OPIOID ANALGESIC PRESCRIBING AND OVERDOSE MORTALITY IN NORTH CAROLINA

Nabarun Dasgupta

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Approved by:

Steve Marshall, Ph.D.

Carri Casteel, Ph.D.

Michele Jonsson Funk, Ph.D.

Scott Proescholdbell, M.P.H.

Kurt Ribisl, Ph.D.

ABSTRACT

NABARUN DASGUPTA: Opioid Analgesic Prescribing and Overdose Mortality in North Carolina
(Under the direction of Steve Marshall)

Mortality from drug overdose has risen since the 1990s. Composite International Classification of Disease (ICD-10) overdose definitions in state vital statistics surveillance may include deaths that do not involve controlled substances while missing deaths that do. We evaluated seven ICD-10-based definitions using North Carolina mortality data from 2008 through 2011. Overdose deaths varied by definition, ranging from 734 to 1,202 per year. Up to 16.1% of deaths using the national definition showed no evidence of controlled substance involvement, however, additional deaths involving controlled substances were not identified. We propose a definition that includes deaths from substance use disorders, but removes deaths from pharmaceutical adverse events, resulting in 1,149 deaths per year from overdoses involving controlled substances.

Strong associations have been observed between amount of opioids dispensed and overdose mortality. Yet, clinical trials consistently show safety of opioid analgesics at high doses. To explore this paradox we conducted a prospective cohort study among North Carolina residents in 2010 to quantify dose-dependent overdose risk in routine clinical practice. Dispensing data were matched to overdose deaths identified in medical examiner records. Incidence rates were estimated using regression models. Exposure of 1,133,957 person-years to opioid analgesics was observed, corresponding to 22.8% of residents. Incidence rates appeared to increase gradually at lower doses,

but stayed elevated beyond 200 mg average daily milligrams of morphine equivalents. The dose-dependent effect was exacerbated by co-prescribed central nervous system (CNS) depressants; rates were ten times higher among opioid analgesic patients receiving benzodiazepines. Since 80% of patients were co-prescribed benzodiazepines, high dose opioid analgesic use during routine clinical practice was more risky than observed in trials that exclude patients receiving other CNS depressants. Exploring formulation impacts, incidence rates were ten times greater among those receiving combinations of extended-release (ER) and immediate-release (IR) opioid analgesics compared to those receiving only IR. At higher doses, for every 1,300 patients treated for a year with ER instead of IR, there would be one additional overdose death. As a society we urgently need to understand what level of prescribing would strike the correct balance between access to care concerns and inadequately trained physicians.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACE	Angiotensin-converting-enzyme
AIDS	Acquired immune deficiency syndrome
ASTHO	Association of State and Territorial Health Organizations
AUC	Area under the curve
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CLR	Confidence limit ratio
C_{max}, C_{min}	Maximum and minimum plasma concentration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CSTE	Council of State and Territorial Epidemiologists
DEA	Drug Enforcement Administration
DMHDDSAS	Division of Mental Health, Developmental Disabilities and Substance Abuse Services
DPH	Division of Public Health
ER	Extended-release
FDA	Food and Drug Administration
GABA	γ-Aminobutyric acid
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICD	International Classification of Disease
INCB	International Narcotics Control Board
IQR	Inter-quartile range
IR	Immediate-release
IRR	Incidence rate ratio

ISW	Injury Surveillance Workgroup
ITTT	Intent-to-treat-type
LOESS	Locally smoothed regression
ln	Natural log
NB2	Negative binomial, type 2
NC	North Carolina
NCHS	National Center for Health Statistics
NDC	National Drug Code
NHANES	National Health and Nutrition Examination Survey
NNH	Number needed to harm
NSAID	Non-steroidal anti-inflammatory drug
NSDUH	National Survey on Drug Use and Health
OCME	Office of the Chief Medical Examiner
OPR	Opioid pain reliever
OR	Odds ratio
mg	Milligrams
MME	Milligrams of morphine equivalents
LL	Lower limit
PMP	Prescription monitoring program
REMS	Risk Evaluation and Mitigation Strategies
SCHS	State Center for Health Statistics
UL	Upper limit
UNC	University of North Carolina at Chapel Hill
US	United States

CHAPTER 1

INTRODUCTION

Overview

Non-medical use and misuse of prescription drugs are large and growing public health problems in the United States. Deaths from drug overdoses now account for more fatalities than motor vehicle-related deaths in the US [1]. The majority (65% nationally) of drug overdose deaths involve prescription opioid pain medications [2]. These fatalities are a result of both patients using the drugs for pain relief and those using the drugs primarily for euphorogenic effects.

Quantifying opioid-related overdose morbidity and mortality has been a persistent public health challenge. Over the last decade, vital statistics data collection systems have adopted the use of International Classification of Disease (ICD) codes to classify events. State-based vital statistics rely on composite ICD-based definitions of “overdose” that may include deaths that do not involve controlled substances, and may also be missing deaths that do involve controlled substances. For example, the main national ICD-based definition includes deaths resulting from “poisoning” by controlled substances, as well as deaths due to unintended adverse drug reactions from non-controlled substances, while ignoring deaths from substance abuse. While seemingly illogical, the origins lie in the idiosyncratic and historical conventions of ICD. Recent guidelines to aid the uniform identification of drug-related morbidity and mortality have

been issued by the Injury Surveillance Workgroup 7 (ISW) [3], but have not been evaluated. The sensitivity and specificity of the various ICD-based definitions of "overdose" is currently unknown.

At the national level, a linear ecological association has been observed between the total amount of opioids dispensed and parallel overdose morbidity and mortality, going back 15 years. This association has been observed at the national, state, and county level [4,5,6,7,8,9,10,11,12]. This has led to the general belief that opioids are overprescribed. However few studies have documented the association at the level of the individual patient [13,14,15,16,17]. Yet, clinical trials and their meta-analyses consistently show safety of opioid analgesics at high doses [18,19,20,21,22,23]. Additionally, there are concerns that many individuals in chronic pain in the United States do not receive adequate analgesic relief, and there is limited safety data on overdose risk at higher doses (e.g., over 150 mg per day) that are commonly prescribed to chronic pain patients in clinical practice. The ecological studies conducted to date have provided limited information relevant to current clinical practices. Among high-dose opioid analgesics, there are clinical choices between immediate-release (IR) formulations dosed every four to six hours, and extended-release (ER) formulations dosed once or twice per day. There is vigorous debate in the policy realm about the relative safety of these two types of formulations.

Thus, there is a pressing need to more clearly quantify the dose-dependent association between opioid analgesic utilization and overdose risk at the individual level. We hypothesized that ER opioids would be associated with greater overdose mortality than IR opioids, including at higher doses. We based this hypothesis on ecological studies that suggested a linear association between amount of opioid analgesics dispensed and overdose mortality at the population level, and the fact that ER opioids have more milligrams of active ingredient per unit than IR opioids. However, in order to

evaluate this hypothesis, we need to evaluate and compare the various definitions of opioid-related mortality.

Specific Aims

Aim 1. Evaluate definitions of opioid-related mortality for internal consistency.

Aim 1 Scope: Use decedent-level characteristics to evaluate differences between seven ICD-10-based definitions of opioid overdose mortality from North Carolina vital statistics. Evaluate the impact of including substance use disorders and pharmaceutical adverse events codes in definitions of overdose. Propose a definition for use in surveillance based on the findings.

Aim 2. Quantify the association between high-dose opioid analgesic utilization and opioid-related mortality.

Aim 2 Scope: Conduct a prospective cohort study using mortality data linked to opioid analgesic dispensing data to examine the association between dose and overdose risk. Describe patterns of clinical opioid analgesic utilization, focusing on prescribers, prescriptions, and patients, with attention to opioid substance and formulation type. Examine the relationship between high dose opioid analgesic prescribing and overdose mortality, evaluate the findings of the most similar published study [17], and assess the influence of benzodiazepine co-prescribing on dose-dependent overdose mortality. Evaluate possible differences between high doses of IR and ER opioid analgesics on overdose mortality.

CHAPTER 2

BACKGROUND

Overview

This section reviews the epidemiological, clinical and pharmacological knowledge base relevant to pain management and overdose. It includes a literature review on published individual-level studies of opioid analgesic dose and overdose death.

International Context

The use of opioids in the management of pain has long been tempered with concerns about abuse, addiction, and diversion of medicinal supplies into illicit channels of trade. The World Health Organization designates four opioids (morphine, codeine, methadone, buprenorphine) used to treat pain and addiction on the *Model List of Essential Medicines* [24]. The cultivation, manufacture, distribution, and dispensing of opioids are subject to international control, with the intent of assuring access for legitimate medical and scientific purposes while minimizing diversion and abuse [25]. These international obligations continue to influence national control programs.

There are significant differences among nations both with respect to utilization of controlled substances and the degree of concern over diversion of such drugs to unsanctioned use [26]. The United States and Canada have the highest per capita consumption of opioids in the world, according to the annual *Report of the International*

Narcotics Control Board (INCB), the United Nations body responsible for monitoring and enforcing the treaties that apply to the international manufacture, sale and distribution ofcontrolled substances [25]. These countries also have high levels of public concern with the non-medical use and abuse of prescription and illicit drugs. The public health problem created by the inappropriate use of opioids is pervasive in both countries.

Drug-related Mortality in the United States

In the United States, rates of mortality attributable to unintentional drug poisoning have risen consistently since the early 1990s [27]. In 2009, the national age-adjusted death rate from drug poisonings was 12.0 per 100,000, making it the leading cause of injury death surpassing motor vehicle-related injuries [28] (Figure 2.1). Overdose is the leading cause of death among young injection drug users in the United States [29] and outpaces mortality from injection-borne infectious diseases [1]. By way of comparison, in 2008 the age-adjusted mortality rates per 100,000 were 2.5 for viral hepatitis and 3.1 for HIV/AIDS [1].

The Centers for Disease Control and Prevention (CDC) report that “in 2007, approximately 27,000 unintentional drug overdose deaths occurred in the United States, one death every 19 minutes” [27]. In 2008, prescription opioid analgesics were involved in 73.8% of drug overdose deaths, meaning they were more frequently involved than heroin, cocaine and methamphetamine combined. The pharmaceutical opioids most often causally identified in post-mortem toxicology reports are fentanyl, hydrocodone, methadone, morphine, oxycodone and oxymorphone [6,27].

The amount of opioids prescribed in the United States has risen substantially over the past decade, leading many to propose that a linear correlation exists between the amount of opioids dispensed and the unintended negative consequences associated

with these medicines (Figure 2.2). This observed association suggests that opioid analgesics are “overprescribed” for post-operative and other types of pain [30].

It is clear that, among the pool of decedents, there are heterogeneous reasons for ingesting prescription opioids. Deaths occur in pain patients who mistakenly take more pain relievers than directed by clinicians (misuse), as well as individuals using diverted opioids for euphoric effect, e.g., to get high. The percent of overdose decedents who had a prescription for the opioid involved in their overdose fatality is in the range of 44% to 91%, varying by state and definition [9,31,32,33,34], suggesting that substantial portions of those dying from an overdose are being exposed to pharmaceutical opioids outside of medical supervision. In contrast to mortality, in a national survey of young adults who endorsed nonmedical use of prescription analgesics, 53% reported they received them free from a relative or friend [35]. However, the median age of overdose death in the United States is around 40 years [36], while the peak in nonmedical use is in the 20s, suggesting that opioid use is causal but not sufficient to result in overdose death. Regardless of the reasons for ingestion of an opioid analgesic (e.g., pain, addiction, etc.), there are multiple factors that influence whether the exposure will result in an overdose, and others that influence whether the overdose will be fatal.

Pain and Public Health

The belief in the causal connection represented by the linear association between opioid prescribing and overdose (Figure 2.2) is at the heart of much of the policy response. The assumption that reducing the amount of opioid analgesics prescribed will result in fewer overdose deaths, although logical, has been subject to limited empirical investigation.

In pharmacoepidemiology, the underlying prevalence of disease that a medicine is intended to treat can be used as a rough measure to address whether a drug is

prescribed at appropriate levels in the population. However, there are substantial limitations in estimating national pain prevalence, let alone the prevalence of painful conditions that would be responsive to opioid therapy. Pain is by its very nature subjective, and no biometric test can accurately predict the amount of pain an individual is in. Definitions of pain in the major federally sponsored self-report surveys (e.g., National Health and Nutrition Examination Survey [NHANES]) vary greatly, do not distinguish acute from chronic pain, do not attempt to link pain to specific medical conditions, and often exclude children and institutionalized populations.

In one of the few population-based estimates of its kind, the CDC reports that 30% of Americans ages 45-64 reported problems with pain lasting more than 24 hours in the previous month [37]. It remains an open question how many of these individuals would benefit from opioid pharmacotherapy for chronic pain. Other CDC data suggest that the most common causes of pain in the last three months are musculoskeletal injuries, with lower back pain being the most common (Figure 2.3). There is relatively little debate on the appropriateness of using opioids in cancer pain, although what constitutes “cancer pain” can depend on the perception of the physician. However, despite the prevalence of musculoskeletal pain, and a plethora of clinical trials showing efficacy, the use of opioid analgesics in chronic non-cancer pain has recently been a highly contested area of clinical and policy debate focused on the Food and Drug Administration (FDA) [38,39].

In a recent report, *Relieving Pain in America*, the Institute of Medicine attributes the observed rise of the prevalence of chronic pain conditions to greater expectations for pain relief among patients, degenerative musculoskeletal disorders of an aging population, obesity, increased survivorship after traumatic injury and cancer, and increases in the number and complexity of surgical procedures [40]. Studies of pain in nursing homes and among war veterans consistently reveal that they receive inadequate pain treatment; even if the patients are receiving opioids, the dose may not be sufficient

to address pain needs [41,42,43]. Paradoxically, pain appears to be under-treated in the United States in some populations, and yet there is a belief that opioids are overprescribed with resulting unacceptable levels of overdose. The continued outpatient use of opioid analgesics is contingent upon our ability to address the health and societal concerns associated with broader availability of these essential medicines.

Opioid Pharmacology and Pain Management

Clinical practice differentiates between three main types of pain frequency: acute, chronic and breakthrough [44]. Acute pain usually arises from minor physical injuries, limited surgical procedures, headaches, etc. The pain is intermittent and resolves in less than a month. Chronic pain (or “persistent pain”) can arise from more serious injuries and invasive surgical procedures, cancer, and degenerative nerve and musculoskeletal diseases (e.g., fibromyalgia, lupus, etc.), often with genetic underpinnings. The pain lasts more than a month. Breakthrough pain is a phenomenon that routinely occurs in patients whose pain is otherwise well-controlled (using opioid analgesics or other pharmacotherapies). In these instances, a sharp and temporary pain may manifest itself and require additional pain medication.

Another dimension of pain is its intensity. Mild pain usually does not require opioid pharmacotherapy, and can be controlled with over-the-counter medications, non-opioid prescription drugs, and physical manipulation (e.g., massage), and often self-resolves without intervention. When pain results in interference with daily functioning and sleep, it is classified as moderate-to-severe, although in practice the differentiation between moderate and severe is often subjective.

The active opioid substance in modern analgesics in the United States can be classified broadly into opioids that are: (1) full mu-opioid receptor agonists (fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone),

and (2) those that have partial effect at the mu-opioid receptor and may also have action in other neurophysiolgical pathways that modulate the perception of pain (e.g., serotonin, γ-Aminobutyric acid [GABA], etc.). The latter have less risk for respiratory depression due to the lower levels of central nervous system depression (tramadol, propoxyphene, buprenorphine, with codeine and meperidine of intermediate risk). Other opioid formulations are used in modern medicine to suppress cough, usually found as syrups and primarily containing codeine (also hydrocodone), but are rarely implicated in overdose deaths. In addition to lower potency of the active ingredient, these liquid formulations contain excipients that make it difficult to consume large quantities, and are therefore placed in a lower controlled substance schedule. We do not include these in the definition of "opioid analgesics," a distinction from many other studies. This distinction becomes relevant when we analyze the association between opioid analgesics and overdose mortality in Aim 2.

In general, opioids increase activity at one or more G-protein–coupled transmembrane molecules, known as the μ-, δ-, and κ-opioid receptors. These receptors are activated by both endogenous opioid peptides and pharmaceutical opioids. Endogenous opioids (endorphins, enkephalins, dynorphins and endomorphins) function as hormones and neuroregulators in the limbic system and elsewhere, and are responsible for feelings of well-being and analgesia. They also control respiration and many other roles that are not fully characterized. The receptors are widely distributed throughout the human body; those in the anterior and ventrolateral thalamus, the amygdala, and the dorsal-root ganglia mediate nociception. Opioid agonists also bind to receptors in the gastrointestinal tract to decrease gut motility (e.g., constipation is a common clinical manifestation of long-term opioid pharmacotherapy). Based on knockout mouse studies, of the three known opioid receptors, the μ-opioid receptor is believed to be responsible for the preponderance of clinical effects of analgesia and

manifestations of tolerance [45]. Unlike endogenous opioids that naturally cycle in concentration in the extracellular matrix, repeated dosing of pharmaceutical opioids or heroin leads to persistent binding and desensitization of these receptors leading to a state of tolerance whereby more of the opioid must be administered over time to achieve the same clinical effects. Thus, when exogenous opioids are abruptly discontinued, resensitization of these receptors leads to symptoms of opioid withdrawal (e.g., agitation, anxiety, diarrhea, muscle aches, insomnia, vomiting, etc.) [46].

There are more than a dozen alkaloids that naturally occur in the plant *Papaver somniferum* (*somniferum* means to cause sleep in Latin). Of these, morphine, codeine and thebaine are the most plentiful, and these molecules can be modified to produce drugs that have varying degrees of biological effects. Modifications of moieties give rise to differing side effect profiles (e.g., more potent opioids cause less constipation, oxymorphone is associated with less itching than codeine, etc.), while maintaining structural similarity. Because of the differences in potencies between opioids, clinicians refer to equianalgesic conversion tables when switching patients from one opioid to another during opioid rotation. Clinically, opioid rotation can assist in improving side effect profiles and reducing tolerance for patients maintained on chronic mono-opioid therapy. While these are rough guidelines for clinical conversion, the tables can be used in epidemiologic research to standardize by potency when analyzing utilization data. Morphine is the archetypical molecule and data are often presented in terms of “milligrams of morphine equivalents” (MME).

Among the pharmaceutical opioid formulations available in the United States there is a broad distinction between short-acting (“immediate release” [IR]) opioid formulations and long-acting (“controlled-release” or “extended-release” [ER]) analgesics. IR opioids are intended for use in acute pain, and often come combined with acetaminophen or ibuprofen. Common branded IR opioids contain oxycodone (Percocet, Tylox, etc.),

hydrocodone (Vicodin, Lortab, Lorcet, etc.), hydromorphone (Dilaudid), and oxymorphone (Opana). ER formulations have labeled indications of moderate-to-severe pain where around-the-clock analgesia is required. These drugs are found as tablets or capsules with slow-release mechanisms and transdermal patches that regulate the elution of opioid over 12 or 24 hours. Some branded ER opioids are: fentanyl (Duragesic patch), hydromorphone (Exalgo), morphine (MS Contin, Kadian, Avinza, Embeda), oxycodone (OxyContin), oxymorphone (Opana ER), tramadol (Ultram ER). Methadone is also prescribed as a solid oral tablet for chronic pain management. Since the plasma half-life of methadone is sufficiently long enough to allow for chronic pain control with single doses (e.g., without a pharmaceutically engineered extended-release mechanism), it is considered a “long-acting” (LA) opioid, but is often classified alongside ER opioids, as we have done in our research. The IR opioids have one recognized sub-category, called “ultra rapid release” that have fentanyl as an active ingredient. Fentanyl is a potent synthetic opioid that has quick onset, a short duration of action, and moderate affinity for the μ-opioid receptor. These products are used for sudden debilitating spikes in pain intensity lasting less than an hour, known as breakthrough pain (“flare ups”), for patients whose pain is being controlled with around-the-clock analgesic(s). These products come in different formulations: oral lozenge (Fentora), on a stick as “lollipops” (Actiq), nasal spray (Lazanda), buccal soluble film (Onsolis), and sublingual tablet (Abstral). These products have labeled indications only for cancer pain, but are widely used for non-cancer pain. In general, they are expensive products and used much less frequently than other IR opioids for breakthrough pain.

The advent of ER opioids in the United States can be traced back to the mid-1980s. While long-acting methadone had been available earlier, the launch of MS Contin (extended-release morphine; Purdue Pharma, Stamford, Connecticut, United States) was the first extended-release opioid product engineered to slowly release a short-acting

opioid during the transit of the tablet through the gut, and allowed for a single tablet to be taken every 12 hours. The other IR opioid formulations on the market at the time required dosing every four to six hours. The ER formulation was lauded by pain patient advocates for allowing patients to receive adequate analgesia to sleep through the night or work through the day, without having interruptions for additional dosing. The pharmacokinetic benefit is that the plasma concentration of the opioid remains at a steady state during the 12 or 24 hour dosing period; using the same amount of IR opioid would result in “peaks and valleys” in plasma concentration with corresponding vacillations in pain relief. The justification for extended-release opioid preparations is that a steady, continuous release of the opioid over 12 or 24 hours would lead to better control of chronic pain because of a smaller mean difference in plasma concentration between C_{max} and C_{min}, while maintaining the same area under the curve (AUC).

In addition to steady state plasma concentration, the other oft-cited benefit of ER opioids is that they do not contain acetaminophen, ibuprofen or naproxen. Many immediate-release opioid pain relievers contain ibuprofen (200mg to 400mg) or acetaminophen (325mg to 750mg) in addition to codeine, hydrocodone, oxycodone, propoxyphene, or tramadol. Some brand names of combination products are Ultracet, Vicodin, Percocet, Tylox, and Lortab. However, long-term ingestion of ibuprofen and acetaminophen is associated with kidney failure and hepatic injury, respectively [47]. This is one of the justifications for using extended-release opioids for chronic pain since they do not contain either ibuprofen or acetaminophen [48,49]. FDA-approved labels for non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen-containing analgesics note that taking these for more than a couple of weeks can lead to liver, kidney and gastrointestinal tract damage. In addition to long-term risks with acetaminophen, there is also concern about patients receiving high doses of acetaminophen even over short periods of time. In recognition of the risk of hepatic

injury, the FDA limited the amount of acetaminophen in opioid analgesic combination products to 325mg on January 13, 2011. The labeled upper limit of daily acetaminophen dosing is 4 grams when taken as an immediate-release combination opioid pain reliever. However, due to concerns about overdose risks with extended-release opioids, there is a belief in the pain management community that high doses of combination opioids are being unjustifiably prescribed to patients, partially out of fear of abuse and overdose associated with ER opioids. Therefore, we will examine high-dose and long-term IR opioid analgesic utilization in Aim 2.

While the clinical upside to ER opioids for chronic pain management has been important in hospice and palliative care, the amount of opioid in each ER tablet, capsule or patch is generally significantly more than in IR formulations. The ER formulations may be more attractive outside the medical realm to those seeking to obtain a larger bolus of opioid for their euphorogenic effect, i.e., to get high. The higher mass of opioid also may increase the overdose risk of ER medications over IR medications when taken other than as indicated, when taken without proper clinical monitoring, or when tampered with (e.g., crushed to snort or inject) to intentionally release all the active ingredient at once.

