2.45)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total Medication Prescribed</td>
<td>1.25</td>
<td>(1.17, 1.33)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Figure 1. Selection of Patients with Opiates and NSAIDs Prescriptions

772,136
Number of injured workers from 01/01/2000 - 06/10/2011

752,688
Number of patients after removing erroneous/incomplete demographics

95,729
Number of patients with pharmacy data

94,364
Number of patients after excluding diagnoses: cancer, pregnancy, HIV disorder, liver disease, respiratory failure, organ transplants, cardiovascular disorder, end stage renal diseases, other end-stage illnesses, autoimmune or systemic inflammatory disorders, severe trauma, hospitalization within 30 days of injury. Patients with intravenous and nasal drug routes are also excluded.

Cases
Patients that took medication of interest exclusively of other groups
Short-Acting Opiates (SA-11,359), Short and long-acting opiates (SLO-743), SLO and/or anti-anxiety and/or sedatives and/or hypnotics (SLO + ASH 182), SLO and/or muscle relaxers and/or antidepressants (SLO +MR/AD-1733)

Controls
Subjects that took NSAIDs only
(2934)
BIBLIOGRAPHY


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