Clinical Practice of Pain Management

As increasing numbers of patients present with chronic pain complaints, it is unavoidable that some will have or have had substance abuse problems. For example, the 2010 federally sponsored “household” National Survey on Drug Use and Health (NSDUH) reported that 12.2% of males and 5.8% of females aged 18 years and older had diagnosable substance dependence or abuse in the past year [50]. While there are clinical tools to differentiate the “legitimate patient” from the “drug seeker,” these distinctions may be difficult to ascertain in a given individual patient. Furthermore, an individual may change their behavior over time. Further complicating medical care is that

those with substance abuse and dependence disorders frequently suffer from severe pain at higher rates than the general population, thus necessitating strategies for addressing both conditions simultaneously [51]. Effective strategies for treating patients with substance use disorders (including opioid therapy) have been articulated [52].

Primary care physicians prescribe more than 40% of the opioids in outpatient use in the United States [53]. ER opioids are prescribed more frequently by anesthesiologists and pain medicine and rehabilitation specialties than others. Prior to the early 1990s, primary care physicians prescribed a much smaller proportion of opioid analgesics, with specialty practices making up the bulk of opioid analgesic prescribing. While increased prescribing by primary care doctors has led to wider access to pain treatment, a general concern is that non-specialized doctors may not have been adequately trained to prescribe these medications safely [53]. At the same time, there are theoretical concerns that physicians will stop prescribing opioid analgesics because of the fear of overdose, leading to decreased access to pain medication. Therefore, we utilized the number of clinicians prescribing opioid analgesics as an important variable in Aim 2.

Opioids are the mainstay for the management of moderate to severe chronic and acute pain the United States. Assessing the evidence for opioid analgesic effectiveness in cancer and non-cancer pain is beyond the scope of this dissertation. A recent review article by the American Society of Interventional Pain Physicians (ASIPP) assessed the evidence of published and unpublished clinical trials and epidemiologic reports about the effectiveness and adverse consequences of opioid therapy [53]. While we have summarized key findings above, we refer readers to this resource for a detailed description of randomized and observational trials.

Etiology of Opioid Overdose

At an individual level, the risk factors for fatal accidental overdose among drug users and pain patients appear to be due to three major factors:

- Opioid exposure in individuals with no or inadequate opioid tolerance

  Examples: new pain patients without a previous history of opioid therapy, infrequent drug users, unexpected fluctuations in purity of heroin
- Opioid exposure after disruption of physiological tolerance

  Examples: resumption of previous dose of opioids after taper for surgery requiring anesthesia, resumption of previously normal dose after release from prison or abstinence-based drug treatment, failure to maintain level of tolerance due to the inability to procure opioids
- Multiple central nervous system depressants

  Examples: combining prescribed opioids and benzodiazepines, drinking alcohol in combination with opioids

Other contributory risk factors for opioid-induced respiratory depression include genetic polymorphisms resulting in idiosyncratic opioid metabolism, place-conditioned responses, and respiratory, circulatory, and metabolic disorders [54]. More broadly construed, deaths involving opioid analgesics result from a combination of physiologic, genetic, and behavioral risk factors, compounded by broader social determinants such as health literacy, poverty, access to healthcare, and farther upstream, the causes of painful conditions such as employment-related injuries, military trauma, motor vehicle accidents and malignancies. Structural determinants, such as stable housing availability, drug laws, and policing practices also play a role. For example, studies of overdose among drug users have documented a “risk environment” that included distrust of medical institutions arising from mistreatment, fear of police, armed international

conflicts, and perceived ineffectiveness of the emergency response as deterrents to seeking medical help in an overdose situation [55,56,57]. Consideration of the risk environment includes the interplay of physical, genetic, behavioral, social, economic, and policy factors that influence opioid-related morbidity and mortality [58,59]. If prevention of opioid analgesic overdose deaths was as simple as reminding people to call 911 in an emergency or improving wording on a prescribed medication's package insert, we would have observed a reversal in the mortality trends involving prescription opioids long ago. Rather, the rising death toll indicates society's failure to recognize the complexity of prescription opioid abuse and the multiple societal and structural factors that contribute to the risk environment and ultimately to overdose mortality.

Beyond overdose mortality, there are social and structural determinants that influence who receives opioid analgesics in the United States. The relationship between poverty, pain and drug abuse is poorly understood. Substance abuse problems and poverty have long reinforced each other, at the extreme intertwined with major psychiatric disorders and homelessness. Employment opportunities in lower income communities are often limited to jobs with considerable physical stress or danger, including military positions; the Institute of Medicine reports that a quarter of those below 100% of the federal poverty level suffer from pain on a regular basis [40]. When sustained over years, on-the-job injuries can give rise to chronic painful conditions, resulting in a downward spiral of disability and poverty. Opioid analgesics may allow those with otherwise debilitating physical injuries to maintain employment, but may also put them at risk of experiencing an overdose. While there is consensus that these factors may influence overdose risk, the individual level measurement of them is beyond the scope of this dissertation analysis.

Published studies on opioid analgesic dose and overdose death

At the societal level, many studies have suggested a co-linear ecologic association between the total amount (by weight or number of prescriptions) of opioids dispensed and overdose morbidity and mortality over the last 15 years [4,5,6,7,8,9,10,11,12]. Locations with the highest levels of opioid prescribing also have the highest rates of overdose deaths involving these substances. Simply summarized: the more that opioid analgesics are dispensed, the greater the overdose morbidity and mortality involving these substances are observed at the population level. These studies universally assume a linear relationship between prescribing and overdose, which may or may not be justified. Although there are caveats about inter-level (ecological) bias [60], there is a tendency in these papers to draw conclusions about individual-level risk of overdose based on opioid exposure.

We identified five peer-reviewed published studies that have attempted to quantify the individual-level dose response between opioid analgesics and mortality. These five studies were identified by tracing references, searches of online databases (e.g., PubMed and Web of Science), but also from having followed the literature and public debate for the past ten years. We did not make an attempt to identify unpublished studies, or to conduct a systematic review or meta-analysis, because that was beyond the scope of this dissertation. However, these studies are widely considered to be the five most important and recent papers on the topic. The five studies are summarized in Table 5.1, and described below.

- *Dunn, 2010:* The earliest and smallest study of note [14] was a cohort study among 9,940 members of a health management organization in Washington, United States, during a nine-year period ending in 2005. That study was limited to patients with chronic non-cancer pain. They observed 51 opioid-related overdoses, six of which were fatal. They reported a HR of 8.9 (95 percent CI:

4.0, 19.7; CLR 4.9) comparing those with at least 100 mg average daily MME to the lowest strata of 1 to less than 20 mg/day MME. This is the only one of the five that includes data on non-fatal overdoses.

- *Bohnert, 2011:* A case-cohort study looked at medical records from a random sample of 154,684 nearly all-male military veterans in the United States during a four-year period ending in 2008, which reported 750 overdose deaths identified through vital statistics [13]. They compared the highest strata, using maximum daily dose, of at least 100 mg/day to a reference group of 1 mg/day to less than 20 mg/day. Their stratified results were HR=12.0 (95 percent CI: 4.4, 32.5; CLR 4.4) for cancer pain, and HR=7.2 (95 percent CI: 4.8, 10.6; CLR 2.2) for chronic non-cancer pain. They did not include transdermal fentanyl in their analysis.
- *Gomes, 2011a:* A nested case-control study [16] in Ontario, Canada included 607,156 non-malignant pain patients receiving opioid analgesics through a public assistance program during a ten-year period ending in 2006, and 498 overdose fatalities identified by coroners. They reported an adjusted odds ratio (OR) of 2.9 (95 percent CI: 1.8, 4.6; CLR 2.5) comparing 200 mg/day or greater to the reference dose of 1 to 19 mg/day. They did not include hydrocodone products.
- *Gomes, 2011b:* Another investigation conducted in Ontario [15] was a cohort study of non-malignant pain patients using records from 154,411 "socioeconomically disadvantaged" beneficiaries of a government drug assistance program. They reported 302 overdose deaths during two years of follow-up ending in 2006. They reported an IRR of 2.2 (95% CI: 1.92.5; CLR 1.3) for 201 to 399 mg/day, with a reference group of average MME >0 to 20 mg/day. They also reported IRR 2.3 (95% CI: 1.7, 3.0; CLR 1.8) for 400 mg/day or greater. This is the only study to provide multiple effect estimates for prescribed dosages over 100 mg/day.

- *Paulozzi, 2012:* The study most similar to Aim 2 was conducted [17] as a population-based case-control study of 730,381 patients, during an 18-month period ending in 2008, which included 300 overdose deaths among residents of New Mexico, United States. They reported an OR of 11.3 (95 percent CI: 8.1, 15.8; CLR 1.9) for those with greater than 120 mg/day average MME, however their control group included controls receiving less than 40 mg/day as well as controls who had not received any opioids. They included buprenorphine products in their exposure, even though these were primarily used for addiction treatment and not pain during the study period.

While it is not surprising to find a dose-dependent association between opioid utilization and associated adverse events, these individual-level studies support the association observed in ecologic studies. However, important limitations to the clinical utility of the evidence base formed by these five studies should be noted. First and foremost, these studies offer limited information on the gradient of risk above 200 mg per day of morphine equivalents. However, there is widespread clinical outpatient use over this level. Second, the interpretation of the studies can be difficult if attempting to distinguish between safety risks inherent to IR versus ER formulations, since both can be used at higher doses. One study reported counts by four specific types of IR and ER formulations but not effect measures [15], and one adjusted for formulation in models without providing stratified results [16]. The generalizability of four out of the five studies is limited due to reimbursement-oriented study settings. The variation between studies in patient selection, drugs included, method of identification of overdose, and duration of observation also makes it difficult to compare them directly to one another. This dissertation sought to address many of these limitations.

FIGURES

Figure 2.1. Annual age-adjusted mortality rates per 100,000 for selected diseases, United States, 2009. There are more drug overdose deaths (pink) than motor vehicle accidents. Drug overdose deaths are a larger cause of death among drug users than HIV or viral hepatitis.

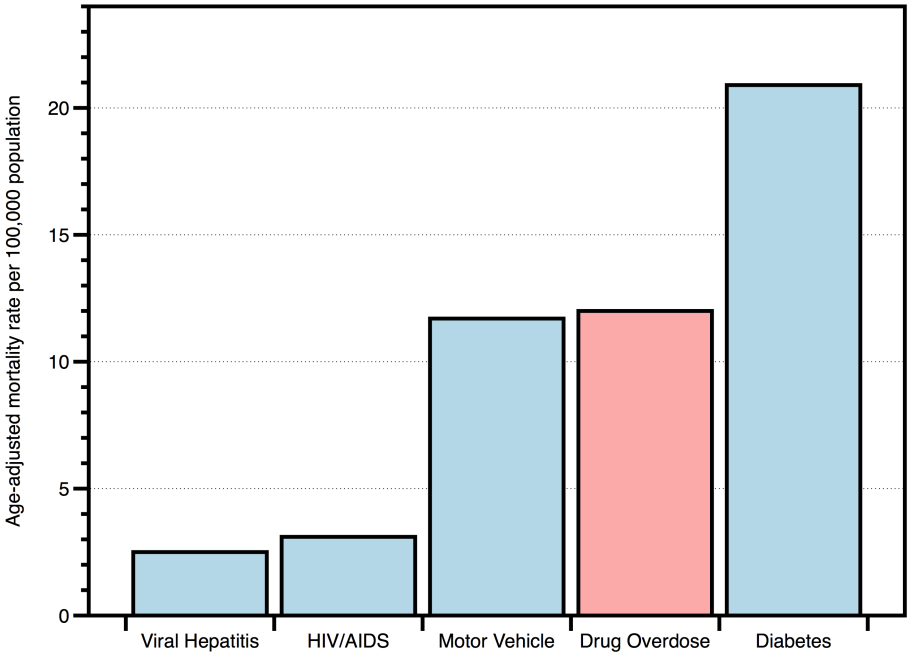


Figure 2.2. **Rates of opioid analgesic overdose death, substance abuse treatment admissions, and kilograms sold, United States, 1999 to 2010.** There has been a co-linear increase in the amount of opioid analgesics dispensed and unintended consequences of their availability. Source: CDC, *Morbidity and Mortality Weekly Report*, November 4, 2011, 60(43); 1487-1492.

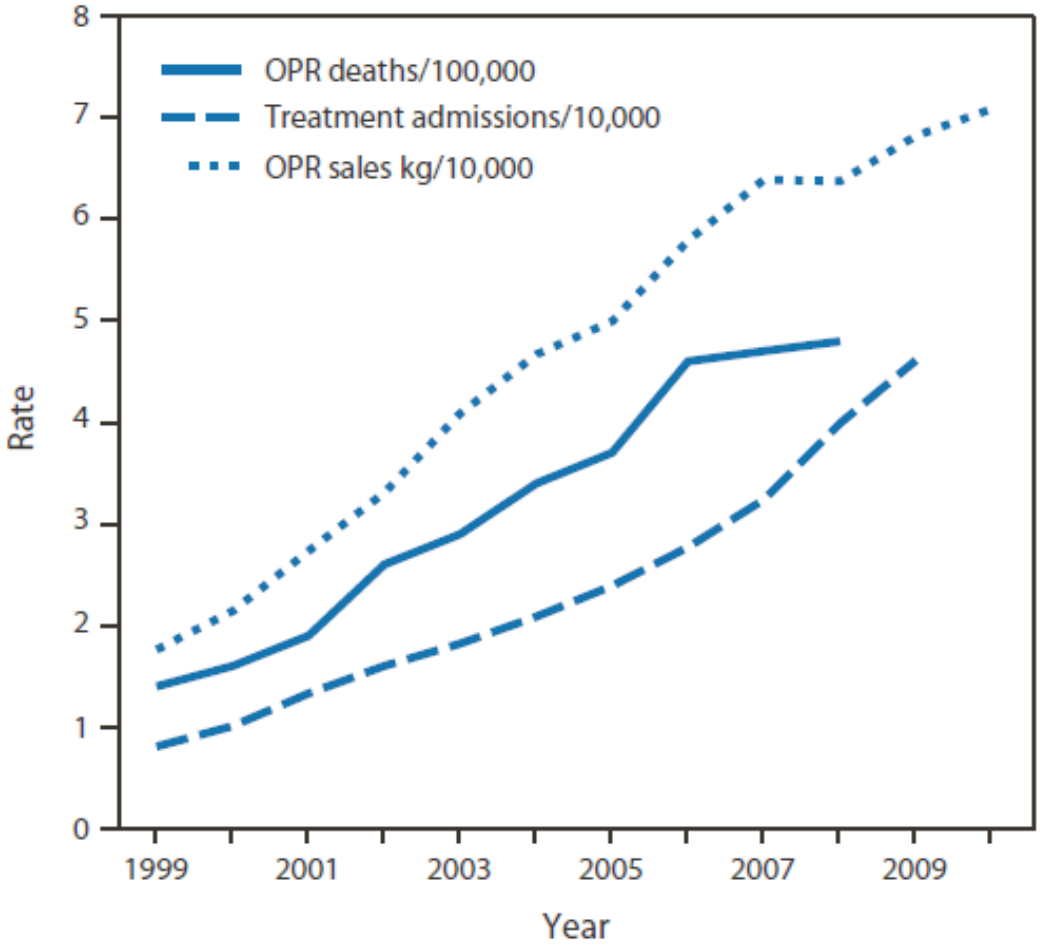
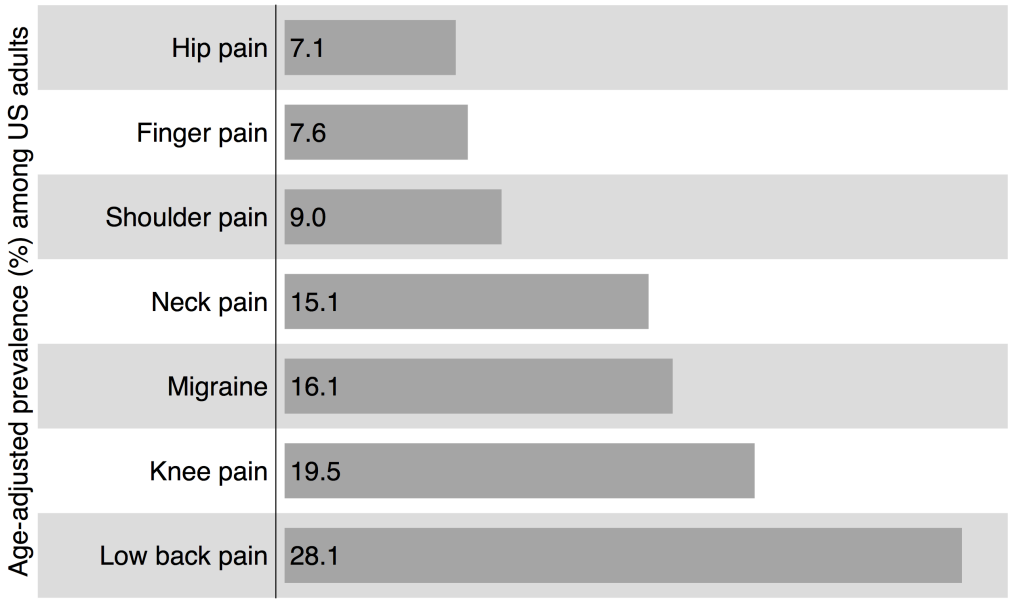


Figure 2.3. Age-adjusted proportion of adults reporting pain in the last three months, by site of pain, United States, 2009. The most common type of chronic pain in the United States is lower back pain. Source: Institute of Medicine, Preface of *Relieving Pain in America*, 2011.



CHAPTER 3

RESEARCH DESIGN AND METHODS

Overview

There are two major types of data used in this analysis, mortality data and prescription utilization data. Aim 1 used only mortality data, while Aim 2 will used both mortality and prescription utilization data. The goal of Aim 1 was to describe in detail the nature of each of seven proposed definitions of overdose and yield a proposed definition for use in surveillance, and evaluate the impact of including substance use disorders and pharmaceutical adverse events codes in definitions of overdose. The goal of Aim 2 was to draw insight from regression models that estimate the association between opioid prescribing dose and overdose mortality risk at an individual level.

In Aim 1, seven ICD-10 based definitions of “drug poisoning” or “overdose” were identified, suggested by ISW and national health authorities in the United States and Australia (described in detail in the following chapter). Deaths matching the seven definitions were identified from among all deaths in NC vital statistics data. Variations in distributions of sociodemographic variables and other drug involvement were explored for each of the seven definitions. Population rates were calculated using Poisson regression with population denominators from NCHS bridged population estimates.

Deaths that may have been due to pharmaceutical adverse events and substance use disorders were identified, and we determined whether these were included in each definition. We compared demographic and co-morbidity information with known deaths from controlled-substance overdoses to judge whether the definitions would benefit from inclusion of these records. Based on these findings, we proposed an ICD-based definition of controlled substance overdose that could be used to potentially generate more accurate estimates of mortality.

An additional analysis, not included as part of the submitted peer-reviewed paper, dealt with “narcotic unspecified” deaths. Despite having markedly different mechanisms of toxicity, the historical artifact of classifying drugs derived from both the opium poppy (*Papaver somniferum*) and the coca leaf (Erythroxylum spp.) as “narcotics” results in a modern day methodological challenge of differentiating deaths involving derivatives of these plants, whether medicinal and illicitly manufactured [3,36]. The differences in the mechanisms of toxicity between opioids and cocaine, as well as separate clinical management, make it important to distinguish between the two in vital statistics data. Therefore, we also evaluated the impact of including “narcotic unspecified” (T40.6) deaths as suggested by three of the seven definitions. There are specific ICD-10 toxicology (T) codes for opium (T40.0), heroin (T40.1), pharmaceutical opioids derived from the opium poppy (T40.2), methadone (T40.3), and synthetic opioids (T40.4); however, cocaine (T40.5) is also included among the T40 codes. The possibility of misclassification arises because deaths involving the catchall “unspecified narcotics” (T40.6) could be due to either opioids or cocaine, leading to inconsistency in whether T40.6 deaths ought be included in opioid overdose surveillance definitions. The fear is that excluding deaths involving T40.6 could lead to an undercount of opioid overdose deaths, but that including them may mean cocaine deaths get counted as opioid deaths.

We used data the same data from NC vital statistics and conducted a subset analysis of all deaths with a T40.5 code. We examined codes for contributing causes-of-death to see if we could identify whether the overdose was due to opioids or cocaine, or other discernible patterns. We supplemented our findings with a brief examination of the literal causes-of-death listed on death certificates as part of ongoing study by the NC Division of Public Health.

We also assessed whether seasonality was present in NC overdose mortality data, in order to determine if this concern would need to be accounted for in modeling when we were originally considering time series modeling. This analysis was not submitted as part of the peer-reviewed paper. We selected Definitions 1 and 4 to represent the broad and more general definitions. Gross time-vary trends were visually assessed with the aid of LOESS smoothing. The Walter and Elwood test for seasonality was applied [61], with and without adjustment for all other deaths among NC residents. This test takes advantage of the coincidence that there are 365 days in a year, and 360 degrees in a circle. Visually, by aggregating counts by day-of-the-year for multiple years, areas of uneven distribution along the perimeter of the circle suggest seasonal trends. Statistically, the amplitude of seasonal variation and the date on which the maximum occurs are modeled as a simple harmonic function, with a goodness-of-fit test based on the chi-squared distribution. Significance was assessed at p=0.10, because the test is low power to detect seasonality. We implemented the test using the SEAST module in STATA version 12 (College Station, Texas, United States) [62].

For Aim 2, we conducted a cohort study of all North Carolina residents (n=9,560,234) in 2010, using electronic controlled substances prescription monitoring program data. The outcomes were identified using data from an ongoing study of overdose mortality conducted by the Division of Public Health. First, we describe patterns of clinical opioid analgesic utilization, focusing on prescribers, prescriptions, and

patients, with attention to opioid substance and formulation type. Then, we examined the relationship between high dose opioid analgesic prescribing and overdose mortality, and potentially confirm the findings of the most similar published study [17]. Finally, we evaluated possible differences between high doses of IR and ER opioid analgesics on overdose mortality.

Data Sources

Three data sources maintained by the North Carolina Division of Public Health provided drug-specific information for this study. Vital statistics were used to identify overdose decedents and describe demographic characteristics. Medical examiner post-mortem toxicology data were used to determine what substances were involved in the overdose death. Finally, data from the North Carolina Controlled Substances Reporting System (CSRS), the state's prescription monitoring program, were used to gather prescription histories for each overdose decedent. These data were combined with CSRS data for all NC residents to create an individual-level analysis dataset. Incidence rate ratios were calculated using Poisson regression implemented with generalized estimating equations.

Mortality Data

Mortality data for 2008 through 2010 were obtained from the North Carolina Vital Statistics Dataverse at The Howard W. Odum Institute for Social Science of the University of North Carolina at Chapel Hill [63]. Vital statistics mortality data for 2011 were obtained from the Injury and Violence Prevention Branch, North Carolina Division of Public Health, Department of Health and Human Services. For the "unspecified narcotics" analysis, death certificate listings of the literal text of the cause-of-death fields for 2010 and 2011 were retrieved. Files from NC Office of the Chief Medical Examiner

were obtained by DPH staff as part of an ongoing collaboration. Information from medical examiner files was extracted into a structured database, for the purpose of this research. Details on determination of death and data abstraction are presented in the methods section of the second paper.

Prescription Data

We used data from the state's Controlled Substances Reporting System (CSRS) to construct exposure variables and quantify opioid analgesic dispensing in North Carolina. The CSRS is one of a set of clinician-oriented databases generally known as prescription monitoring programs (PMP). These state government-run programs are centered around electronic databases with the general goal of limiting overdose and illicit activities (e.g., diversion of medicines from "legitimate" channels) associated with prescription controlled substances. PMPs are funded largely by federal grants through the Department of Justice, supplemented with funding from state governments. Clinicians can query the database before prescribing a controlled substance to determine if the patient has received controlled substances from other healthcare providers; law enforcement and medical examiners are allowed access to the database when they are investigating specific cases. The CSRS was approved by the General Assembly in August 2005 and became operational on July 1, 2007. Data are generated when a prescription for a controlled substance is dispensed at regulated pharmacies in North Carolina. The data that are captured basically include each field of information legally required to be on a North Carolina prescription for a controlled substance. The data are stored locally at the pharmacy and transmitted periodically (within two weeks) to a central database owned by the NC Division of Mental Health, Developmental Disabilities and Substance Abuse Services (DMHDDSAS). We obtained de-identified

data with permission from the Division of Public Health for all prescriptions dispensed from 2009 through 2011.

Converting prescription-level data to a person-level analysis dataset required extensive formatting. The starting dataset was 7.1 gigabytes in size, with 54,825,930 observations. Data cleaning steps are described below, and represented in Figure 3.1.

- 964,678 observations were deleted because county of residence was not a NC county, resulting in 53,861,252.
- In order to eliminate non-controlled substances from the dataset, we decided to manually classify the top 400 named drugs by the number of prescriptions by listing their active ingredient and therapeutic class. This represents 54,757,801 prescriptions from the original dataset, or 99.931% of all the prescriptions. The top 400 drugs in the CSRS dataset included all the major drugs of interest; the top 175 are used by state health department officials to roughly clean the data, however, we wanted greater confidence for individual-level modeling. We were able to include any dispensed controlled substance that had more than five prescriptions per month on average in the whole state. 62,975 observations were deleted because they were neither a controlled substance nor in the top 400, resulting in 53,731,213 observations.
- Days supply was missing or zero for 5,370,484 observations. We imputed the days supply from the rest of the dataset using NDC number for all but 3,364 records, which were dropped. Singly imputed values were derived from non-missing records by NDC.
- In order to classify records by whether they were an ER versus IR opioid analgesic, we matched by NDC number using a MarketScan 2011 Redbook master file obtained from the Centers for Disease Control and Prevention (CDC)

in March 2013. The CDC file had classifications for each product by ER vs. IR, however there were observable mistakes. We therefore used Perl regular expressions to find discrepancies between the literal drug name and the CDC classification, with the literal name considered the higher authority. Search strings included phrases such as “extended-release” and “controlled-release” and “CR”, as well as the known brand names of all market opioids. Further logic checks were implemented based on knowledge of the class of medicines, including ensuring no hydrocodone or oxycodone products were considered ER, all methadone was treated as ER, etc.

- Liquids were also identified using regular expressions (e.g., “liquid,” “tincture”, “syrup,” etc.).
- After reconciliation of the classification, MME conversion factors were used as suggested by CDC to convert each record MME by multiplying the quantity dispensed times the strength times the conversion factor.
- The resulting file had 53,712,910 records.
- Benzodiazepine, stimulant and sleep aid exposure was then determined for 2010.
- Prescriptions for liquids were dropped because it was not possible to determine the units that quantity was measured in (milliliters, vials, ampoules, etc.), thereby making it impossible to calculate MME: 382,872 records.
- We analyzed data from 7,393,375 prescriptions for opioid analgesics dispensed for use in 2010 (including those dispensed in 2009 with days supply that ran into 2010).
- Data for all prescriptions active for at least part of 2010 were identified. Any that crossed the 2009-2010 year threshold were duplicated and treated as separate

prescriptions, with person-days of supply and quantity split proportional to the number of days in each year. Only the active prescriptions in 2010 were retained.

- Then, each prescription active in 2010 was duplicated, one copy each corresponding to the start and end date.
- A brace counting algorithm was implemented using this new date variable to determine the number of days between consecutively alternating open and closed dates, accounting for the day of dispensing.
- The total number of days exposed in 2010 was summed for the exposure person-days, and the balance from 365 was treated as unexposed, with exposure time going into two possible observations per person. Throughout this process, county of residence, benzodiazepine exposure status and other explanatory variables were retained.
- Dummy records were then added to the dataset, corresponding to 365 days of unexposed time for every NC resident who did not receive an opioid analgesic.
- The final analysis dataset had 9,560,234 unique identifiers, with 11,261,504 lines.
- Since CSRS records for decedents were collected by DPH using a separate process, the variable formats did not allow us to positively identify the corresponding prescription-level records in the total CSRS dataset. Therefore, we created a duplicate record for each decedent, and set it to the negative value of any exposed time, thereby mathematically eliminating their exposed person-time contribution when collapsed for Poisson regression.

Once the data were cleaned, many descriptive analyses of interest were possible. We were interested in assessing whether the number of unique prescribers for different opioids had changed over time, from 2009 through 2011. We plotted

time series graphs to examine this. Of particular interest was proproxyphene utilization after it was withdrawn from the market in early 2011.

Time-at-risk Calculations and Determination of Dose "Cutpoints" for Aim 2

We explored the possibility of calculating person-time "as treated" or following "intent-to-treat" principles. Under the former, exposure time is only accrued during the time when the prescription is active. If an event occurs after the end of exposure, it would be classified as having occurred among the unexposed. In the intent-to-treat type (ITTT) method, person-time is accrued from the day the first prescription is received. As illustrated in Figure 3.2, there would be much less exposed time accrued (solid black lines) for the as-treated analysis. There would be fewer cases among the exposed (337 as-treated; 478 for intent-to-treat) among the 629 overdose deaths in Aim 2. We felt that the ITTT was a more appropriate choice for person-time accrual because non-adherence to therapy is a serious concern with opioid analgesics, especially IR formulations prescribed *pro re nata* in the outpatient setting. Put another way, once patients receive opioid analgesics, there is a credible expectation that they may continue to have them around the house if they don't use them all. The ITTT approach better reflects this scenario.

We classified MME exposure initially by tertile and quintiles, but this led to a clustering of deaths at highest stratum. We then divided MME by 20 mg increments, and had strata with few observations at higher MME that could be collapsed to preserve precision. The final strata were chosen to have approximately 15 events per level.

Mortality and Prescription Data Linkage

We used a deterministic one-to-one process to link the mortality and CSRS data. For each overdose decedent, we identified prescriptions in the CSRS that were dispensed within 365 days of death using a two-step process. First, we queried each decedent using the web interface of the CSRS using the first five letters of their last name and their date of birth. Confirmatory matching was the second step, and involved matching the first name, last name and date of birth as recorded on the death certificate. Matching records were extracted electronically. The matching was conducted by staff of DPH and de-identified data were made available to us for analysis.

Statistical Approach for Aim 2

Since an individual could be represented twice in the dataset (exposed, unexposed) we wanted to account violation of independence of observations assumed in regression models. Generalized estimating equations (GEE) offered a flexible and efficient solution that could be used in conjunction with Poisson regression to estimate rates. GEEs use the quasi-likelihood method to solve for parameters. GEE also have the benefit of allowing us to use robust variance estimators to generate standard errors. The choice of GEE also means that we cannot use the likelihood ratio test, or similar metrics, because the quasi-likelihood methods does not produce a numeric solution for log-likelihood. The general form of the Poisson equation is given below.

$$\lambda = e^{\beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k}$$

To generate state-level overdose rates for Aim 1 we used the following equation:

$$\text{Ln(Rate)} = \ln(a/n) = \beta_0 + \beta_1 X_1$$

$$\Rightarrow \quad \ln(a) = \beta_0 + \beta_1 X_1 + \ln(n)$$

Where β_1 represents the number of overdoses, and n is the population at risk, and β_0 is the intercept. For modeling in Aim 2, we used dichotomous indicators (1,0) for each level of the exposure variable (e.g., by MME quantile) to calculate strata-specific rates.

$$\ln(a) = \beta_0 + [\beta_1 X_1 + \ldots + \beta_n X_n] + \ln(n)$$

To calculate the incidence rate ratio, we divided the rate for the contrasting strata of interest by the rate for the reference group, equivalent to back-exponentiating the coefficient for the indicator variable of interest to arrive at the IRR. We multiplied the standard error of the coefficient by 1.96 to derive the 95 percent confidence intervals following standard large-sample assumptions of asymptomatic normality for the model's beta coefficients.

Overdispersion in the Poisson models was assessed using the deviance divided by the degrees of freedom, with greater than 1.0 suggesting the need to consider other models. Overdispersion was not detected (e.g., dispersion of 1.0026757 was observed in the benzo exposed model). We also fit negative binomial models (NB2) for the sake of comparison, and these yielded nearly identical results to the Poisson models.

The estimated covariance matrix was examined during model selection for GEEs. We also fit models specifying independent and exchangeable covariance structures, which yielded nearly identical results. We therefore decided to use Poisson

GEE with an independent structure as the final model in Aim 2, in large part because this model form imposed the fewest assumptions on the data.

Data transformations and statistical modeling were performed in Stata/MP 12.1 (College Station, Texas, USA), running on eight parallel core processors in a Linux-based computing system.

Human Subjects Protection

This research was reviewed by the University of North Carolina Non-Biomedical Institutional Review Board and deemed to be exempt according to federal standards because mortality data and prescription data were provided in de-identified form from government sources.

FIGURES

Figure 3.1. Data cleaning steps for prescription data. Flowchart of data transformations and cleaning steps. Numbers represent the count of unique prescription records in the dataset.

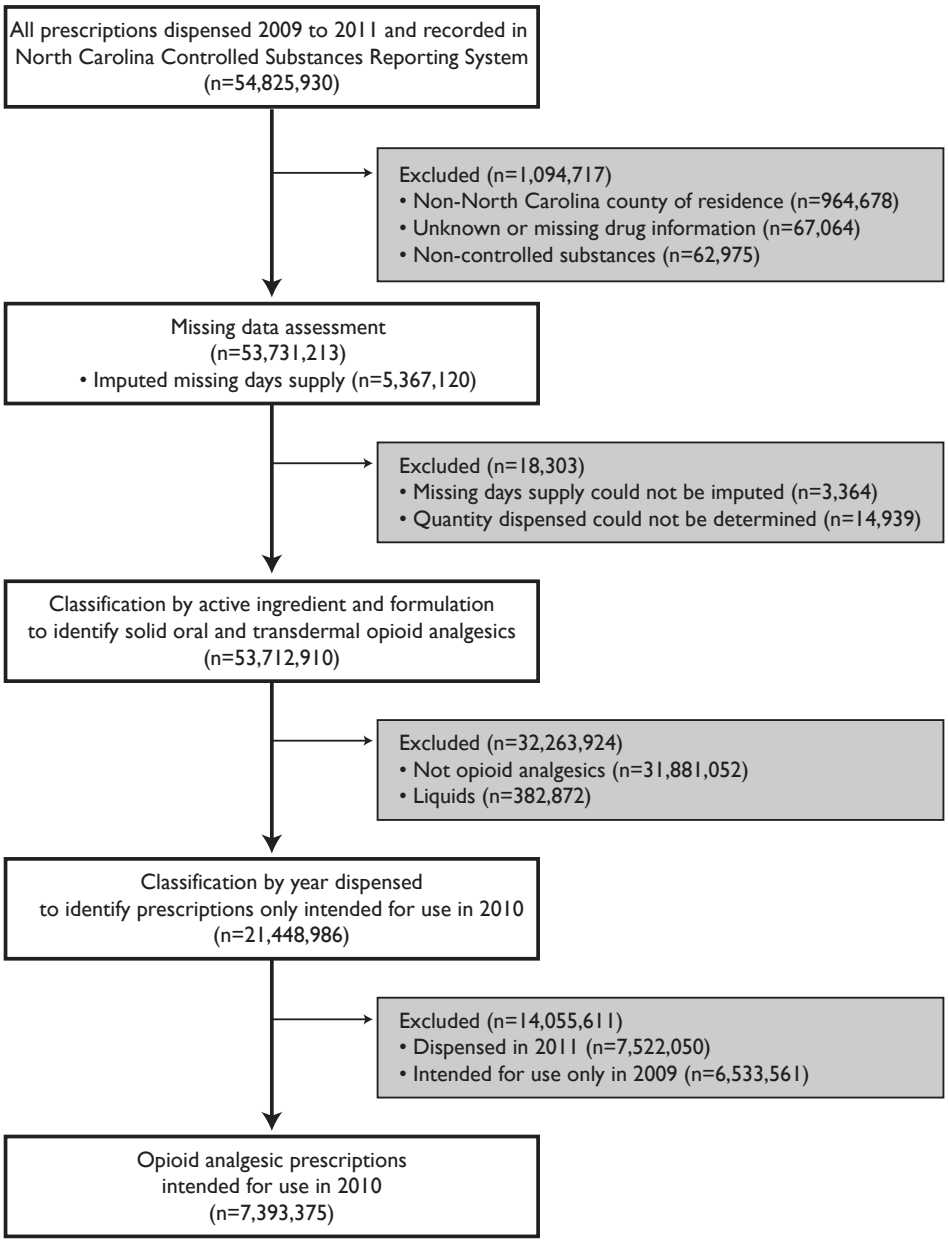
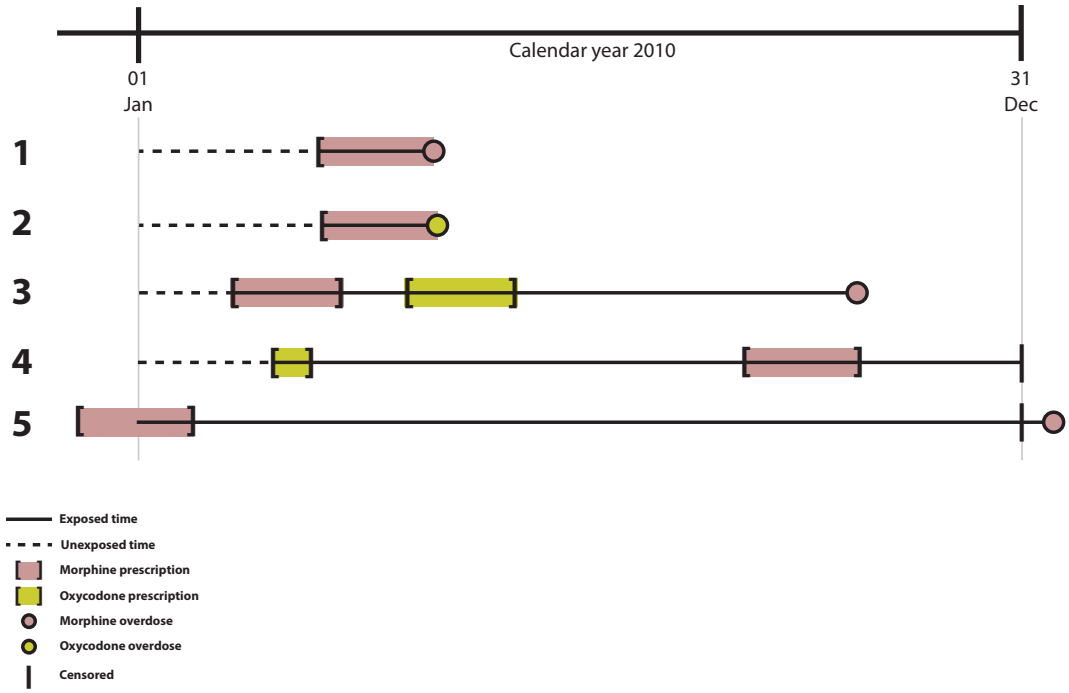


Figure 3.2. Visual representation of person-time accounting. Person-days were calculated using intent-to-treat principles.



CHAPTER 4

EXPLORATION OF DEFINITIONS OF OVERDOSE MORTALITY

Overview

The rate of mortality attributable to drug poisoning has risen consistently since the 1990s. State-based vital statistics registries estimate the incidence of drug overdose deaths using International Classification of Disease 10th revision (ICD-10) codes. Composite ICD-10-based definitions of "overdose" may include deaths that do not involve controlled substances while missing deaths that do.

We evaluated the impact of including substance use disorders and pharmaceutical adverse events codes in definitions of overdose. Seven proposed ICD-10-based definitions, including ones from the Injury Surveillance Workgroup (ISW) and the Centers for Disease Control and Prevention (CDC), were applied to North Carolina mortality data from 2008 through 2011. We examined whether overdose deaths varied among definitions and made a proposal for a definition to be used in future research.

Introduction

In the United States, the rate of mortality attributable to drug poisonings has risen consistently since the early 1990s [64,65]. In 2008, the national age-adjusted death rate

from drug poisonings was 11.9 per 100,000, making it the leading cause of injury death, surpassing motor vehicle-related fatalities [66]. Drug poisoning mortality outpaces injection-borne infectious diseases, including HIV and viral hepatitis, as the leading cause of death among young injection drug users in the United States [67].

Since 1999, national mortality data have been coded using the International Classification of Disease 10th Revision (ICD-10) maintained by the World Health Organization. Using ICD-10, each death is assigned a single underlying cause and up to 20 contributing causes. To compute incidence estimates for poisonings, death certificate data and medical examiner case records are tabulated in state and territorial vital statistics systems, and reported nationally through the National Vital Statistics System of the National Center for Health Statistics (NCHS) for the Centers for Disease Control and Prevention (CDC).

There is considerable interest in the timely and accurate identification of deaths from ingesting psychotropic (controlled) substances in amounts that directly cause or contribute to a fatality (consistent with the US Food and Drug Administration (FDA) definition of a serious adverse event; 21 CFR § 314.80). For controlled substances the most relevant ICD-10 codes are: poisoning by narcotics and hallucinogens (X42, X60 and Y12; unintentional, intentional and undetermined intent, respectively); and three codes (X41, X61, Y11) that include other controlled substances, such as sedatives and other psychotropic drugs, as well as less frequently prescribed non-controlled medicines for epilepsy and Parkinson's disease that are dopaminergic precursors or otherwise increase dopamine activity. We collectively refer to these codes (X42, X60, Y12, X41, X61, Y11) as "poisonings from controlled substances."

The National Center for Injury Prevention and Control (NCIP) and NCHS identify drug poisoning deaths only using X- and Y- chapter poisoning codes (Table 4.1) [68]. However, there is concern that using these codes alone may underestimate overdose

deaths in surveillance data [69,70]. The multi-disciplinary Injury Surveillance Workgroup (ISW) of the Safe States Alliance recently suggested five possible consensus-based recommendations of ICD codes to be used for identifying overdose events, based on more expansive definitions that include substance use disorder and a wide list of pharmaceutical adverse event codes [3,71]. However the inclusion of non-controlled medicines in the definition may overestimate overdose events.

We evaluated definitional issues of using ICD-10 codes for drug overdose death surveillance in a two-step process. First, we assessed the effect of including substance use disorder codes with the goal of implementing a more inclusive ("broad") definition of drug overdose involving controlled substances. Second, we evaluated the effect of excluding deaths due to pharmaceutical adverse events in "broad" surveillance definitions for drug overdose involving controlled substances.

All of the NCHS and ISW definitions (Table 4.1) include deaths from pharmaceutical adverse events, even if the medicines involved were not controlled substances [3,28,72]. We could not find a clear justification for this. The FDA has used some of these exact codes to identify adverse event deaths *unrelated* to controlled substances, for example when reviewing the risk of infection associated with corticosteroid treatment [73,74]. Discrepancies such as these between federal health agencies necessitate a closer look at the definitions of overdose. This study explored which pharmaceutical adverse event deaths should be included in definitions of overdose mortality for controlled substances. This topic is of significance worldwide, for surveillance and incidence estimates and for researchers seeking to evaluate interventions to prevent overdoses from controlled substances.

We applied seven ICD-10 based definitions of "drug poisoning" or "overdose" to four years of mortality data from North Carolina (NC). NC vital statistics data are

collected in a statewide electronic medical examiner records system overseen by the North Carolina Office of the Chief Medical Examiner [70].

Methods

The study population was any NC resident whose death was recorded in NC vital statistics as having occurred from January 1, 2008 through December 31, 2011.

Mortality Data Source

Each death triggers a registration of the death with a local or municipal health authority, a mandated administrative task. The cause-of-death is determined by local health directors, attending physicians, or medical examiners based on autopsies or other investigations. Once the cause(s) of death are determined, the death record is appended, i.e., with the literal words used to describe the cause of death, which may occur months after the issuance of the original certification of death. The death records are converted by individual nosologists or computer software to alphanumeric ICD-10 codes. Mortality data for 2008 through 2010 were obtained from the North Carolina Vital Statistics Dataverse at The Howard W. Odum Institute for Social Science of the University of North Carolina at Chapel Hill [63]. Vital statistics mortality data for 2011 were obtained from the Injury and Violence Prevention Branch, North Carolina Division of Public Health, Department of Health and Human Services, as were death certificate data listing the literal text of the cause-of-death fields for 2010 and 2011.

Definitions

We analyzed one definition of overdose used by NCHS, five consensus-based definitions proposed by ISW, and one used for surveillance of opioid-related mortality by

public health authorities in Australia [71] (Table 4.1). Definitions 1, 2, and 3 are intended to broadly identify all overdoses due to “drugs” and controlled substances. Definitions 4, 5, and 7 are intended to specifically identify opioid overdoses, whereas Definition 6 only identifies prescription opioid overdoses. All seven definitions include the aforementioned six codes for poisonings from controlled substances. All definitions include homicidal poisoning using drugs or biological substances (X85). The definitions can also include deaths due to substance use disorders (Definitions 2, 3, 4, 7), pharmaceutical adverse events (all), the involvement of heroin (all except Definition 6), cocaine and other drugs (Definitions 1, 2, 3), or unspecified narcotics (all except Definition 6).

Substance use disorder codes are found in chapter F of ICD-10, with the following two-digit number indicating the substance, e.g., opioids are F11. A fourth digit suffix indicates the chronicity of substance use that led to the death. The codes of greatest relevance for mortality are: acute intoxication (.0), harmful use (.1), dependence syndrome (.2), withdrawal (.3), and unspecified chronicity (.9). The presence of an acute intoxication code (e.g., F11.0 for opioids) is in conflict with unintentional poisoning code (e.g., X42 for opioids). Accordingly, in 2007 NCHS discontinued the use of acute intoxication F codes for underlying cause-of-death in favor of X- and Y- chapter poisoning codes [3] (this convention may have continued at the state level beyond 2007). However, substance use disorder codes of other chronicity (e.g., not .1) continued to be used.

Among the seven definitions, pharmaceutical adverse events were identified using three approaches, the first of which uses poisoning codes as underlying causes (X40, X43, X44, X60, X63, X64, Y10, Y13, Y14). This results in Definitions 1 through 6 including deaths from controlled substances and non-controlled medicines. Some of these are: non-opioid analgesics, fever reducers (aspirin), tumor necrosis factor inhibitors, acetylcholine, albuterol, atropine, propanol, and ergotamine, as well as “other

and unspecified drugs that act on the autonomic nervous system or elsewhere." We collectively refer to these as "poisonings from other and unknown substances."

In the second approach, Definitions 2 and 4 also include deaths with an underlying cause in the range of Y40 through Y59, which are poisonings resulting from medicines causing adverse events during therapeutic use, i.e., iatrogenic exposures. Medicines could include: anti-coagulants, antibiotics, bacterial vaccines, immunosuppressive agents, angiotensin-converting-enzyme (ACE) inhibitors, and others. Of particular interest is Y45.0 which designates deaths due to the use of opioids and related analgesics during therapeutic use. The third way to identify adverse events is by using outcomes codes that suggest physiologic harm. ISW constructed Definitions 2 and 4 to include 34 specific drug-induced underlying causes including medicine-induced versions of conditions such as aplastic anemia, pancreatitis, gout, obesity, osteoporosis, and lupus erythematous, traditionally used for pharmaceutical adverse event reporting. We collectively refer to these as "adverse events during therapeutic use."

The Australian surveillance definition (Definition 7) uses a different approach to specifically identify opioid overdose deaths (Table 4.1). It includes deaths due to *any* underlying cause that is opioid related, defined as the presence of any of the following in contributing cause-of-death fields: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6, or F11 [71]. For example, Definition 7 includes deaths with underlying causes for asthma or chronic obstructive pulmonary disease (COPD) that also have contributing causes that show opioid toxicity. None of the other definitions include these cases but they are likely cases of interest to us.

To examine the involvement of multiple controlled substances in overdose deaths, we defined controlled substance toxicology collectively as the following ICD-10 codes: opioids (T40.0, T40.1, T40.2, T40.3, T40.4), cocaine (T40.5), "narcotic"

unspecified (T40.6), benzodiazepines (T42.4), amphetamine-type stimulants (T43.6), ketamine (T41.2), cannabis (T40.7), hallucinogens (T40.8, T40.9), barbiturates (T42.3) and gamma hydroxybutyrate (T52.8). Ethanol toxicity (T51.0) was considered separately. The intent of the ICD-10 schema is that these codes are not intended to represent the mere presence of the substance in post-mortem toxicology findings or circumstantial evidence, but rather indicate their causal involvement in the fatality.

Statistical Analysis

We compared seven definitions to each other using bivariate and descriptive statistics, with particular attention to Definition 1 because it is used by NCHS. Variables of interest included: sex, race and ethnicity, age, marital status, whether an autopsy was conducted, and place of death. Sex differences were examined because differences in opioid effects have been documented in clinical trials [75,76]. Age and racial differences have been observed in opioid metabolism [77,78] and dependence [79]. We also compared definitions on whether the death was intentional, unintentional or of undetermined intent. Previous analyses have noted empirical interstate variation in the classification of intent of overdose deaths [36] and we explored whether variations within a state could also be ascertained. All data analysis was conducted in STATA 12 (College Station, Texas). Population rates were calculated using Poisson regression with population denominators from NCHS bridged population estimates.

Results

Describing Drug Overdose Deaths

There were 322,458 deaths recorded in vital statistics for North Carolina from January 1, 2008 through December 31, 2011. Of these, 312,287 deaths were among

North Carolina residents, after removing two decedents for whom exact dates of death were missing. Among the resulting records, 4,898 deaths (1.5%) fit at least one of the seven definitions during the four-year study period. Definition 1 used by NCHS and Definition 3 proposed by ISW identified exactly the same deaths (Table 4.2).

Annual drug poisoning mortality rates among North Carolina residents were 12.7 per 100,000 residents in 2008, 12.3 in 2009, 11.2 in 2010, and 12.6 in 2011, using Definition 1 or 3. Nearly all deaths were certified by medical examiners (95.8%) or physicians (3.4%), with 37 occurring outside of NC certified by coroners. Autopsies were performed in 76.6% to 88.4% of cases depending on the definition, with the prescription opioid-specific definitions (Definitions 4 through 7) more likely to have had an autopsy performed. By comparison, 7.2% of all deaths among NC residents had an autopsy performed.

The seven mortality definitions shared common demographic characteristics. The sex distribution showed minor variation, ranging from 38% female in the most opioid-specific definitions to 41% for the broader ones (Table 4.3). The racial and ethnic distribution of decedents meeting Definition 1 or 3 was non-Hispanic white (89.0%) or black (8.0%), Native American (1.8%), any race Hispanic (0.9%), and other races and ethnicities (0.3%). The opioid-specific definitions had a slightly higher percent of white non-Hispanic decedents, for example 92.5% in Definition 5. Marital status at time of death was known for 99.5% of decedents included in Definition 1 or 3. One-third of the decedents never married, one-third were married at the time of death, and a quarter were divorced. The age distributions generally had a smaller peak in the mid-to-late 20s, a second greater peak in the middle-to-late 40s, and rapid decline thereafter.

The seven definitions had similar proportions of intentional, unintentional, and intent-unspecified deaths. As an example, Definition 1 or 3 had 3,761 (81.1%) that were unintentional, 694 (15.0%) that were intentional or suicides, and 178 (3.8%) of

undetermined intent. Only two deaths from poisoning homicide with controlled substances were identified, both in children.

Prescription opioids were involved in 61% to 63% of all drug overdose deaths identified using Definitions 1, 2, and 3, Table 4.3. When reviewing definitions restricted to opioids (definitions 4 through 7) in North Carolina, prescription opioids were involved in 90% to 91% of all deaths involving opioids, whereas heroin was identified in 7.7% to 7.9% of all deaths involving opioids. Cocaine was implicated in 8.5% to 9.7% of the opioid-specific deaths (Definitions 4 through 7).

Definition 2 identified the greatest number of overdose deaths. However, definition 7 identified the greatest number of opioid overdose deaths since it could include any underlying cause-of-death, Table 4.3. The two broadest ISW Definitions 4 and 5 only differed by 12 deaths since they take the same approach of relying on toxicity codes in contributing cause fields for the identification of opioid deaths. For the sake of brevity the former was not considered in subsequent analysis.

Identifying Pharmaceutical Adverse Event and Substance Use Disorder Codes

Since we were concerned about a potential underestimate of overdose deaths, we focused our attention on the two definitions that identified the most cases, Definition 2 for all drugs and Definition 7 for opioid-related deaths. Definition 2 included 4,807 (annual average: 1,202) deaths during four years, representing a 3.7% increase over the 4,635 deaths (annual average: 1,159) identified with Definition 1 or 3, Figure 4.1. Poisonings due to controlled substances made up 68.6% (n=3,299) of drug overdose deaths identified using Definition 2 (Table 4.4 and white circle in Figure 4.1). However 1,334 poisoning deaths from other and unknown substances make it difficult to understand which substances were implicated. Deaths in this category were of interest because theoretically some could have been excluded since they are pharmaceutical

adverse events not involving controlled substances. The underlying cause-of-death field provides little additional information; 94% were due to a trio of codes for “poisoning by other and unspecified drugs, medicaments and biological substances”: X44 (n=887), X64 (n=303), and Y14 (n=69), of unintentional, intentional, and undetermined intent, respectively. However, the contributing cause-of-death fields provided additional information to characterize these deaths. Despite an underlying cause-of-death that suggested that the substance involved was unknown, 586 of the 1,334 deaths had controlled substance toxicity codes as contributing causes (Figure 4.1, left box): opioids (n=553), cocaine (n=369), benzodiazepines (n=86), and amphetamine-type stimulants (n=24), with more than one controlled substance toxicity code in 362 records. Of the remaining 748 deaths, the only toxicology code listed for 52.5% (n=393) records was “unspecified drugs, acidifying agents, alkalizing agents, immunoglobulin, parathyroid hormones” (T50.9). Among the remaining 355 deaths, 61 had codes for disorders due to the use of multiple substances (e.g., F19). That left 294 deaths that had toxicology codes for a variety of medicines that had no evidence of involving controlled substances: anti-allergic and antiemetic drugs, acetaminophen, respiratory system agents, non-steroidal anti-inflammatory drugs, insulin and oral diabetes medicines, aspirin, anti-coagulants, calcium-channel blockers, cardiac-stimulant glycosides and anti-dysrhythmic drugs, and anti-depressants, Figure 4.1. These do not appear to be deaths of interest for this analysis.

Another way to assess the contribution of pharmaceutical adverse events is by comparing the 172 additional overdose deaths identified using Definition 2 versus Definitions 1 or 3 (Figure 4.1, grey penumbra). This also provides insight into the importance of including substance use disorder codes. Among the 172 deaths there were 112 with substance use disorder underlying causes (F11 to F19), including sedatives, cocaine, amphetamine-type stimulants, and multiple drugs (Figure 4.1, right

box). The F codes were used in deaths statewide and do not appear to be an artifact of isolated individual medical examiner conventions. The median age of decedents with substance use disorder codes was 50.0 years (IQR: 42.5, 58), compared to 42 years (IQR: 31, 50) for poisonings from controlled substances, Table 4.4. Other demographic characteristics were similar between deaths identified using the substance use disorder and poisonings from controlled substances codes.

Of the remaining 60 deaths, 58 deaths were caused by adverse events involving medicines in therapeutic use (Y40 through Y59) (Figure 4.1, right box). Only two deaths were due to controlled substances, specifically opioids during therapeutic use (Y45.0). As a group, the deaths involving adverse events during therapeutic use were older (median 65.5 years, IQR: 48, 77.5) than substance use disorder deaths or poisonings from controlled substances, Table 4.4, and may not be a death from an overdose of the type in which we are interested.

Two remaining deaths due to pharmaceutical adverse events were identified using Definition 2 proposed by ISW one from drug-induced secondary Parkinsonism (G21.1) and one death from drug-induced myopathy (G72.0). These two deaths also do not appear to be of interest in this analysis, as there were multiple co-morbid conditions and both deaths were among 70-year-olds.

Expanding the Definition

We also explored whether the approach in Definition 7 of including deaths with controlled substance poisoning and toxicology codes in *contributing* cause-of-death fields would change the number of drug overdose deaths identified. Including deaths with *any* underlying cause that have contributing causes among the six controlled substance poisoning codes (X41, X42, X61, X62, Y11, Y12) adds 108 deaths not identified by Definition 2, Figure 4.1. Similarly, Definition 2 did not include 126 deaths

where controlled substance toxicology codes were present. There was an overlap of 90 deaths between these two approaches, so a total of 145 additional deaths were identified that may be drug overdoses from controlled substances, Figure 4.1. The most common underlying causes were circulatory system disorders, such as non-congestive heart failure.

There were 145 overdose deaths involving controlled substances that were not identified using either the NCHS or ISW definitions, Figure 4.1. These deaths were identified by allowing records with any underlying cause with at least one contributing cause from among the controlled substance poisoning or toxicity codes. For example, the death of a 32-year-old male had an underlying cause of pneumonitis from aspirated vomit, but was accompanied by a controlled substance poisoning X code, adult respiratory distress syndrome, and opioid, benzodiazepine and cocaine toxicity codes. These deaths should be considered for inclusion in overdose definitions for controlled substances (Table 4.5).

Discussion

We propose a refined definition that borrows upon the work of NCHS, ISW and the Australians (Definition 8, Table 4.5). Conceptually starting with the definition that identified the greatest number of records (Definition 2 from the ISW) our proposed definition removes 354 deaths that were due to pharmaceutical adverse events and homicide, and adds 145 deaths not previously identified, yielding 4,598 overdose deaths involving controlled substances during four years, indicated in Figure 4.1 with asterisks. The total number of deaths among NC residents over four years identified using the NCHS definition (Definition 1) (n=4,635) and our proposed definition (n=4,598) differ only slightly.

In addition to the three broad definitions for overdose deaths from controlled substances, we evaluated four opioid-specific ones (including three proposed by ISW)

for the sake of completeness and because deaths involving opioids have become a major public health concern [65]. Also, we borrowed concepts from Definition 7 described by Jauncey and colleagues (2005) in proposing our own definition.

The ICD defines T50.9 as a catchall for medical products not explicitly mentioned in the coding schema, including medicines acting on the cardiovascular and gastro-intestinal system, hormones, antibiotics, vaccines, and topical preparations, to name a few. The choice to include the 393 records in our proposed definition can be called into question, as there may be a desire by some to only attribute events to controlled substances where a specific psychotropic drug is identified (e.g., positive evidence). While we acknowledge that this code may result in including deaths from non-controlled substances, given the lack of standardization of assays, autopsy, and coding practices, the absence of negative evidence implores us to consider these deaths in the definition. One practical solution would be to conduct a sensitivity analysis with and without the T50.9-only poisonings deaths, and present both results. In our study, the number of overdose deaths would accordingly range from 4,205 to 4,598, a change of less than 100 deaths per year.

We entertained the possibility of including deaths with controlled substance use disorder codes in contributing cause fields. While there were some deaths that could possibly have been due to overdose, the most common underlying causes of death included chronic harms of injection drug use, such as viral hepatitis and HIV. In some of these instances the last exposure to the substance may have been days, or even decades, ago. It is possible that our proposed definition is also an underestimate of the actual overdose deaths from controlled substances.

In the absence of a gold standard against which to compare definitions of overdose deaths using vital statistics we have chosen to focus on internal validity. This is the primary limitation of our analysis. We anticipate that the availability of electronic

health records and medical examiner systems will allow us to compare overdose deaths identified in vital statistics with those identified using medical records in the future, extending analyses of others [11].

It is possible that not all deaths determined to be overdoses by medical examiners are accordingly identified [80,81]. To address this concern, qualitative and quantitative methods that include interviews with active drug users, overdose survivors and family members of decedents can be used [10,29,82,83,84]. It may also be important to differentiate instances where illicitly manufactured drugs may contain contaminants that are the primary cause-of-death [85], and the controlled substance is in low concentration. Further work is needed to uncover what convention coding practices are under this scenario.

TABLES AND FIGURES

Table 4.1. ICD-10-based definitions for identifying drug overdose deaths.

			Cause-of-Death			Substances Involved			
#	Title	ICD-10 Codes	Poisoning	Substance Use Disorders	Pharmaceutical Adverse Event	Prescription Opioids	Heroin	Cocaine and Other Drugs	Unspecified Narcotics
1	National Center for Health Statistics drug poisoning	Any underlying COD: X40-X44, X60-X64, X85, and Y10-Y14	●		●	●	●	●	●
2	Acute or chronic poisonings due to the effects of drugs from ISW [9]	Deaths with underlying COD: D52.1, D59 (.0, .2), D61.1, D64.2, E06.4, E16.0, E23.1, E24.2, E27.3, E66.1, F11-F16, F19, G21.1, G24.0, G25 (.1, .4, 6), G44.4, G62.0, G72.0, I95.2, J70 (.2-.4), K85.3, L10.5, L27 (.0, .1), M10.2, M32.0, M80.4, M81.4, M83.5, M87.1, R50.2, X40-X44, X60-X64, X85, Y10-Y14, or Y40-Y59	●	●	●	●	●	●	●
3	Acute poisonings due to the effects of drugs from ISW [9]	Deaths with underlying COD: [F11 - F16] (.0), F19.0, X40-X44, X60-X64, X85, or Y10-Y14	●	●		●	●	●	●
4	Acute or chronic drug poisonings associated with the effects of opium, heroin and/or opioid analgesics from ISW [9]	Deaths with an underlying COD code: F11 or Y45.0 ----- *or* ----- Underlying cause-of-death: D52.1, D59 (.0, .2), D61.1, D64.2, E06.4, E16.0, E23.1, E24.2, E27.3, E66.1, F12-F16, F19, G21.1, G24.0, G25 (.1, .4, 6), G44.4, G62.0, G72.0, I95.2, J70 (.2-.4), K85.3, L10.5, L27 (.0, .1), M10.2, M32.0, M80.4, M81.4, M83.5, M87.1, R50.2, X40-X44, X60-X64, X85, Y10-Y14, Y40-Y44, or Y46-Y59 ***and*** Any contributing COD: F11, T40.0, T40.1, T40.2, T40.3, T40.4, T40.6	●	●	●	●	●		●
5	Acute drug poisonings associated with the effects of opium, heroin and/or opioid	Deaths with underlying COD: [F11 - F16] (.0), F19.0, X40-X44, X60-X64, X85, or Y10-Y14 ***and*** Any contributing COD: F11.0, T40.0, T40.1, T40.2, T40.3, T40.4, T40.6	●			●	●		●
6	Acute drug poisonings associated with the effects of opioid analgesics	Deaths with an underlying COD: [F11 - F16] (.0), F19.0, X40-X44, X60-X64, X85, or Y10-Y14 ***and*** Any contributing COD: T40.2, T40.3, T40.4	●				●		
7	All possible opioid-related deaths Australian surveillance definition [8]	"Opioid toxicity" means T40.0 to T40.4 and T40.6 are present in any contributing COD field. Any death that has: (1) underlying COD F11.0-F11.9; (2) underlying COD X42, with contributing COD opioid toxicity; (3) underlying COD X44, with contributing COD opioid toxicity; (4) underlying COD F19.0-F19.9, with either contributing COD opioid toxicity, or F11.0-F11.9; (5) underlying COD X60-X69 with opioid toxicity; (6) underlying COD Y10- Y19 with opioid toxicity; (7) underlying COD F10, F12-F18 with opioid toxicity; (8) underlying COD X85 with opioid toxicity; (9) underlying COD X40-X41 or X43-X49 with opioid toxicity; (10) any underlying COD with opioid toxicity not otherwise specified; (11) any underlying COD with F11.0 through F11.9 as a contributing COD	●	●	●	●	●		●
8	Proposed definition of overdoses involving controlled substances	See Table 4.5	●	●		●	●	●	●

Table 4.2. Annual overdose deaths, by fatal overdose definition, NC residents, 2008 though 2011.

	Definitions	2008	2009	2010	2011	4 year total
Definitions of drug poisonings						
1	North Carolina drug overdoses	1,180	1,162	1,071	1,222	4,635
2	Acute or chronic poisonings due to the effects of drugs (ISW)	1,222	1,201	1,114	1,270	4,807
3	Acute poisonings due to the effects of drugs (ISW)	1,180	1,162	1,071	1,222	4,635
Definitions of opioid poisonings						
4	Acute or chronic drug poisonings associated with theffects of opium, heroin, and/or opioid analgesics (ISW)	840	843	757	782	3,222
5	Acute drug poisonings associated with the effects of opium, heroin, and/or opioid analgesics (ISW)	839	836	755	780	3,210
6	Acute drug poisonigns associated with the effects of opioid analgesics (ISW)	765	763	707	703	2,938
7	Australia all possible opioid-related	797	781	691	753	3,022

1 Any underlying or contributing cause-of-death: X40-X44, X60-X64, X85, and Y10-Y14

2 Deaths with an underlying cause of death code of D52.1, D59 (.0, .2), D61.1, D64.2, E06.4, E16.0, E23.1, E24.2, E27.3, E66.1, F11-F16, F19, G21.1, G24.0, G25 (.1, .4, 6), G44.4, G62.0, G72.0, I95.2, J70 (.2-.4), K85.3, L10.5, L27 (.0, .1), M10.2, M32.0, M80.4, M81.4, M83.5, M87.1, R50.2, X40-X44, X60-X64, X85, Y10-Y14, or Y40-Y59

3 Deaths with an underlying cause of death code of [F11 - F16] (.0), F19.0, X40-X44, X60-X64, X85, or Y10-Y14

4 Deaths with an underlying cause of death code of F11 or Y45.0 OR deaths with an underlying cause of death code of D52.1, D59 (.0, .2), D61.1, D64.2, E06.4, E16.0, E23.1, E24.2, E27.3, E66.1, F12-F16, F19, G21.1, G24.0, G25 (.1, .4, 6), G44.4, G62.0, G72.0, I95.2, J70 (.2-.4), K85.3, L10.5, L27 (.0, .1), M10.2, M32.0, M80.4, M81.4, M83.5, M87.1, R50.2, X40-X44, X60-X64, X85, Y10-Y14, Y40-Y44, or Y46-Y59 AND one or more of the following codes in any multiple cause of death field: F11, T40.0, T40.1, T40.2, T40.3, T40.4, T40.6

5 Deaths with an underlying cause of death code of [F11 - F16] (.0), F19.0, X40-X44, X60-X64, X85, or Y10-Y14 and one or more of the following codes in any multiple cause of death field: F11.0, T40.0, T40.1, T40.2, T40.3, T40.4, T40.6

6 Deaths with an underlying cause of death code of [F11 - F16] (.0), F19.0, X40-X44, X60-X64, X85, or Y10-Y14 AND one or more of the following codes in any multiple cause of death field: T40.2, T40.3, T40.4

7 "Opioid toxicity" means T40.0 to T40.4 and T40.6. Deaths includes are: (1) underlying cause of death F11.0 through F11.9; (2) underlying cause of death X42, with contributing cause of death due to opioid toxicity; (3) underlying cause of death X44, with contributing cause of death due to opioid toxicity; (4) underlying cause of death F19.0-F19.9, with either contributing cause of death due to opioid toxicity, or F11.0-F11.9; (5) X60 through X69 with opioid toxicity; (6) Y10 through Y19 with opioid toxicity; (7) F10, F12 through F18 with opioid toxicity; (8) X85 with opioid toxicity; (9) X40 through X41 or X43 through X49 with opioid toxicity; (10) opioid toxicity in any contributing cause-of-death field not otherwise specified; (11) mental and behavioral disorder due to use of opioids F11.0 through F11.9 in any contributing cause-of-death field

Table 4.3. Drug toxicology codes reported, by fatal overdose definition, NC residents, 2008 though 2011.

	Definitions	4 year total	% Female	% Cocaine	% Heroin	% Rx opioid
Definitions of drug poisonings						
1	North Carolina drug overdoses	4,635	41.3%	13.8%	5.5%	63.4%
2	Acute or chronic poisonings due to the effects of drugs (ISW)	4,807	41.4%	13.3%	5.3%	61.1%
3	Acute poisonings due to the effects of drugs (ISW)	4,635	41.3%	13.8%	5.5%	63.4%
Definitions of opioid poisonings						
4	Acute or chronic drug poisonings associated with the effects of opium, heroin, and/or opioid analgesics (ISW)	3,222	38.4%	9.7%	7.9%	91.2%
5	Acute drug poisonings associated with the effects of opium, heroin, and/or opioid analgesics (ISW)	3,210	38.5%	9.5%	7.9%	91.5%
6	Acute drug poisonings associated with the effects of opioid analgesics (ISW)	2,938	40.3%	8.5%	1.1%	100.0%
7	Australia all possible opioid-related	3,022	37.2%	10.0%	8.4%	89.3%

1 Any underlying or contributing cause-of-death: X40-X44, X60-X64, X85, and Y10-Y14

2 Deaths with an underlying cause of death code of D52.1, D59 (.0, .2), D61.1, D64.2, E06.4, E16.0, E23.1, E24.2, E27.3, E66.1, F11-F16, F19, G21.1, G24.0, G25 (.1, .4, 6), G44.4, G62.0, G72.0, I95.2, J70 (.2-.4), K85.3, L10.5, L27 (.0, .1), M10.2, M32.0, M80.4, M81.4, M83.5, M87.1, R50.2, X40-X44, X60-X64, X85, Y10-Y14, or Y40-Y59

3 Deaths with an underlying cause of death code of [F11 - F16] (.0), F19.0, X40-X44, X60-X64, X85, or Y10-Y14

4 Deaths with an underlying cause of death code of F11 or Y45.0 OR deaths with an underlying cause of death code of D52.1, D59 (.0, .2), D61.1, D64.2, E06.4, E16.0, E23.1, E24.2, E27.3, E66.1, F12-F16, F19, G21.1, G24.0, G25 (.1, .4, 6), G44.4, G62.0, G72.0, I95.2, J70 (.2-.4), K85.3, L10.5, L27 (.0, .1), M10.2, M32.0, M80.4, M81.4, M83.5, M87.1, R50.2, X40-X44, X60-

5 Deaths with an underlying cause of death code of [F11 - F16] (.0), F19.0, X40-X44, X60-X64, X85, or Y10-Y14 and one or more of the following codes in any multiple cause of death field: F11.0, T40.0, T40.1, T40.2, T40.3, T40.4, T40.6

6 Deaths with an underlying cause of death code of [F11 - F16] (.0), F19.0, X40-X44, X60-X64, X85, or Y10-Y14 AND one or more of the following codes in any multiple cause of death field: T40.2, T40.3, T40.4

7 "Opioid toxicity" means T40.0 to T40.4 and T40.6. Deaths includes are: (1) underlying cause of death F11.0 through F11.9; (2) underlying cause of death X42, with contributing cause of death due to opioid toxicity; (3) underlying cause of death X44, with contributing cause of death due to opioid toxicity; (4) underlying cause of death F19.0-F19.9, with either contributing cause of death due to opioid toxicity, or F11.0-F11.9; (5) X60 through X69 with opioid toxicity; (6) Y10 through Y19 with opioid toxicity; (7) F10, F12 through F18 with opioid toxicity; (8) X85 with opioid toxicity; (9) X40 through X41 or X43 through X49 with opioid toxicity; (10) opioid toxicity in any contributing cause-of-death field not otherwise specified; (11) mental and behavioral disorder due to use of opioids F11.0 through F11.9 in any contributing cause-of-death field

Table 4.4. Deaths from different causes among decedents identified using Definition 2*, North Carolina residents, from 2008 through 2011.

ICD-10 Codes	Underlying Cause-of-Death	n	Percent	Median age	IQR
X41 X61 Y11 X42 X62 Y12	Poisonings from controlled substances	3,299	68.6%	42	31, 50
X40 X43 X44 X60 X63 X64 Y10 Y13 Y14	Adverse events from non-controlled and unknown substances	1,334	27.7%	44	33, 52
F11 F12 F13 F14 F15 F16 F19	Substance use disorders**	112	2.3%	50	42.5, 58
D521 D590 D592 D611 D642 E064 E160 E231 E242 E273 E661 F12 F13 F14 F15 F16 F19 G211 G240 G251 G254 G256 G444 G620 G720 I952 J702 J704 K853 L105 L270 L271 M102 M320 M804 M814 M835 M871 R502 Y40 Y41 Y42 Y43 Y44 Y45 Y46 Y47 Y48 Y49 Y50 Y51 Y52 Y53 Y54 Y55 Y56 Y57 Y58 Y59	Adverse events during therapeutic use**	60	1.2%	65.5	48, 77.5
X85	Poisoning homicide	2	< 0.1%	0, 5	
	Total	4,807			

IQR: interquartile range

* Cases were identified as those deaths with underlying cause-of-death: D52.1, D59 (.0, .2), D61.1, D64.2, E06.4, E16.0, E23.1, E24.2, E27.3, E66.1, F11-F16, F19, G21.1, G24.0, G25 (.1, .4, 6), G44.4, G62.0, G72.0, I95.2, J70 (.2-.4), K85.3, L10.5, L27 (.0, .1), M10.2, M32.0, M80.4, M81.4, M83.5, M87.1, R50.2, X40-X44, X60-X64, X85, Y10-Y14, or Y40-Y59.

** Not included in Definition 1 or 3.

Table 4.5. Proposed ICD-10-based definition of overdose mortality from controlled substances for vital statistics (Definition 8)

Steps	ICD-10 Codes
1. Include all deaths with an underlying COD for poisonings from controlled substances	X41 X61 Y11 X42 X62 Y12
2. Include deaths with an underlying COD from poisonings due to unknown and other substances only if there is an associated controlled substance toxicology code	X40 X43 X44 X60 X63 X64 Y10 Y13 Y14 and controlled substance toxicology codes
3. Include deaths with an underlying COD from poisonings due to unknown and other substances, where no controlled substance toxicology is specified, but a controlled substance use disorder code is present in contributing COD	X40 X43 X44 X60 X63 X64 Y10 Y13 Y14 and controlled substance use disorder codes
4. Include deaths with an underlying COD from poisonings due to unknown and other substances, where no controlled substance toxicology is specified, no controlled substance use disorder code is present in contributing COD, but the only poisoning T code is T50.9	X40 X43 X44 X60 X63 X64 Y10 Y13 Y14 and T50.9
5. Include deaths with underlying COD of a controlled substance use disorder	F11 F12 F13 F14 F15 F16 F19
6. Include deaths with underlying COD of Y45.0	Y45.0
7. Among deaths not yet included, add those records where there is controlled substance toxicity or controlled substance poisoning in the contributing COD fields, but no X85 in the underlying COD	X85 and controlled substances poisoning and toxicology codes
Definitions	
Controlled substance toxicology codes	T40.0 T40.1 T40.2 T40.3 T40.4 T40.6 T40.5 T42.4 T42.3 T43.6 T41.2 T40.7 T40.8 T40.9 T52.8
Controlled substance use disorder codes	F11 F12 F13 F14 F15 F16 F19
Poisoning T codes	T36 through T65
Controlled substance poisoning codes	X41 X61 Y11 X42 X62 Y12

ICD-10: International Classification of Disease, 10th revision
COD: cause-of-death

Figure 4.1. Schematic representation of definitions of drug overdose deaths, North Carolina residents, 2008 through 2011. This figure depicts the definitions that yielded the greatest number of possible drug overdose deaths, and a breakdown of the component causes-of-death that contribute to the definitions. The asterisks (*) designate deaths included in the definition for drug overdose mortality proposed in this paper. The large white circle in the middle is overdose deaths identified using Definitions 1 or 3 (n=4,635). An additional 112 deaths were identified using Definition 2, larger darker circle, and can be broken down into three mutually exclusive categories of substance use disorders, pharmaceutical adverse events and iatrogenic opioid deaths, right grey box. The enclosed grey circle represents 1,334 poisoning deaths from other and unknown substances. These deaths can be further broken down into four mutually exclusive categories as shown in the left box. The two overlapping circles in the top left depict possible overdose deaths not identified by Definition 2. The proposed definition removes 354 deaths that were due to pharmaceutical adverse events and homicide, and adds 145 deaths not previously identified, resulting in a total of 4,598 overdose deaths during the four years of observation. Please refer to text and Table 4.5 for exact ICD-10 codes used for each definition. Note that the circle for the additional deaths not identified by Definition 2 (overlapping circles in top left) and the homicide circle are not drawn to scale.

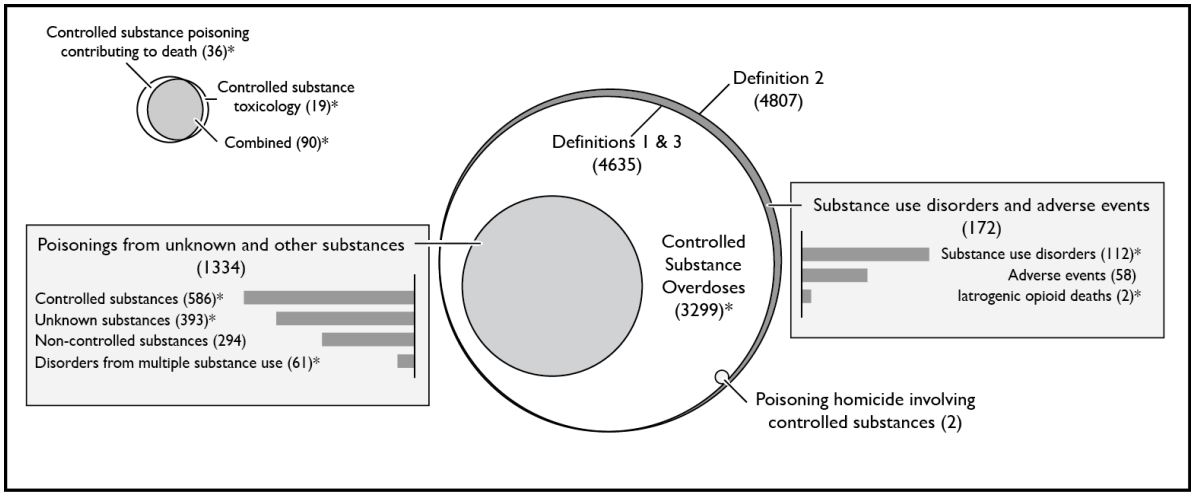
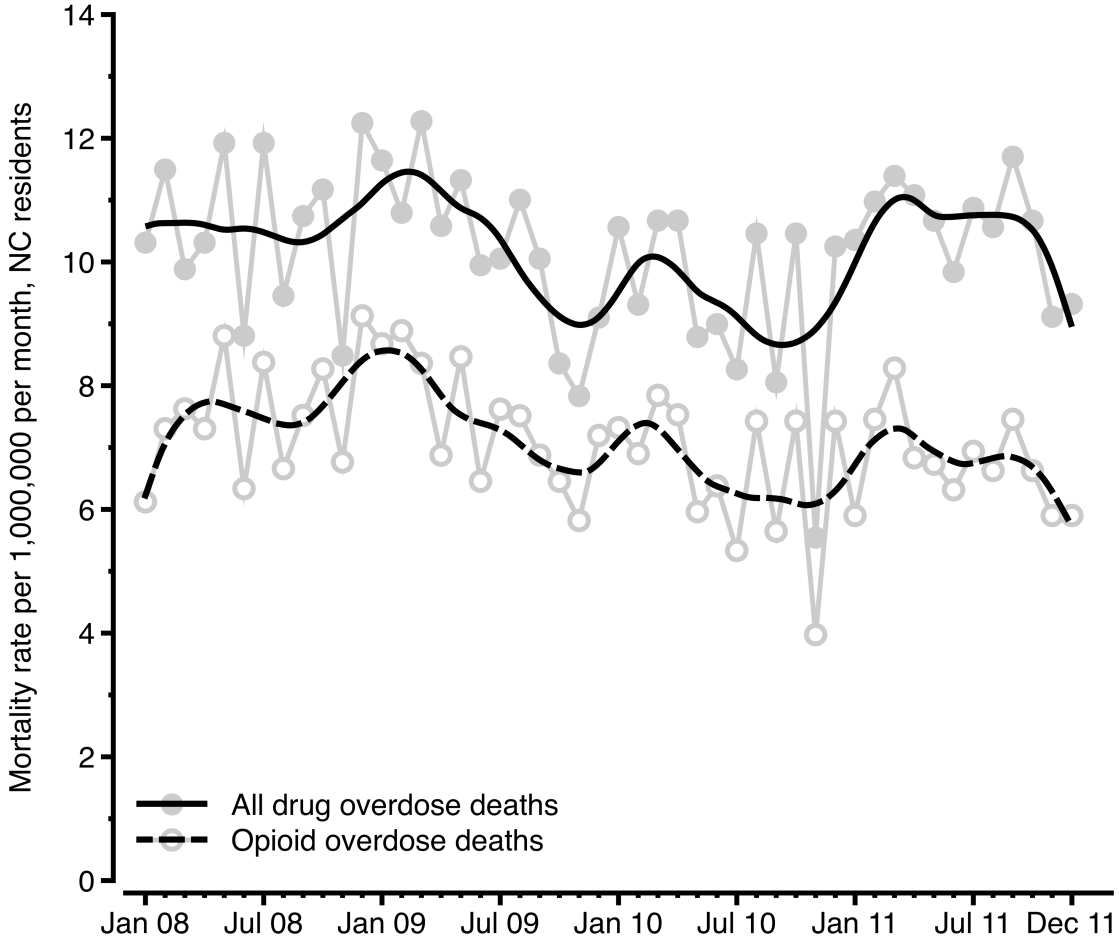


Figure 4.2. All drug and opioid overdose death rates, North Carolina residents, 2008 through 2011. Overdose mortality by month using Definitions 1 (solid black line) and 4 (dashed line).



CHAPTER 5

A PROSPECTIVE COHORT STUDY OF OPIOID ANALGESICS AND OVERDOSE MORTALITY

Overview

Opioid analgesics have been associated with dose-dependent increases in overdose risk. There is limited safety data on overdose risk at higher doses that are relatively common in clinical practice (e.g., over 150 mg per day). In addition, there is little information on comparative risks between immediate-release (IR) and extended-release (ER) formulations, and whether the dose-dependent effect is influenced by central nervous system depressant benzodiazepines.

We conducted a prospective cohort study of all North Carolina residents (n=9,560,234) in 2010, using electronic controlled substances prescription monitoring program data. Exposure of 1,133,957 person-years to opioid analgesics was observed using intent-to-treat principles. Overdose deaths were identified from medical examiner records and vital statistics. Incidence rates, rate differences, and incidence rate ratios were calculated using regression models to describe the rate of overdose at higher doses of opioid analgesics.

Introduction

The use of opioids in the management of pain has long been tempered with concerns about fatal overdose arising from respiratory depression. The United States and Canada

have the highest per capita consumption of opioids in the world and the highest overdose rates as well [25]. The public health problem created by the inappropriate use of opioid analgesics is pervasive, however in much of the world, strong opioid analgesics are unavailable even for end-of-life pain control among cancer patients [86].

Part of the resistance regarding opioid use may stem from safety concerns at high doses and increasing trends of overdose deaths in the United States and Canada. At the societal level, many studies over the last 15 years have suggested a linear ecologic association between the total mass of opioids dispensed and overdose morbidity and mortality [4,5,6,7,8,9,10,11,12]. Simply summarized: the more opioid analgesics that are prescribed, the greater the overdose morbidity and mortality involving these substances are observed at the population level.

In contrast, at the individual level, there continues to be legitimate concern that those experiencing pain in the United States and Canada do not receive basic analgesic relief, even in the context of massive opioid prescribing. For example, studies of pain in nursing homes and hospices consistently reveal that they receive inadequate pain treatment [87,88]. Some patients who could benefit from pain relief are not medicated, and, even if the patients are receiving opioids, the dose may not be sufficient to address pain needs [89].

Among the pharmaceutical opioid formulations available in the United States and Canada, there is a broad distinction between immediate-release (IR) formulations (dosage every four to six hours), and extended-release (ER) formulations (dosage once or twice per day). IR opioids are intended for use in acute or breakthrough pain, and often come combined with paracetamol (acetaminophen) or ibuprofen, whereas ER opioids are indicated for chronic pain and contain larger amounts of active ingredient per tablet or deliver medicine via a transdermal patch.

Few individual-level studies have examined the association between higher doses of opioid analgesics and overdose mortality in the United States and Canada [13,14,15,16,17]. The five individual-level studies with overdose deaths as an outcome are summarized in Table 5.1. All studies show increasing risk of overdose mortality with dose strength. However direct comparison between studies is difficult because of variations in whether deaths due to illicit drugs and suicide were included, which opioid analgesics were considered in the exposure, and whether relative effect measures included comparison to opioid unexposed individuals in the general population as part of the reference group. In addition, these studies offer limited information on the gradient of risk above 200 mg per day of morphine equivalents, despite widespread use over this level. Only one study reported separate rates of IR versus ER opioid analgesics [15], and one adjusted for formulation in models [16]. None of the studies examined whether the dose-dependent effect may be influenced by co-prescribed benzodiazepines, a well-established risk factor for respiratory depression [65,90,91].

As described above, strong associations have been observed between amount of opioids dispensed and overdose mortality. Yet, clinical trials and their meta-analyses consistently show safety of opioid analgesics at high doses [18,19,20,21,22]. To explore this paradox we conducted a prospective cohort study among North Carolina residents in 2010 to quantify dose-dependent overdose risk in routine clinical practice. We suspected that the routine clinical practice of outpatient pain management may be sufficiently different from the clinical trial setting as to lead to increased risk of overdose in the general population.

We hypothesized that ER opioids would be associated with greater overdose mortality than IR opioids, including at higher doses. We based this hypothesis on ecological studies that suggest a linear association between the mass of opioid analgesics dispensed and overdose mortality at the population level, and the fact that ER opioids have more milligrams

of active ingredient per unit than IR opioids. We also hypothesized that the dose-dependent risk of mortality associated with opioid analgesics could partially be explained by additional attributable risk from exposure to co-prescribed benzodiazepines.

Our study has three goals. First, to describe patterns of clinical opioid analgesic utilization, focusing on prescribers, prescriptions, and patients, with attention to opioid substance and formulation type. Second, we examine the relationship between high dose opioid analgesic prescribing and overdose mortality, and whether benzodiazepines may influence the dose-dependent response. Third, we examine whether there are differences between IR and ER opioid analgesics on overdose mortality.

Methods

Data Sources

The North Carolina Controlled Substances Reporting System (CSRS) is a state-mandated prescription monitoring program in operation since 2007. CSRS data are generated when prescriptions for a controlled substance are dispensed at regulated pharmacies in North Carolina. The data captured include each field of information legally required to be on a prescription for a controlled substance including: the drug name, quantity of units, date of dispensing, and prescriber and pharmacy Drug Enforcement Agency (DEA) registration numbers. Data are stored locally at the pharmacy and transmitted within two weeks of dispensing to a central database owned by the NC Division of Mental Health, Developmental Disabilities and Substance Abuse Services (DMHDDSAS). The database is maintained under contract by Health Information Designs (Auburn, Alabama, United States), using the RxSentry database management tool. We were provided with a dataset that included a unique identifier for each recipient of a controlled substance derived using a proprietary de-duplication algorithm. Due to federal policy and state laws, the CSRS does

not receive prescriptions data from pharmacies in Veterans Administration and Department of Defense facilities, Indian Health Service clinics, physician in-clinic dispensing, veterinary clinics, and outpatient opioid dependence treatment programs.

Death certificate data from North Carolina's State Center for Health Statistics were used to identify overdose deaths. We then obtained electronic records on these decedents from the Office of the Chief Medical Examiner (OCME). All deaths that occurred in North Carolina were certified by licensed medical examiners or attending physicians. The post-mortem serum toxicological analyses were conducted as part of autopsy and included drug details for all major controlled substances, differentiating between types of pharmaceutical opioids and isomers of diacetylmorphine (heroin).

Data on the numbers of total licensed clinicians practicing in the state in 2010 were obtained from state medical licensure boards, via the North Carolina Health Professions Data System stored at the Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill.

Study Design

We structured our analysis as a prospective cohort study of all NC residents in 2010. Exposure was defined as having received a dispensed prescription of an opioid analgesic for use in 2010. The outcome was overdose mortality involving opioid analgesics. Mortality rates were calculated using regression models.

Data Linkage

We used a deterministic one-to-one process to link the mortality and CSRS data. For each overdose decedent, we identified prescriptions in the CSRS that were dispensed within 365 days of death using a two-step process. First, we queried each decedent using the web

interface of the CSRS using the first five letters of their last name and their date of birth. Confirmatory matching was the second step, and involved matching the first name, last name and date of birth as recorded on the death certificate. Matching records were extracted electronically.

Exposure Definition

Figure 5.1 depicts the data cleaning process in detail. A total of 54,825,930 records for dispensed prescriptions were available for analysis from 2009 through 2011. First, we removed prescriptions dispensed to non-residents, records with unknown or missing drug information, and non-controlled substances (n=1,094,717). Next, person-days were calculated using a measure typically referred to as “days supply.” Days supply is a legally required prescription element, and is defined by the prescriber, noted on the prescription, and incorporated in a field of the CSRS database. Days supply was truncated to 182 days for 1,228 prescriptions for opioid analgesics of greater duration because these illogical values fell outside of DEA guidelines for controlled substances prescribing. Days supply was imputed for 5,369,748 prescription records with missing or zero days supply by assigning the median days supply from the rest of the dataset, matched by quantity and National Drug Code (NDC) number (the NDC number is a FDA-issued unique product identifier that encompasses strength, formulation, active ingredient and manufacturer). Some records were excluded because drug name and NDC number were missing or the quantity dispensed could not be determined (n=18,303).

We then positively identified 21,448,986 prescriptions for solid oral or transdermal opioid analgesics labeled for acute and chronic pain containing codeine, hydrocodone, hydromorphone, fentanyl, methadone, morphine, oxycodone and oxymorphone. Of these, 7,393,375 prescription records were intended for use in 2010.

We used a two-step process to identify prescriptions for opioid analgesics. The active ingredient, milligram strength, and formulation type (e.g., extended-release/immediate-release, and solid oral/patch/liquid) were determined by matching by NDC number using a commercial standard MarketScan 2011 Redbook master file obtained from the Centers for Disease Control and Prevention (CDC) in March 2013. Second, to maximize inclusion of data with incorrect or missing NDC numbers, a regular expressions-based parser on the drug name field was utilized to determine the active ingredient and formulation, with discrepant prescriptions reviewed individually to determine the correct assignment using the drug name field as the standard (via REGEXM in Stata). Of the eight opioid substances analyzed in this paper, two were available only as IR (codeine, hydrocodone), and five were available as both ER and IR (fentanyl, hydromorphone, morphine, oxycodone, oxymorphone). In tablet form, methadone is used for chronic pain management, and as a liquid for management of opioid dependence; for consistency with regulatory classification we included methadone tablets in the ER category [92].

In order to explore whether the opioid formulation (ER versus IR) modified the relationship between MME and overdose risk among those who had received any opioid analgesic, we dichotomized residents by IR opioid status, with one category containing those who had only received IR opioid prescriptions, versus those who had at least one ER prescription, in the 365 days prior to death or end of the study. We similarly dichotomized benzodiazepine exposure status to ascertain if any benzodiazepine exposure may influence overdose risk. We assessed the impact of stratification on incidence rate ratios by inspecting overlapping 95 percent confidence intervals resulting from regression models.

We calculated the average daily dose in terms of milligram equivalence to morphine. Because of the differences in potencies between opioids, clinicians refer to equianalgesic conversion tables when switching patients from one opioid to another during opioid rotation;

conversion ratios by active ingredient are standardized to morphine. In order to have comparable results with previous studies, we used the conversion ratios suggested by CDC: codeine (0.15), fentanyl (25.0), hydrocodone (1.0), hydromorphone (4.0), methadone (3.0), morphine (1.0), oxycodone (1.5) and oxymorphone (3.0) (Leonard Paulozzi, personal communication, March 1, 2013). Total milligrams of MME per prescription were calculated by multiplying the milligrams per dosage unit times the quantity of units dispensed times the conversion factor. The average daily MME per individual in 2010 was calculated by taking the total milligrams and dividing by the days supply, taking into account overlapping prescription days for each individual. Two concurrent prescriptions for 30 days (e.g., an extended-release opioid for chronic pain and an immediate-release opioid for breakthrough pain) would both contribute milligrams to the numerator but the total person-days of exposure would be 30 if the prescriptions were completely contemporaneous. Four individuals with MME greater than 5,000 milligrams per day were outliers and not included in regression models because they did not experience overdose deaths during the observation period.

Outcome Definition

We included residents who died in 2010 and whose underlying cause-of-death was an unintentional or undetermined drug overdose (ICD-10 codes X40-X44, Y10-Y14). The role of each drug in the death was determined by OCME toxicologists according to a standardized classification system, drawing from investigations at the scene of death, toxicological findings, available medical records, and interviews. Two categories of drug involvement were analyzed: *primary* (the drug was at a concentration sufficient to have caused the death alone regardless of other drugs detected), and *additive* (the drug was at a concentration not sufficient to have caused the death alone but acted in an additive manner with other drugs to have caused the death). We did not include cases where opioid

analgesics' contribution to death was circumstantial only, such as when drugs were present but determined not to have played a role in the death. For cocaine, heroin, and ethanol, however, we also included the presence of these substances in descriptive analyses. Records for 2010 were abstracted into a database using a standardized extraction form for decedents with available toxicology results, corresponding to 824 (92%) deaths identified using vital statistics and ICD-10 codes. Because we were interested in the class-level effect of exposure to opioid analgesics, we defined the outcome event as any overdose where at least one of the eight opioid substances was deemed by the medical examiner to be a primary or additive substance that directly contributed to death.

Access to Care Definition

Using data from the North Carolina Health Professions Data System we defined the number of potential controlled substance prescribers as all state-licensed physicians (n=20,752), nurse practitioners (n=3,679), physician assistants (n=3,652), and dentists (n=4,178), and an estimated 100 clinical pharmacist specialists [93]. As a proxy for an access-to-care measurement, we calculated what proportion of all potential prescribers wrote dispensed prescriptions for opioid analgesics by dividing the number of unique NC-registered DEA numbers for each prescription type recorded in the CSRS by the total number of NC-based licensed clinicians eligible to obtain a DEA registration number to prescribe controlled substances (n=32,361).

Analysis

We first sought to understand opioid analgesic prescribing practices through descriptive analyses. We plotted the number of prescribers, prescriptions and patients who received opioid analgesics in 2010, stratifying by formulation type (extended-release or immediate-release) and active ingredient. To gain a better understanding of opioid overdose mortality,

we examined age and sex distributions of decedents, and the contributions of ethanol, heroin, and cocaine. We also explored whether the opioid ingredients involved in death had been prescribed to the decedent in the previous 365 days.

Our analysis was a prospective cohort study of all North Carolina residents in 2010. The state population was represented by the mid-year population of 9,560,234 persons estimated by the National Vital Statistics System [94]. Individuals without a prescription record for an opioid analgesic in the CSRS contributed unexposed person-days for all of 2010.

Data were analyzed according to intent-to-treat (ITT) principles where an individual was considered exposed from the date of the first opioid prescription in 2010 among individuals who did not experience an event. For overdose decedents, first date of opioid prescription in the 365 days preceding death was used as the starting point to allow for equal potential observation time to those who did not have the outcome. The ITT approach has been suggested for use in observational safety studies of pharmacotherapy because it reduces bias arising from excluding those who stop therapy or are lost to follow-up, is used extensively in the clinical trial setting, and avoids inducing selection bias during follow-up that would result from censoring the outcomes of those who changed treatment [95]. Person-days exposed and unexposed to opioids were calculated separately, and accrued in calendar year 2010 or in the 365 days prior to overdose death. Therefore each individual could have either one or two records in the analysis dataset, corresponding to the person-days exposed and unexposed.

Stratified mortality rates were calculated by dividing the number of deaths by person-years of exposure calculated using intent-to-treat principles. Standard errors were calculated using the exact method [96]. Number needed to harm was calculated by taking the inverse

of the rate difference between mortality at different levels of MME for ER versus IR opioid analgesic exposure. Incidence rate ratios were calculated using Poisson regression with person-days at risk as the offset, implemented with generalized estimating equations (GEE) to account for repeated observations of an individual [97,98]. An independent structure was assigned after initial inspection of the covariance matrix. Standard errors were calculated using the Huber-White robust variance method [99], with the modification of subtracting the number of covariates from the number of observations. Data transformations and statistical modeling were performed in Stata/MP 12.1 (College Station, Texas, USA), running on 8 parallel core processors in a Linux-based computing system.

Human Subjects Protection

This research was reviewed by the University of North Carolina Non-Biomedical Institutional Review Board and deemed to be exempt according to federal standards.

Results

Opioid Analgesic Utilization Patterns

A total of 2,182,374 North Carolina residents received opioid analgesics for use in 2010, representing 22.8% of the total population, Figure 5.2. The most commonly dispensed opioids were hydrocodone and oxycodone, Figure 5.3. Immediate-release formulations were dispensed to 22.5% of the population (n=2,154,949), whereas 1.4% (n=139,520) received extended-release opioid analgesics. Immediate-release formulations accounted for 6,535,257 prescriptions, and extended-release accounted for 858,118 prescriptions, a ratio of about 15-to-2.

Residents filled prescriptions for opioid analgesics written by 28,998 North Carolina-based prescribers. Prescriptions for opioid analgesics came from 89.6% (n=28,998) of all

licensed clinicians in the state. By way of comparison, opioid analgesics were the most commonly prescribed type of controlled substance: 83.3% (n=26,953) of licensed clinicians prescribed benzodiazepines, 57.2% (n=18,518) sleep aids, and 44.8% (n=14,487) stimulants.

Fewer licensed clinicians had records indicating they prescribed extended-release opioids 40.0% (n=12,939), compared to immediate-release opioids 88.5% (n=28,649). The more potent synthetic opioids had the lowest numbers of prescribers: oxymorphone 6.2% (n=2,006), methadone 16.2% (n=5,256), hydromorphone 24.8% (n=8,037), and fentanyl 25.0% (n=8,087).

We observed 61,879 patients who received more than 150 mg average daily MME. Of these, 24.9% (n=15,430) of patients received their entire dose only in IR opioid formulations, while the remaining received both IR and ER opioids. Among those receiving more than 150 mg/day MME as only IR, the median intended duration of use indicated on the prescription was 4 days (IQR: 1, 30), however 14.1% (n=2,176) were on therapy for longer than 182 days.

Overdose Deaths

There were 629 deaths involving opioid analgesics in a primary or additive role among North Carolina residents in 2010, Figure 5.2. Females (n=234) comprised 37.2% percent of decedents, and the median age for both sexes was 43 years (inter-quartile range: 32 to 51 years). Deaths among females peaked a few years earlier than males. The most common pharmaceutical opioids involved in overdose deaths were: oxycodone, methadone, hydrocodone and fentanyl, Figure 5.3. Ethanol was involved in 12.2% (n=77) of overdoses involving opioid analgesics. Heroin was present in only 1.3% (n=8) of opioid analgesic overdoses, whereas cocaine was present in 8.4% (n=53).

Among the 629 deaths, 24.0% (n=151) had no record of having being dispensed a solid oral or transdermal opioid analgesic in the 365 days prior to death. Among the 478 decedents who had received an opioid, 43.1% (n=208) had received at least one extended-release formulation. Only half of all decedents (51%, n=244) had a current prescription at the time of death, confirming the decision to calculate exposure according to intent-to-treat principles.

Extended-release and Immediate-release Opioid Analgesics

There were 2,181,843 person-years of opioid analgesic exposure accrued during the study period calculated according to intent-to-treat principles, with 478 overdose deaths among patients receiving opioid analgesics for use in 2010, Table 5.2. Rates of overdose death increased incrementally as average daily MME increased, Table 5.2 and Figure 5.4. Incidence rates appeared to increase gradually, but stayed elevated beyond 200 mg/day MME. Using the lowest opioid exposed group (average daily MME dose >0 to 39.9 mg/day) as a reference, once 200 mg/day MME had been achieved, rates of overdose did not increase substantially with increasing dose.

Rates of overdose were about ten times greater among those receiving ER and IR opioid analgesics in combination, 14.9 per 10,000 person-years (95 percent CI: 12.9, 17.1), compared to those receiving only IR opioid analgesics, 1.3 per 10,000 person-years (95 percent CI: 1.2, 1.5), Table 5.3 and Figure 5.5. When compared to patients receiving the same MME of opioid analgesics, mortality rates among patients receiving ER and IR in combination were higher than those receiving only IR opioid analgesics. At the lowest strata, >0 to 99.9 mg/day average daily MME, the rate difference was 5.0 per 10,000 person-years, increasing to 7.5 per 10,000 person-years for 100 to 149.9 mg/day and stabilizing at 7.7 per 10,000 person-years at higher doses. Correspondingly, the number needed to harm ranged

from 2,003 to 1,291.

Benzodiazepines

The percent of all opioid analgesic recipients who were also prescribed a benzodiazepine was 80.0% (n=1,747,166). Benzodiazepines were implicated in 61.4% (n=386) of overdose deaths involving opioid analgesics. Rates of overdose death were about ten times higher among those receiving benzodiazepines in combination with opioid analgesics (7.0 per 10,000 person-years, 95 percent CI: 0.6, 0.9), compared to only opioid analgesics (0.7 per 10,000 person years, 95 percent CI: 6.3, 7.8), Table 5.4 and Figure 5.6. When compared to patients receiving the same MME of opioid analgesics, differences in mortality rates among those receiving benzodiazepines was greater at higher opioid analgesic doses. At the lowest stratum, >0 to 74.9 mg/day average daily MME, the rate difference was 2.8 per 10,000 person-years, increasing to 45.8 per 10,000 person-years at the highest stratum of 300 to 5,000 mg/day average daily MME. Correspondingly, the number needed to harm ranged from 3,623 to 218.

Discussion

This study reports findings from a large prospective cohort study of opioid analgesic use. Five previous studies have attempted to quantify the dose response between opioid analgesics and mortality, Table 5.1. Our analysis has more than three times as many exposed patients as the next largest published study. Our results extended the knowledge of the relationship between opioid dose and mortality by clarifying dose-specific risks of overdose for a more nuanced gradient of opioid analgesic doses than previous studies, including a dose range routinely used in clinical practice. This study is one of the first to quantify the additional risk of death associated with ER opioid analgesics. We also documented that the dose-dependent relationship between opioid analgesic dose and

overdose mortality is strongly influenced by concurrent benzodiazepine exposure, especially in the presence of higher opioid doses.

In our study, the incidence rate of overdose mortality appeared to rise gradually at lower doses, and increase distinctly at doses greater than 200 mg average daily MME. Like previous studies, we observed a dose-response relationship between MME and mortality risk, but we were also able to clarify that the shape of the curve is not linear. There appears to be relatively small additional risk of overdose death after patients reach 200 mg average daily MME, relative to the lowest strata, on the log-linear scale. We suspect that influences of clinical management may explain the change in the trajectory, with patients receiving higher doses of opioid analgesics receiving closer attention from the treating physician and caregivers, mitigating some of their risk for overdose. Opioid tolerance may also be part of the explanation for the shape of the curve. Increased opioid tolerance results in a rightward shift of the median effective dose, which may be accompanied by a corresponding shift in the median toxic dose, resulting in a broader or shifted therapeutic window where medication errors may be less likely to lead to respiratory depression. Unlike previous studies, we did not observe a meaningful inflection of the incidence rate at 100 mg/day average daily MME [14]. While the absolute rate of overdose continued to rise, above 200 mg average daily MME there was slowing increased overdose risk with subsequent increases in MME dose on a log-linear scale.

The results are consistent with our hypothesis that ER opioids would be associated with higher rates of overdose than IR opioids at comparable levels of MME. At lower doses (less than 100 mg/day MME), for approximately every 2,000 patients treated for a year with ER opioid analgesics instead of IR, there would be one additional overdose death. At higher doses, there would be one additional overdose death for approximately every 1,300 patients treated for a year with ER instead of IR opioid analgesics. Stated in terms of benefit and

risk, our results lead to the following question: Do the benefits of around-the-clock pain control using high dose ER opioid analgesics among 2,000 patients for a year outweigh the grief caused by a single untimely death? The answer to this question can only be derived from collective discussion, and highlights the need for additional information on the nature of the benefits of ER opioid analgesics experienced by patients. By way of comparison, the number needed to harm is reported to be 112 for suicidality associated with anti-depressant use among adolescents [100].

To inform the answer to the question presented above, we must also understand the underlying prevalence of chronic pain and the availability of treatment. The authors of a telephone-based study using a stratified probability sample of North Carolina households reported that approximately 10% of respondents suffered from chronic disabling back pain [101]. There are concerns that limiting the number of clinicians who prescribe ER opioids may adversely affect pain patients' ability to achieve analgesic relief, construed as an "access to care" problem, especially among racial and ethnic minorities [102]. While "access to care" is a commonly described concern in pain management, there have been few attempts to quantify it. While increased prescribing by primary care doctors has led to wider access to pain treatment, a general concern is that non-specialized clinicians may not have been adequately trained to prescribe these medications safely [103]. This analysis is one of the first to quantify the extent of prescribing of ER and IR opioid analgesics among *all* licensed clinicians in a population-based study, which provides a clearer picture of what access to opioid therapy may mean at a population level. While it may not be surprising that 89.6% of licensed clinicians prescribe opioid analgesics, we were surprised that so many (40.0%) had prescribed an ER opioid at least once in the previous year. We also report that 22.8% of the population received an opioid analgesic in 2010, and 1.4% received an ER opioid analgesic, consistent with the national estimate of 1.2% for 2009 presented by FDA

based on commercially available data [104] (and in line with utilization patterns from other high-income countries [105]). As a society we urgently need to understand what level of ER opioid prescribing would strike the correct balance between access to care concerns and inadequately trained physicians. We also need to objectively understand and quantify what benefits patients receive from ER versus IR opioid analgesics.

Many dosage strengths of ER opioid analgesics have approved single unit doses greater than 100 mg/day MME. There is limited information from general practice settings to guide clinical decisions at higher doses. Comparing to the most similar published study to ours, the range of our observed effect measures (IRR 2.6 through 6.7 for categories up to 119.9 mg/day) were lower than the odds ratio (OR) reported by Paulozzi et al. for average daily MME of 40 to 120 mg/day (OR 12.2, 95% CI: 9.2, 16.0). Our effect measures were greater than theirs (OR 11.3, 95% CI: 8.1, 15.8) for the highest categories, with IRR ranging from 16.6 through 90.4. This may be explained in part by the fact that that study combined unexposed and low-exposure individuals in the referent category, but also included suicides and deaths involving only illicitly manufactured drugs, limiting direct comparison. Despite this, the curves plotting relative risk against average daily MME from both studies were very similar in shape (e.g., Figure 2 in Paulozzi et al.), although we were able to provide greater resolution at higher doses.

We also found that benzodiazepines were prescribed to eight-out-of-ten patients receiving opioid analgesics. At opioid analgesic doses less than 75 mg/day MME, there was one additional overdose death from concurrent receipt of a benzodiazepine for approximately every 3,600 patients treated for a year with opioid analgesics. At the highest doses, there was one additional overdose death attributable to concurrent benzodiazepine exposure for every 218 patients treated for a year with opioid analgesics. Is there a substantial benefit to patients who receive both benzodiazepines and opioid analgesics to

justify co-prescribing them? While the risk of overdose from combinations of opioid analgesics and benzodiazepines has been well-documented in samples of drug users and toxicology studies [91], our results suggest that much of the previously noted dose-dependent mortality associated with opioid analgesics in general may be due to the widespread clinical practice of giving patients both classes of central nervous system depressants.

Given that 24% of decedents had no recent prescription history, it is clear that some of the drugs used in overdose deaths are obtained through social sharing outside of sanctioned medical use. Our findings suggest that history of opioid analgesic prescription is neither necessary nor causal to experience an overdose, but that opioid availability from a licensed clinician is one factor in a likely complex individual risk environment [58,59,106].

Many high dose IR opioids contain paracetamol (acetaminophen). Patients receiving these does may also experience hepatic injury, leading to morbidity, and possibly even death [107]. Among the overdose deaths we examined, none had a contributing cause-of-death suggesting liver injury, however diagnostic suspicion bias may have influenced this observation and we cannot preclude hepatic injury contributing to death. Since our focus was on overdose involving opioid analgesics caused by respiratory depression, our methodology would not have detected deaths where the underlying cause-of-death was hepatic injury that may be a result of high levels of exposure to paracetamol (acetaminophen) from IR opioids. According to North Carolina vital statistics data, there were 18 deaths in 2010 possibly related to paracetamol (acetaminophen) toxicity (ICD-10 codes: K71.1, Y45.5, Y10, X40, T39.9, T39.1), but we acknowledge there may be underreporting cases. Only two of these deaths included codes consistent with possible controlled substances poisoning, but both were deemed to be intentional (e.g., suicide). We speculate that if there were more exact ascertainment of cause-of-death, and probable

deaths involving hepatic injury and opioid analgesics had been included, the difference between IR and ER opioids might be even wider than observed.

It is welcome news that opioid analgesic and benzodiazepine co-prescribing is common, but is not associated with observable increases in risk at higher doses. While we cannot conclude that concomitant benzodiazepine use is generally safe at higher opioid doses, it appears that mortality risk is more closely linked to average daily opioid dose than the co-prescription of benzodiazepines.

Strengths and Limitations.

Population-based cohort studies of limited-duration like ours have the benefit of limiting selection bias such as that arising from changes due to patient selection over multiple years of observation. They also avoid the complications inherent in selection of controls in case-control studies. Another strength of our study is that the toxicological assessment conducted was able to distinguish between heroin and its metabolites, most notably morphine, thereby allowing us greater specificity in identifying outcomes of interest. Our data indicate that 132,732 patients in North Carolina received doses of opioid analgesics greater than 100 average daily MME in 2010, and this level can be reached by a single tablet or patch of many ER opioid analgesics. There is clearly a place for high-dose opioid formulations in modern medicine. However, previous research provided little insight on risks above 100 MME by treating higher doses all the same.

The study has limitations. First, our models assumed continuous risk during exposed and unexposed time. This assumption is unlikely to be tenable at higher opioid doses; the riskiest time may be after the initiation of therapy. We also did not take into account previous duration on therapy. External factors could have influenced overdose mortality during our observation period. Efforts to increase access to treatment for opioid dependence,

prescriber education programs for pain management, and harm reduction programs are known to have existed in North Carolina in 2010 [108]. All studies relying on medical examiner or vital statistics data are subject to limitations on identifying overdose [70]. As with the other studies on this topic, we also cannot eliminate the possibility that patients obtained opioid analgesics from other states or from outside medical distribution channels. Similarly, we cannot assume that a patient took the entire dispensed prescription as instructed. Therefore the actual exposure may have differed somewhat from the prescribed dose.

Two changes in the pharmaceutical supply of opioid analgesics occurred during the study. First, August 2010 saw the release of a new formulation of a commonly abused medicine (OxyContin, oxycodone extended-release) with features that made it more difficult to crush for injection or insufflation. Second, propoxyphene was withdrawn from the United States market on November 19, 2010, leading to the possibility that patients were switched to full mu-opioid receptor agonists in preparation for the lack of availability. These will be explored in future analyses.

There is an inherent question of exchangeability when comparing patients at different doses of the same medication in observational studies. Patients receiving higher doses are more likely to have more serious illnesses which necessitate, at least in the mind of the clinician, higher doses. The direct comparison of IR and ER opioid analgesics within strata of MME may be less influenced by this bias, and both showed elevated risks of overdose from reference groups. Even though we did not have covariate information that would allow us to adjust for likelihood of receiving treatment, observational studies such as ours might offer insight into medical practice outside of the clinical trial setting where high doses of IR opioids containing paracetamol (acetaminophen) would be unethical. In addition, the use of equianalgesic conversion factors treats all opioids as the same, ignoring feasible subjective

differences between them that likely influence treatment choice, including pill burden, patient preference, side effect profile, adverse event risk, and insurance coverage. Simply put, a generic codeine tablet is not the same as a branded fentanyl patch. The results of our study must be interpreted in this light.

Deaths involving opioid analgesics result from a combination of physiologic, genetic, and behavioral factors, compounded by broader social determinants such as health literacy, poverty, access to healthcare, and further upstream causes of painful conditions from injuries, cancer and violence [54,106]. These characteristics may also influence the likelihood of receiving a prescription for an opioid analgesic. Data on these potential confounders are not routinely available at an individual level in large population-based studies, and we were not able to control for them in ours.

Conclusion

Using the largest population-based cohort study published to date, we have quantified the dose-response relationship between opioid prescribing and overdose mortality, at higher doses than previously examined. We hope that our work will facilitate more nuanced clinical decisions about dose escalation. Higher doses of opioid analgesics were associated with increased overdose risk, however there were smaller incremental increases in risk above 200 mg average daily MME. Much of the risk at higher doses appears to be associated with co-prescribed benzodiazepines. At higher doses, there would be one additional overdose death for approximately every 1,300 patients treated for a year with ER instead of IR opioid analgesics. As a society we urgently need to understand what level of ER opioid prescribing would strike the correct balance between access to care concerns and inadequately trained physicians. We also need to objectively understand and quantify what benefits patients receive from ER versus IR opioid analgesics.

TABLES AND FIGURES

Table 5.1. Published studies of opioid analgesic dose and mortality.

Author	Study Years	Study Design	Drug substances	Sample Size	Outcome	Effect Measure	Notes
Peer-reviewed publications							
Bohnert et al.	2004 - 2008	Case-cohort study using medical records from random sample of military veterans, United States	codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone	143,684	Unintentional prescription opioid overdose deaths identified in vital statistics, n=750	Reference group: 1 mg/day to less than 20 mg/day *Cancer pain* 20 to <50 mg/day: HR 1.7 (95% CI: 0.7, 4.3; CLR 6.1) 50 to <100 mg/day: HR 6.0 (95% CI: 2.3, 15.8; CLR 6.9) 100 mg/day or greater: HR 12.0 (95% CI: 4,4, 32.5; CLR 4.4) *Chronic non-cancer pain* 20 to <50 mg/day: HR 1.9 (95% CI: 1.3, 2.7; CLR 2.1) 50 to <100 mg/day: HR 4.6 (95% CI: 3.2, 6.7; CLR 2.1) 100 mg/day or greater: HR 7.2 (95% CI: 4.8, 10.6; CLR 2.2)	93.3% male; separate estimates for chronic pain, cancer pain, acute pain and substane use disorder history; controls identified using 5% random subsample of all medical records
Dunn et al.	1997 - 2005	Cohort study of non-cancer pain patients receiving opioid analgesics using data from prepaid private health insurance plan, Washington, United States	Not specified, but includes: hydrocodoone, IR and ER oxycodone, codeine combination, ER morphine, propoxyphene, tramadol, hydromorphone, methadone, transdermal fentanyl	9,940	Intentional, unintentional, and undetermined intent prescription opioid overdose-related emergency department admissions (n=45) and deaths (n=6) from electronic medical records	Reference group: avergae MME 1 to < 20 md/day 20 to <50 mg/day: HR 1.4 (95% CI: 0.6, 3.6; CLR 6) 50 to <100 mg/day: HR 3.7 (95% CI: 1.5, 9.5; CLR 6.3) 100 mg/day or greater: HR 8.9 (95% CI: 4.0, 19.7; CLR 4.9)	Average daily dose calculated using 90 day exposure windows
Gomes et al.	1997 - 2006	Nested case-control study using records from individuals enrolled in a government assistance drug benefit program, Ontario, Canada	codeine, hydromorphone, meperidine, morphine, oxycodone, transdermal fentanyl	607,156	"Opioid-related deaths" identified by coroners, n=498	Reference group: Average MME 1 to 19 mg/day 200 mg/day or greater: adjusted OR 2.9 (95% CI: 1.8, 4.6; CLR 2.5)	Ages 15 to 64 years; adjusted for previous medicine use, number of drugs, duration of treatment, number of physicians, number of pharmacies, ER opioid status
Gomes et al.	2004	Cohort study of non-malignant pain patients using records from socioeconomically disadvantaged beneficiaries of government drug assistance program, Ontario, Canada	codeine, morphine, oxy- codone, hydromorphone, meperidine and transdermal fentanyl; excluded parenteral and intranasal preparations	154,411	"Opioid-related" deaths identified in government health benefits registry, n=302	Reference group: average MME >0 to 200 mg/day 201 to 399 mg/day: IRR 2.2 (95% CI: 1.92.5; CLR 1.3) 400 mg/day or greater: IRR 2.3 (95% CI: 1.7, 3.0; CLR 1.8)	Ages 15 to 65; Exposure measured in first 90 days of year and followed-up for up to 2 years
Paulozzi et al.	2006 - 2008	Case-control study using government prescription monitoring prorgam data, New Mexico, United States	buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, propoxyphene	730,381	Unintentional overdose deaths involving prescription and illicit drugs identified by chart review of medical examiner data, n=300	Reference group: average MME 0 to 40 mg/day >40 to 120 mg/day: OR 12.2 (95% CI: 9.2, 16.0; CLR 1.7 >120 mg/day: OR 11.3 (95% CI: 8.1, 15.8; CLR 1.9)	Reference group includes individuals not exposied to opioids; includes overdose deaths from only illicitly manufactured substances
Current Study							
Dasgupta et al.	2010	Cohort study using government prescription monitoring prorgam data, North Carolina, United States	solid oral, film and transdermal forms of: codeine combination tablets, fentanyl, hydrocodone combination tablets, hydromorphone, methadone tablets, morphine, oxycodone, oxymorphone;	2,182,374	Unintentional and undetermined inent prescription opioid overdose deaths identified in vital statistics, n=629	Reference group: average MME >0 to 39.9 mg/day 40 to 59.9 mg/day: IRR 2.6 (95% CI: 2.0, 3.5; CLR 1.8) to 500 through 12,0000 mg/day: IRR 125.8 (95% CI: 84.4, 186.6; CLR 2.2) See Table 2	All ages

Abbreviations: confidence interal (CI), extended-release (ER), hazard ratio (HR), immediate-release (IR), incidence rate ratio (IRR), milligrams (mg), milligrams of morphine equivalents (MME), odds ratio (OR)

Table 5.2. Incidence rates and incidence rate ratios for overdose deaths involving opioid analgesics, by average daily milligrams of morphine equivalents, North Carolina Residents, 2010.

	Deaths	Person-years	n	Rate per 10,000 Person-Years	95% Confidence Interval	Incidence Rate Ratio	95% Confidence Interval
Unexposed	151	4,700,647	7,377,860	0.3	0.27, 0.38	0.57	0.44, 0.73
>0 to 39.9 mg/day	98	259,735	1,305,969	3.8	3.1, 4.6	1.	
40 to 59.9 mg/day	90	457,223	457,322	2.0	1.6, 2.4	2.6	2.0, 3.5
60 to 79.9 mg/day	47	213,813	213,868	2.2	1.6, 2.9	2.9	2.1, 4.1
80 to 99.9 mg/day	34	72,447	72,483	4.7	3.2, 6.5	6.2	4.2, 9.2
100 to 119.9 mg/day	23	45,536	45,559	5.0	3.2, 7.6	6.7	4.3, 10.6
120 to 139.9 mg/day	22	20,699	20,721	10.6	6.7, 16.1	14.1	8.9, 22.5
140 to 159.9 mg/day	14	14,585	14,599	9.6	5.2, 16.1	12.8	7.3, 22.4
160 to 179.9 mg/day	15	6,769	6,784	22.1	12.4, 36.5	29.5	17.1, 50.7
180 to 199.9 mg/day	11	9,604	9,615	11.4	5.7, 20.5	15.2	8.2, 28.4
200 to 249.9 mg/day	24	11,654	11,678	20.6	13.2, 30.6	27.4	17.5, 42.8
250 to 299.9 mg/day	20	7,405	7,425	27.0	16.5, 41.7	35.9	22.2, 58.0
300 to 349.9 mg/day	17	4,495	4,512	37.8	22.0, 60.5	50.2	30.0, 84.0
350 to 399.9 mg/day	17	3,563	3,580	47.7	27.8, 76.4	63.2	37.8, 105.7
400 to 499.9 mg/day	14	3,527	3,541	39.7	21.7, 66.6	52.7	30.1, 92.2
500 to 5,000 mg/day	32	2,892	4,718	110.6	75.7, 156.2	90.4	60.7, 134.6
Total	629	5,834,594	9,560,234	1.1	1.0, 1.2		

Table 5.3. Incidence rates per 10,000 person-years for overdose deaths involving opioid analgesics, by average milligrams of morphine equivalents and formulation type, North Carolina residents, 2010.

	Deaths	Person-years	n	Rate	95% CI
Immediate-release only					
>0 to 99.9 mg/day	227	1,980,893	1,981,163	1.1	1.0, 1.3
100 to 149.9 mg/day	21	46,031	46,052	4.6	2.8, 7.0
150 to 199.9 mg/day	9	10,823	10,832	8.3	3.8, 15.8
200.0 to 5,000 mg/day	13	4,582	4,595	28.4	15.1, 48.5
Total	270	2,042,329	2,042,642	1.3	1.2, 1.5
Extended-release alone or in combination with immediate-release					
>0 to 99.9 mg/day	42	68,433	68,475	6.1	4.4, 8.3
100 to 149.9 mg/day	30	24,772	24,802	12.1	8.2, 17.3
150 to 199.9 mg/day	25	15,568	15,593	16.1	10.4, 23.7
200.0 to 5,000 mg/day	111	30,742	30,855	36.1	29.7, 43.5
Total	208	139,514	139,725	14.9	12.9, 17.1

Table 5.4. Incidence rates per 10,000 person-years for overdose deaths involving opioid analgesics, by average milligrams of morphine equivalents and benzodiazepine prescription status, North Carolina residents, 2010.

	Deaths	Person-years	n	Rate	95% CI
No benzodiazepine(s)					
>0 to 74.9 mg/day	85	1,479,019	1,479,135	0.6	0.4, 0.7
75 to 124.9 mg/day	11	153,681	153,694	0.7	0.3, 1.3
125 to 299.9 mg/day	11	34,317	34,328	3.2	1.6, 5.7
300.0 to 5,000 mg/day	14	6,478	6,493	21.6	11.8, 36.2
Total	121	1,673,494	1,673,650	0.7	0.6, 0.9
Received benzodiazepine(s)					
>0 to 74.9 mg/day	141	422,794	422,945	3.3	2.8, 3.9
75 to 124.9 mg/day	56	47,604	47,660	11.8	8.9, 15.3
125 to 299.9 mg/day	94	28,164	28,259	33.4	27.0, 40.8
300.0 to 5,000 mg/day	66	9,787	9,853	67.4	52.1, 85.8
Total	357	508,349	508,717	7.0	6.3, 7.8

Table 5.5. Rate differences per 10,000 person-years and number needed to harm for overdose deaths involving opioid analgesics, by average milligrams of morphine equivalents, formulation type and benzodiazepine prescription status, North Carolina residents, 2010.

Additional mortality from exteneded-release opioid analgesics, compared to similar doses of immediate-release opioid analgesics

Average daily MME	Rate difference per 10,000 person-years	Number needed to harm
>0 to 99.9 mg/day	5.0	2003
100 to 149.9 mg/day	7.5	1325
150 to 199.9 mg/day	7.7	1291
200.0 to 5,000 mg/day	7.7	1293

Additional mortality from concurrent benzodiazepine and opioid analgesic prescribing

Average daily MME	Rate difference per 10,000 person-years	Number needed to harm
>0 to 74.9 mg/day	2.8	3623
75 to 124.9 mg/day	11.0	905
125 to 299.9 mg/day	30.2	331
300.0 to 5,000 mg/day	45.8	218

Figure 5.1. Data cleaning steps for prescription data used in study, North Carolina, 2009 through 2011. Numbers in figure represent the unique count of prescription records included or excluded at each data cleaning step.

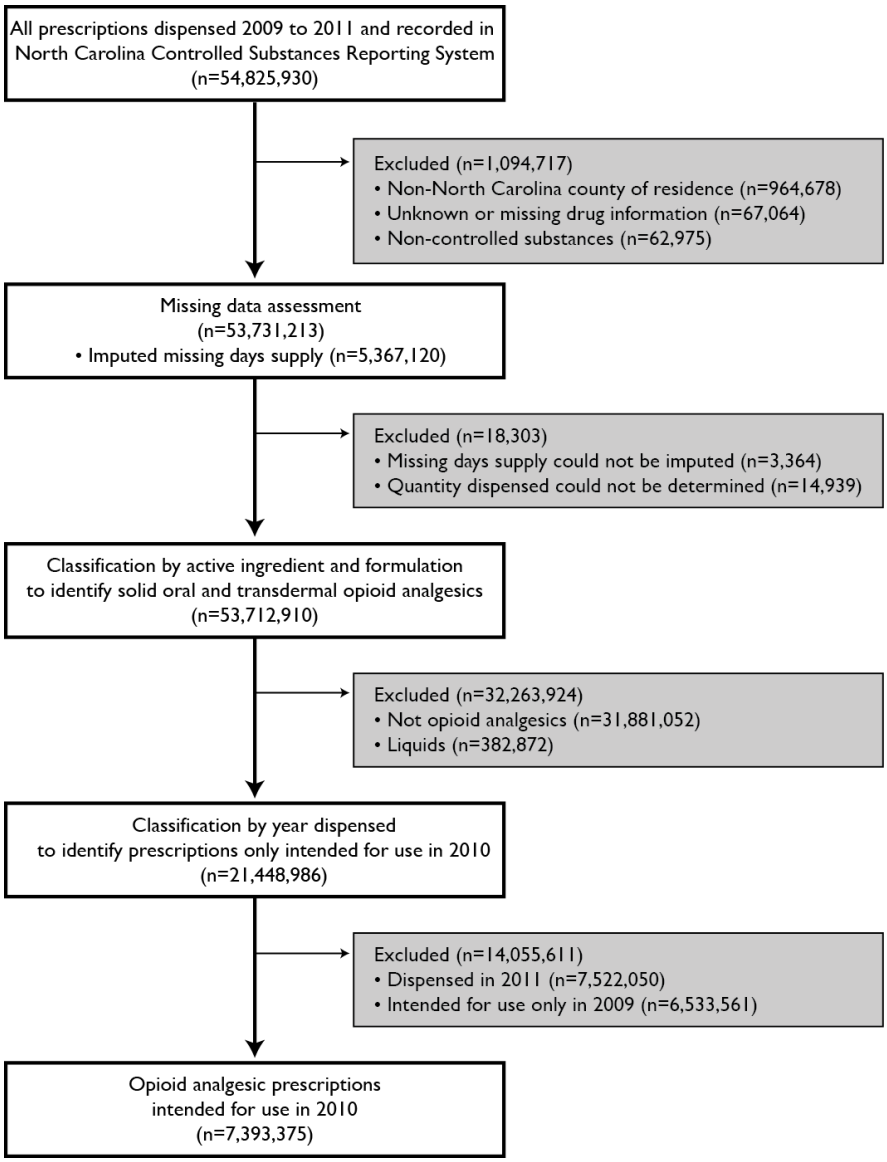


Figure 5.2. Study participant patient flow diagram, North Carolina residents, 2010.
This schematic represents the number of individuals who were included in analyses.

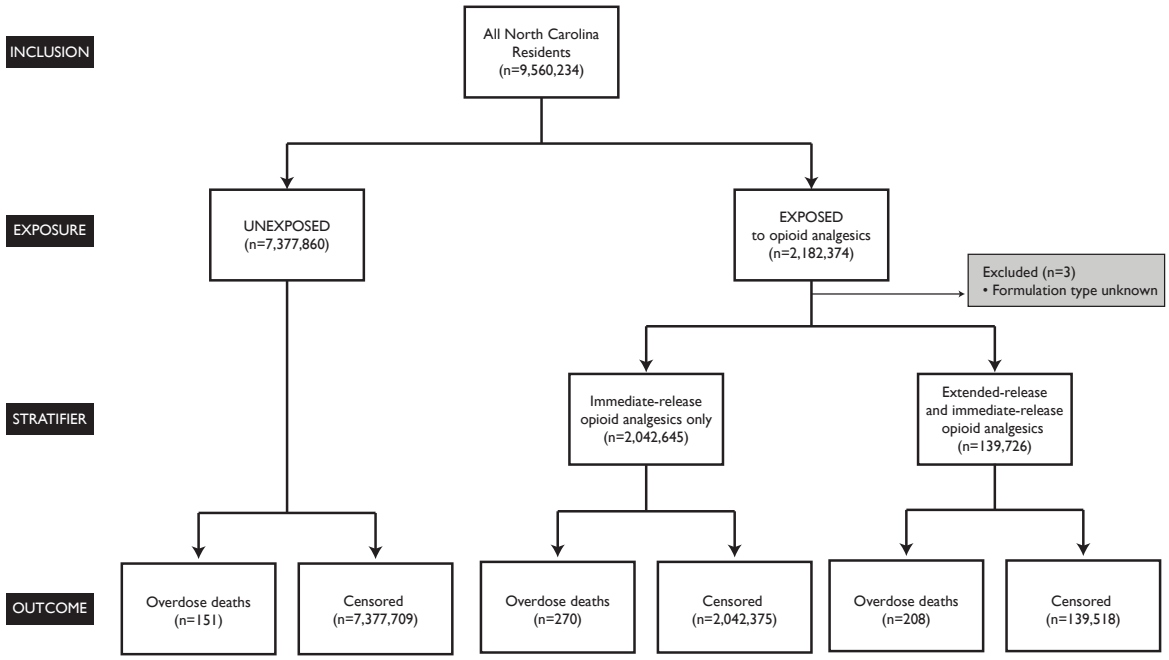


Figure 5.3. Percents of prescribers, prescriptions, patients receiving opioid analgesics, and overdose deaths, by active ingredient and formulation, North Carolina Residents, 2010. Numbers in parenthesis in the figure represent the approximate relative potency to morphine. Columns 1, 3, 4, and 5 do not sum to 100% because individuals could appear in more than one category. The denominator for column 1 is all licensed clinicians in North Carolina including doctors, nurse practitioners, physician assistants, and clinical pharmacists (n=32,361). The denominator for column 2 is the total number of prescriptions dispensed for opioid analgesics (n=7,393,375). Column 3 represents the percent of total opioid analgesic prescriptions (column 2) that were extended-release (ER) (n=858,118). The denominator for column 4 is the total number of unique recipients of opioid analgesics (n=2,182,374). The denominator for column 5 is the number of deaths involving opioid analgesics in a primary or additive role (n=629).
*Methadone involved in overdose deaths is not differentiated by formulation, and include mentions of methadone in tablet form (pain management) as well as liquid (management of opioid dependence).

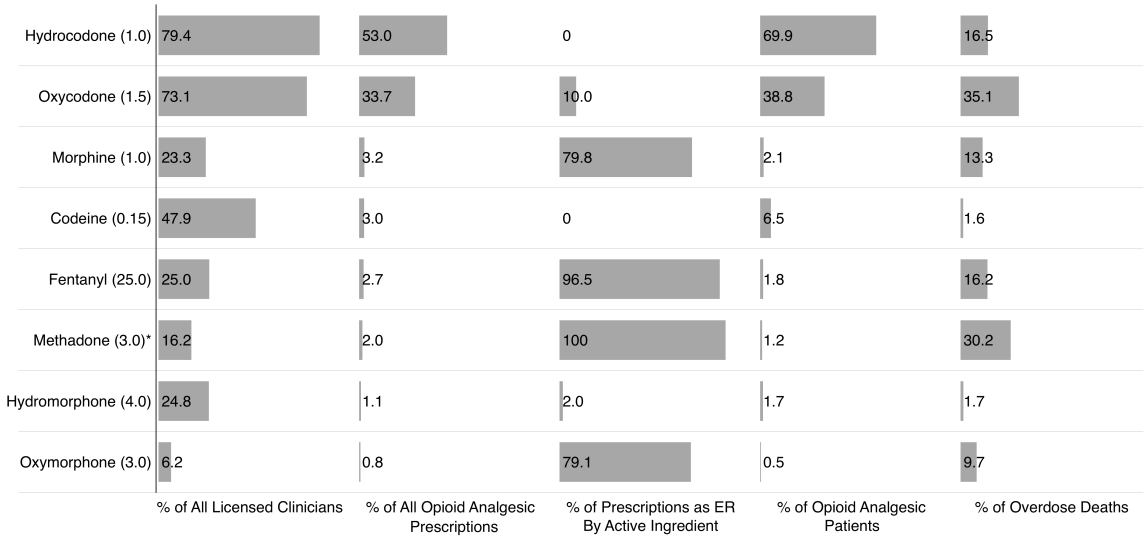


Figure 5.4. Incidence rates and incidence rate ratios for overdose deaths involving opioid analgesics, by average milligrams of morphine equivalents, North Carolina residents, 2010. The incidence rate appears to be distinctly elevated at doses greater than 200 mg average daily MME, top graph. Dotted lines are the bounds of the 95 percent confidence intervals (CI). In the bottom graph, the reference group for incidence rate ratios (IRR) is >0 to 19.9 mg of average daily milligrams of morphine equivalents, represented by the solid black square. IRRs and CIs (dotted lines) were estimated using Poisson regression, with person-days of exposure accrued in an intent-to-treat-type manner. The vertical axis in the lower graph is plotted on the $\log_{10}$ scale. Average daily MME are plotted at the midpoint of the each category range; the last point includes 500 through 5,000 mg/day.

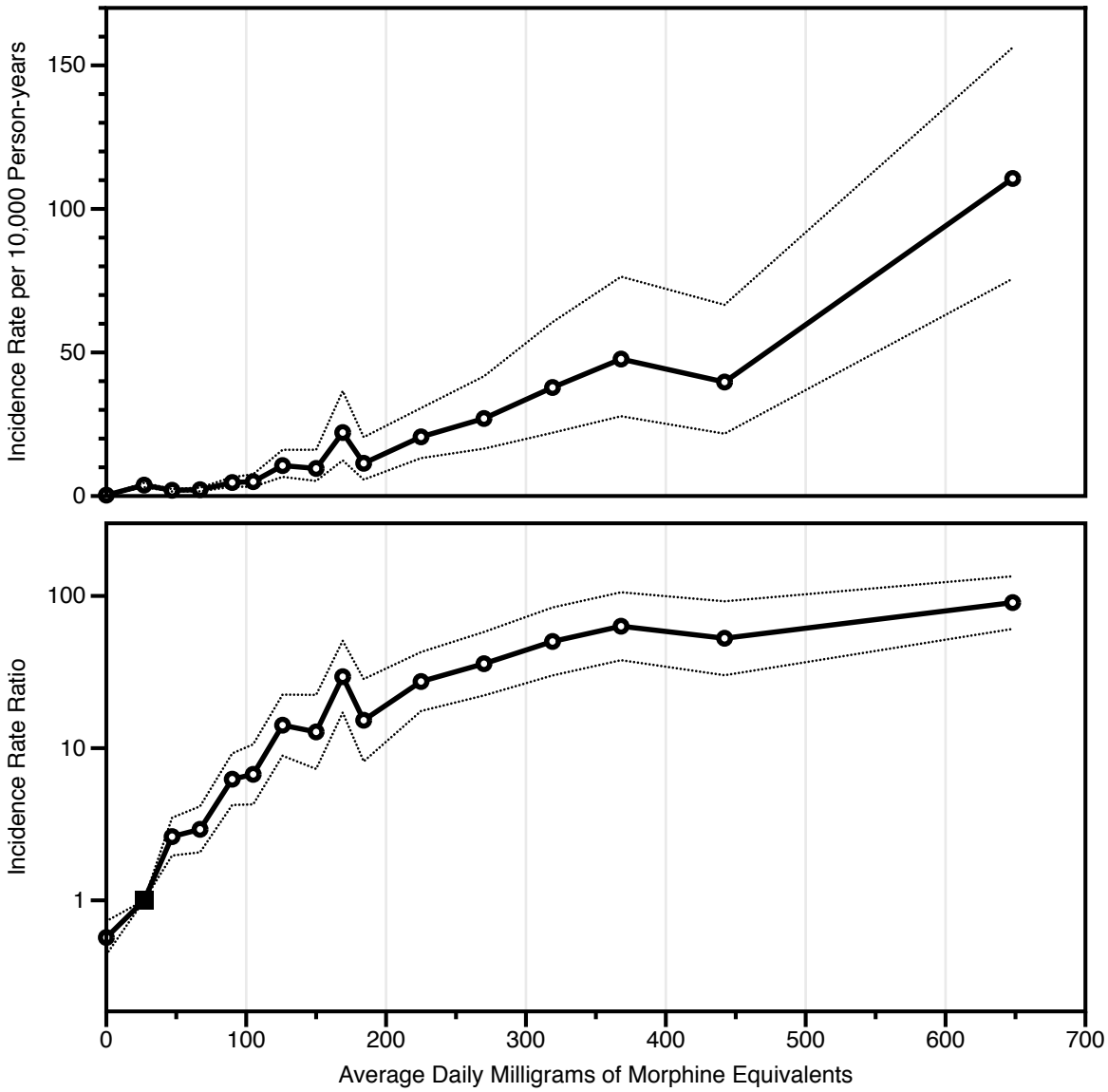


Figure 5.5. Mortality rates for overdose involving opioid analgesics, by average milligrams of morphine equivalents and formulation type, North Carolina Residents, 2010. The IR-only category contains those who had only received IR opioid prescriptions in the 365 days prior to death or end of the study, versus those who had at least one ER prescription. Reference group for incidence rate ratios (IRR) is >0 to 19.9 mg/day of average daily milligrams of morphine equivalents (MME). Grey lines are the bounds of the 95 percent confidence interval (CI). IRRs and CIs were estimated using Poisson regression, with person-days of exposure accrued in an intent-to-treat-type manner. The vertical axis is plotted on the $\log_{10}$ scale. Average daily MME are plotted at the midpoint of each category range; the last point includes 300 through 5,000 mg/day.

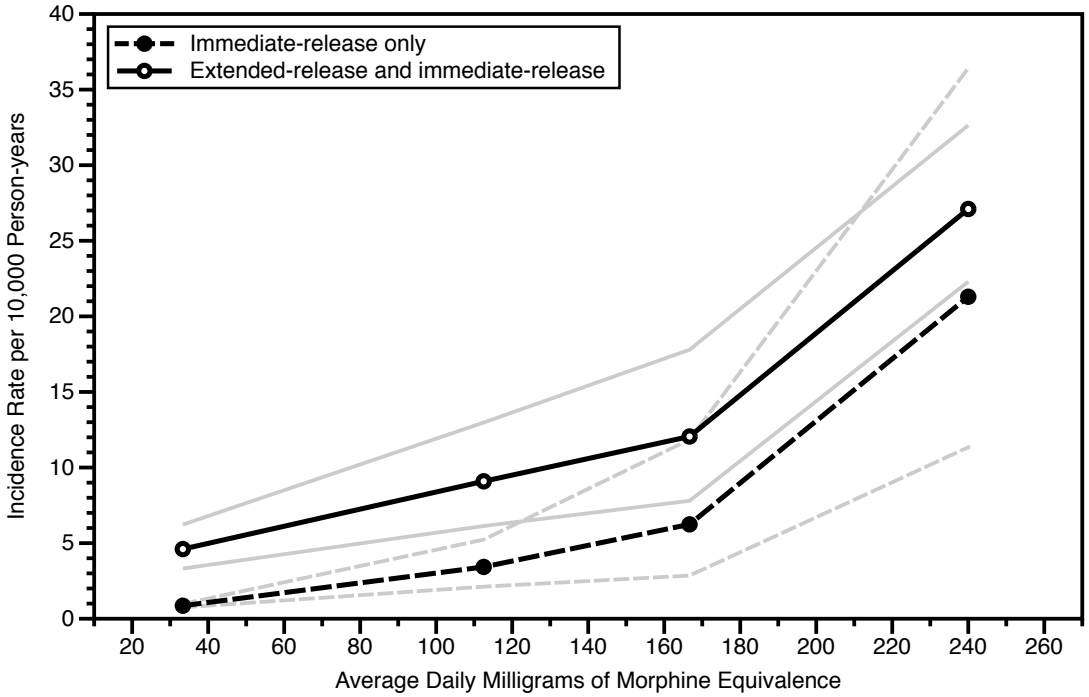
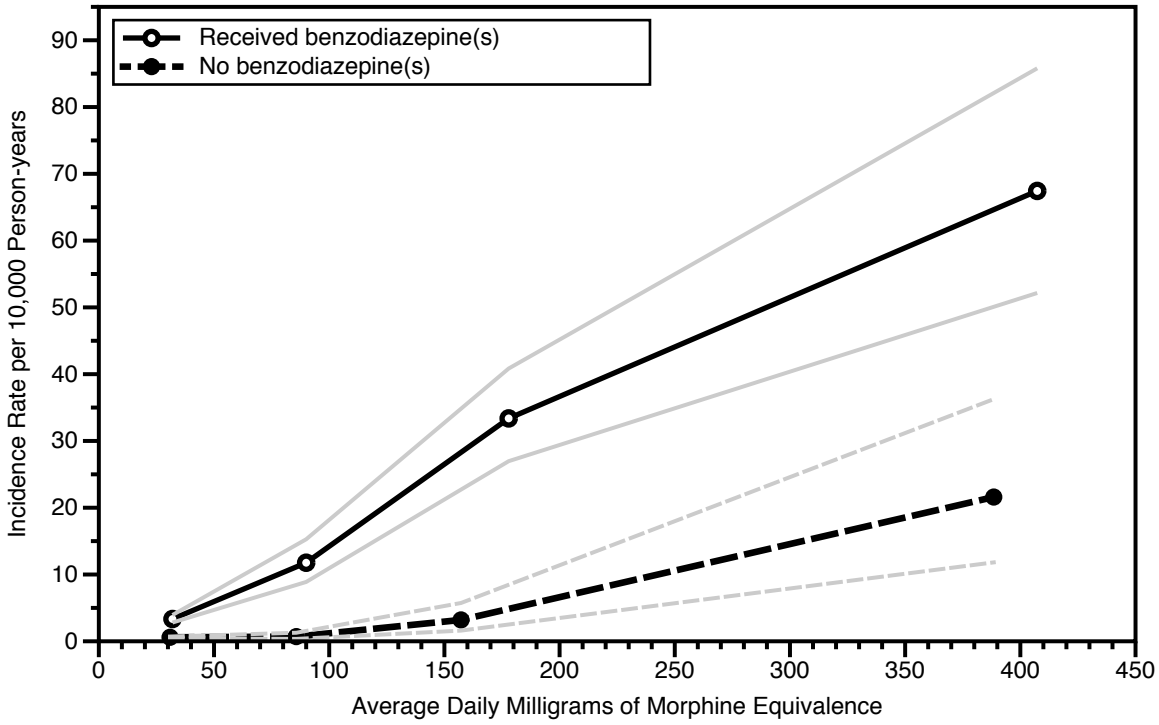


Figure 5.6. Incidence rate ratios for overdose deaths involving opioid analgesics, by average milligrams of morphine equivalents and benzodiazepine prescription status, North Carolina Residents, 2010.
Benzodiazepine exposure was determined by receipt of at least one prescription for a benzodiazepine in 365 days prior to death or end of the study, versus those who had no record of such a prescription. Reference group for incidence rate ratios (IRR) is >0 to 19.9 mg/day of average daily milligrams of morphine equivalents (MME). Grey lines are the bounds of the 95 percent confidence interval (CI). IRRs and CIs were estimated using Poisson regression, with person-days of exposure accrued in an intent-to-treat-type manner. The vertical axis is plotted on the $\log_{10}$ scale. Average daily MME are plotted at the midpoint of the each category range; the last point includes 500 through 5,000 mg/day.



CHAPTER 6

SYNTHESIS

Overview

The scope of Aim 1 was to evaluate between seven ICD-10-based definitions of opioid overdose mortality from North Carolina vital statistics. We evaluated the impact of including substance use disorders and pharmaceutical adverse events codes in definitions of overdose. Our suggestion is to include deaths attributable to substance abuse, but not pharmaceutical adverse events where controlled substances are not mentioned. We also proposed a definition for use in surveillance based on the findings.

The scope of Aim 2 was to conduct a prospective cohort study using mortality data linked to opioid analgesic dispensing data to examine the association between dose and overdose risk. First, we described patterns of clinical opioid analgesic utilization, focusing on prescribers, prescriptions, and patients, with attention to opioid substance and formulation type. Second, we examined the relationship between high dose opioid analgesic prescribing and overdose mortality, and confirmed the findings of previous studies. Third, we evaluated the differences between high doses of IR and ER opioid analgesics on overdose mortality, and how this relationship may be influenced by benzodiazepine co-prescribing. We found that overdose risk increases with MME dose, as expected, increasing substantially after 200 mg average daily MME. We also found

that benzodiazepine prescription significantly increased the risk of overdose, especially at high doses.

Major Findings

The major findings from Aim 1 (first manuscript) were as follows:

- Deaths resulting from adverse events involving non-controlled substances are included in routinely used ICD-10-based definitions of "drug overdose." While adverse events involving controlled and unknown substances could benefit from inclusion in overdose definitions, deaths explicitly involving non-controlled substances should be analyzed separately.
- Deaths resulting from substance use disorders are included in some, but not all, definitions of overdose. These deaths are likely to be of interest in surveillance and would benefit from inclusion in overdose definitions.
- Controlled-substance toxicology codes are mentioned as contributing causes-of-death among death records with non-poisoning and non-substance abuse underlying cause-of-death. These deaths are likely to be of interest in surveillance and would benefit from inclusion in overdose definitions.

The major findings from Aim 2 (second manuscript) were as follows:

- Annually, 22.8% of North Carolina residents are dispensed opioid analgesics, and nearly all licensed clinicians prescribe them.
- Risk of overdose increased continuously with MME, but no threshold dose was

found corresponding to a notable inflection.

- At lower doses (less than 100 mg/day MME), for every 2,003 patients treated for a year with ER opioid analgesics instead of IR, there would be one additional overdose death. At higher doses, there would be one additional overdose death for approximately every 1,300 patients treated for a year with ER instead of IR opioid analgesics.
- Benzodiazepine prescription status substantially modified the risk of overdose at higher doses of opioid analgesics. Since 80% of opioid analgesic patients also received benzodiazepines, overdose risk during routine clinical practice may be largely different from the controlled settings of clinical trials.

Limitations

Four major limitations from this work are summarized here. First, the most serious limitation is inherent to the design of observational studies and pertains to the second paper. There is a fundamental question of exchangeability when comparing patients at different doses of the same medication. Patients receiving higher doses could potentially be more likely to have serious illnesses (e.g., cancer pain) and co-morbid conditions, relative to those receiving opioids for acute and less severe and transient conditions (e.g., routine dental procedures). As such, the risk of respiratory distress or depression may be different at the point of starting therapy. In addition, there is likely to be more careful patient selection and monitoring by the physician for patients with severe chronic pain conditions that may be receiving opioids. For example, more frequent follow-up visits, urine toxicology screens, and other tools may be used preferentially among high-dose patients, resulting in decreased risk for overdose. We did not have access to these treatment decision-related covariates, and it is unlikely that such data would be available for all 22.8% of NC residents who received opioid

analgesics.

The second major limitation is that we did not take into account time on therapy in our models. Like the first major limitation, this is mainly pertinent to the second paper. We dichotomized person-time as either exposed to therapy or not, similar to the approach taken by others [13,14,15,16,17]. The first weeks of starting opioid therapy may pose the greatest risk for overdose, and that overdose risk declines as tolerance increases and plasma concentration reaches steady state. We could examine this hypothesis with a new user design and looking at time to death, and this will be the subject of future analyses.

A third limitation applies to both papers, and all studies of overdose mortality using vital statistics. Medical examiners are required to investigate suspicious and unnatural deaths, however, we have limited information on deaths that should have been considered an overdose but were not observed because an autopsy was not performed. In general these are forms of outcome identification bias or diagnostic suspicion bias where the outcome is more likely to be investigated because exposure is suspected. The underlying cause-of-death may be marked as a non-poisoning and non-substance abuse code. Of note, there were 36 additional deaths per year on average where controlled-substances toxicology codes were present. However, stigma associated with overdose and life insurance benefit considerations may also influence those certifying the death to leave out mention of substance abuse or overdose, in favor of less stigmatized respiratory depression or cardiac arrest mentions. We anticipate that the effect of this bias is likely to be small.

A fourth limitation concerns the data source for prescription data. Dispensing data from PMPs, while relatively new and potentially important, have not been used

extensively in research. There may be unanticipated limitations that are not apparent at this time. The analyses are necessarily dependent on reliable identification of unique patients, an assumption we cannot test within the data we have access to. We are encouraged that others have noted similar prevalence of utilization of opioid analgesics from other commercial and national sources [104], using data from a different source likely to de-duplicate patients using a different proprietary algorithm. Collaboration with the data vendor and matching of PMP records to prescription benefits claims data could be one way to examine the reliability of de-duplication algorithms.

Strengths

Overdose numbers issued by state and national governments are dependent on quantification of vital statistics data based on ICD-10 coding. As others have suspected [70,71], and we were able to confirm, there are many opportunities for misclassification of deaths. However, there have been very few studies dissecting the implications of using particular ICD-10 codes for surveillance. Aim 1 (first manuscript) is one of the most detailed examinations of ICD-10 coding of overdose deaths conducted to date.

Aim 2 (the second manuscript) is the largest cohort study to date examining the association between high-dose opioid analgesic utilization and overdose risk. This analysis has more than three times as many exposed patients as the next largest study. The large sample size allowed us to estimate dose-specific risks of overdose for a more nuanced gradient of opioid analgesic doses than previous studies, including a dose range routinely used in clinical practice. The analysis is also one of the first to use PMP data for epidemiologic research. The proliferation of these and other electronic prescription databases has opened up an opportunity for drug safety research, but they are limited in that they do not include outcome data. Fortunately, the North Carolina

Division of Public Health had recently conducted a painstaking matching of PMP records to medical examiner data. By conceptualizing this Aim as a statewide cohort study, we were able to combine this large-scale chart review with the statewide prescription database. This methodology has not been previously applied to the study of prescription drug overdose deaths.

Public Health and Policy Impact

The two Aims presented here have distinct audiences and applications. As a definitional study, the first investigation is likely to be of interest to injury surveillance epidemiologists at the state and national level, in particular to ISW, CSTE, ASTHO, and CDC. Ultimately we hope that the analyses may inform future revisions to ICD to clarify and help consolidate some of the disparate sets of codes that can be used for overdose. We observed that up to 16.1% of purported overdose deaths might be adverse events unrelated to controlled substances. This has implications for incidence estimates, government and foundation funding priorities, and intervention evaluation. The evaluation of interventions tailored specifically at preventing controlled substance overdose, such as the long-acting and extended-release opioid REMS, will be hard to evaluate if the non-controlled substance adverse events are included. Assuming no change in the methods of measurement over time, these extra decedents could be conceptualized as being immune to the intervention and their inclusion may decrease the apparent impact of any intervention.

The implications of Aim 2 are relevant to clinical decision-making. Our data indicate that 132,732 patients in North Carolina received doses of opioid analgesics greater than 100 average daily MME in 2010, and this level can be reached by a single tablet or patch of many ER opioid analgesics. There is clearly a place for high-dose

opioid formulations in modern medicine. However, previous research provided little insight on risks above 100 MME by treating higher doses all the same. Aim 2 is the first study to describe the shape of the curve of overdose risk above 200 mg. We hope that our work will facilitate more nuanced clinical decisions about dose escalation.

There are possible policy implications from Aim 2. While the FDA has chosen to focus on long-acting and extended-release opioids, it is clear that immediate-release opioids are also prescribed in a manner that raises concerns. The Aim 2 analysis is among the first to document off-label use of high-dose opioids. The FDA has required REMS to limit off-label use of transmucosal immediate-release fentanyl products, and it is reasonable to expect that other IR opioids may warrant REMS as well. However, most IR opioid analgesics are made by generic manufacturers who have traditionally been exempted or given lesser REMS requirements than innovator products. Our Aim 2 results suggest that a comprehensive approach to all opioid analgesics is needed.

There is policy pressure on FDA from advocacy groups to limit the doses of opioid analgesics through label changes. One example is the Physicians for Responsible Opioid Prescribing (PROP) which has petitioned the Agency to “Add a maximum daily dose, equivalent to 100 milligrams of morphine for non-cancer pain” [109], which the DEA and CDC have endorsed as well. The petition cites three of the other individual-level studies on this topic [13,14,16], but does not justify why 100 milligrams should be a cut-off. While we do not address the question of cancer versus non-cancer pain, our study does provide the first published examination of the gradient of risk at higher MME. We hope that Chapter 5 will contribute to the informed debate on what are safe thresholds for opioid prescribing.

Concerns about inadequately managed pain in chronic pain patients are credible, yet publications about overdose statistics tend to only include data on the negative consequences of opioid availability. Injury prevention research and the clinical practice of pain management are relatively separated in the scientific literature. In the spirit of trying to create collaborative linkages, we made efforts to include a measure of access to care in our analysis of opioid analgesic dose and mortality. By including data from licensing authorities, we were able to compute the percent of providers who prescribe each type of opioid analgesic, and estimate the prevalence of off-label use. This type of information is important because it provides scope for future intervention design, e.g., a meaningful sense of the magnitude of medical education for opioid prescribers.

Directions for Future Research

The studies presented here naturally suggest avenues for further exploration. Below we list some of the possible avenues of further research.

- *New user design*: To understand the time-varying risk of overdose, we propose to study only those patients who are new to opioid therapy, using data from the CSRS. A suitable washout period would have to precede eligibility. Patients could be followed forward in time to overdose endpoint using modeling techniques such as proportional hazards regression.
- *Understanding why patients receive off-label high-dose and long-term IR opioid analgesics*: Clinical insight, chart review, and qualitative information from patients would be required to generate hypotheses. Based on these findings, electronic medical records, and possibly claims data, could be useful to understand opioid prescribing preferences. Models could be developed that account for propensity to be prescribed certain types of opioids based on underlying medical

comorbidities.

- *Investigation of non-fatal overdose*: Non-fatal overdoses are observed during interactions with the medical system in hospital emergency departments, poison centers and through pre-hospital emergency medical services. Surveys of drug users are also important sources of information on overdose survivorship. Few analytic studies have been conducted with non-fatal overdose. Data quality assessment (e.g., ICD coding consistency in hospital emergency department data) is required as a first step, possibly through matching data from surveillance systems with chart review. If data are deemed to be of acceptable quality, similar dose-dependent modeling of opioid analgesic use and non-fatal overdose as paper two could be envisioned.
- *Consistency in medical examiner determination of death*: Medical examiner data for overdose mortality are the cornerstone of vital statistics-based surveillance in this field. However, the impact of medical examiner operating procedures on epidemiologic outcomes for overdose mortality have not been fully elaborated. For example, we have limited understanding how *primary* and *additive* are assigned to substances detected in post-mortem toxicology, and how this may influence the results of our study. Research methodology in this area would have to be developed in close conjunction with medical examiner officials.
- *Cancer vs. non-cancer pain:* There are major policy questions about the use of opioid analgesics for long-term non-cancer pain. While the data we had did not allow us to explore this dimension, using electronic data from academic hospitals or public assistance drug benefit programs might allow us to align clinical diagnoses with prescriptions and overdose.
- *Access to care:* We have provided initial direction for a population-level access to care measure: the percent of licensed prescribers within a state writing

prescriptions for ER opioid analgesics. Methods for estimating serious pain prevalence have evolved. A telephone stratified probability sample of 5,357 North Carolina households revealed that approximately 10% of respondents suffered from chronic disabling back pain [101]. Combining data from surveys with electronic prescription records could allow for more nuanced population-level measures of access to care.

- *Framework for intervention evaluation*: Continuing from the previous bullet, access to care measures could be used in combination with prescribing patterns and overdose mortality or morbidity data to provide a comprehensive framework for evaluation of interventions intended to reduce overdose involving opioid analgesics, in North Carolina and beyond.

Overdose death involving prescription opioids is a major public health problem in the United States. The first part of this dissertation informs the methodology for calculating the prevalence of overdose deaths using vital statistics. The second part of this dissertation provides detailed information on the dose-response between opioid analgesics and overdose risk. We hope our investigations will inform epidemiology and clinical decision-making related to this important topic.

APPENDIX 1. ANALYSIS OF NARCOTIC UNSPECIFIED DEATHS

Only 62 (1.3%) death records out of 4,635 overdoses had a “narcotic unspecified” code in the contributing cause-of-death fields, with 27 containing no other specified toxicology code for a controlled substance.

Of the 62 deaths, many had some indication that they were opioid-related. Eleven had T codes for a prescription opioid (T40.2, T40.3 or T40.4) and one had a code for heroin. There were six deaths with codes for cocaine (T40.5) in conjunction with T40.6 (but no T40.0 through T40.4 opioids), with the “unspecified narcotic” code suggesting the presence of an opioid. Of the remaining 44 deaths, benzodiazepine toxicity (T42.4) was listed in 17 cases; given the known risk of respiratory depression between opioids and benzodiazepines, these may be more likely to be deaths involving opioids than cocaine. Six deaths had a code for anoxic brain damage (G93.1), which is more indicative of opioid poisoning than cocaine toxicity.

The remaining 21 deaths are a complicated mix with contributing cause-of-death codes that include major depressive disorder, asphyxiation, cardiovascular and cerebrovascular disease, alcohol dependence, HIV-related encephalopathy, and chronic pain. Examination of the literal text of the cause-of-death fields for 2010 and 2011 confirmed the findings from ICD-10 coded vital statistics data for deaths with T40.6. Multiple drug toxicity (including ethanol and benzodiazepines) was commonly mentioned, but deaths involving T40.6 also mentioned the involvement of tapentadol, tramadol and propoxyphene, opioids atypically found in overdose deaths in the United States, as well as gabapentin.

We chose to include T40.6 in the opioid definition at this time because most deaths with this code had other indications of the involvement of opioids. This may change over time and should be assessed in each state. Only about half of the deaths with T40.6 had an autopsy performed, compared with about 80% for overdoses in

general. While the magnitude of the potential for misclassification is fairly limited in the North Carolina data when used for surveillance purposes, if the research question focuses on drug-related deaths in the hospital setting the treatment of T40.6 will have to be handled with care to minimize the potential for bias.

It should be noted that T40.2 (codeine, morphine, oxycodone, etc.), T40.3 (methadone), and T40.4 (buprenorphine, fentanyl, propoxyphene, etc.) are intended to identify the psychoactive substance involved in the poisoning death, and are not *per se* intended to identify whether they are pharmaceutical preparations. This distinction was important during the outbreak of overdose deaths in the United States due to heroin adulterated with illicitly manufactured fentanyl [85]. Unless ICD is revised to reflect the source or manufacturing method of the opioid, the existing structure of this class of T codes will limit long-term and cross-national comparisons since opioids that were originally pharmaceuticals may one day become predominantly manufactured illicitly (e.g., heroin, methamphetamine) or may have geographically isolated modifications of the medicine (e.g., Krokodil) [110]. T codes also do not differentiate methadone tablets used in analgesia from liquid methadone used in opioid dependence treatment programs, or transdermal buprenorphine used for chronic pain versus sublingual buprenorphine formulations used for outpatient management of opioid dependence disorders.

These results suggest that the majority of these deaths are due to opioid poisoning and that T40.6 should be included in definitions of opioid mortality. The relative proportion of deaths with a T40.6 code was small, and bias from including this code is low at a state level. It appears that the majority of T40.6 deaths are likely to involve opioids, including opioids that have incomplete agonism at the mu-opioid receptor but can nevertheless contribute to central nervous system depression. It

appears to be warranted to retain T40.6 deaths in definitions of opioid overdose for the sake of surveillance using vital statistics data in North Carolina.

APPENDIX 2. SEASONALITY AMONG OVERDOSE DEATHS

Definitions 1, 2, and 3 to the North Carolina data generated three monthly time series of overdose deaths that were nearly indistinguishable from each other, and opioid-specific Definitions 4, 6, and 7 yielded similar results (data not shown). We selected Definition 1 and 4 to represent the broader and more general definitions in seasonality analysis. Both sets of definitions showed similar patterns over time, suggesting that the drug overdose epidemic in North Carolina was largely driven by opioids. When monthly time series were smoothed using LOESS regression, possible seasonality may be present with a peak in April, Figure 4.2. For all drug overdoses identified using Definition 1, the Walter and Elwood test suggested the presence of seasonality (chi-square 8.2, p=0.016, 2 df) with a peak in the middle of April (106.0 degrees), but with poor fit (chi-square 20.6, p=0.037, 2 df) and not taking into account general seasonality of deaths. Taking into account background fluctuations in mortality confirmed that seasonality was present (chi-square 17.3, p=0.0002, 2 df), but with a peak in early June (158.0 degrees) relative to other deaths, and with reasonable model fit (chi-square 15.4, p=0.17, 2 df). For opioid overdoses identified using Definition 4, the results were more conclusive. The simple Walter Elwood exact method test suggested the possible presence of seasonality (chi-square 5.8, p=0.05, 2 df) with a peak in middle-to-late March (82.9 degrees) and reasonable model fit (chi-square 17.1, p=0.10, 2 df). Seasonality persisted after taking background deaths into account (chi-square 8.8, p=0.032, 2 df), with good model fit (chi-square 13.3, p=0.272, 2 df), but reaffirmed that the peak was in late May (147.4 degrees) for opioid deaths relative to all other deaths.

Despite the suggestion of a small peak in late Spring, we felt that any effect of seasonality was relatively minor in these data. As the project shifted from time series modeling to causal inference, the importance of seasonality adjustments was diminished.

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