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Original Research Articles

Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality

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Abstract

Objective. Previous studies examining opioid dose and overdose risk provide limited granularity by milligram strength and instead rely on thresholds. We quantify dose-dependent overdose mortality over a large spectrum of clinically common doses. We also examine the contributions of benzodiazepines and extended release opioid formulations to mortality.

Design. Prospective observational cohort with one year follow-up.

Setting. One year in one state (NC) using a controlled substances prescription monitoring program, with name-linked mortality data.

Subjects. Residential population of North Carolina (n = 9,560,234), with 2,182,374 opioid analgesic patients.

Methods. Exposure was dispensed prescriptions of solid oral and transdermal opioid analgesics; person-years calculated using intent-to-treat principles. Outcome was overdose deaths involving opioid analgesics in a primary or additive role. Poisson models were created, implemented using generalized estimating equations.

Results. Opioid analgesics were dispensed to 22.8% of residents. Among licensed clinicians, 89.6% prescribed opioid analgesics, and 40.0% prescribed ER formulations. There were 629 overdose deaths, half of which had an opioid analgesic prescription active on the day of death. Of 2,182,374 patients prescribed opioids, 478 overdose deaths were reported (0.022% per year). Mortality rates increased gradually across the range of average daily milligrams of morphine equivalents. 80.0% of opioid analgesic patients also received benzodiazepines. Rates of overdose death among those co-dispensed benzodiazepines and opioid analgesics were ten times higher (7.0 per

10,000 person-years, 95 percent CI: 6.3, 7.8) than opioid analgesics alone (0.7 per 10,000 person years, 95 percent CI: 0.6, 0.9).

Conclusions. Dose-dependent opioid overdose risk among patients increased gradually and did not show evidence of a distinct risk threshold. There is urgent need for guidance about combined classes of medicines to facilitate a better balance between pain relief and overdose risk.

Key Words. Opioids; Epidemiology; Overdose; Dose–Response; Cohort Study; Prescriptions; Chronic Pain; Risk Factors; Cloud Computing; Big Data

Introduction

The dose-dependent relationship between opioids and fatal respiratory depression have been documented by medical professionals for millennia [1–4]. In modern times, the United States and Canada have the highest per capita consumption of opioids in the world and the highest overdose rates [5–10]. In contrast, in much of the world opioid analgesics are unavailable even for end-of-life pain control among cancer patients [11].

Ecologic studies suggest a near-linear association between the total amount of opioids dispensed and overdose morbidity and mortality [10,12–20]. Yet, fatal and nonfatal overdoses are rarely reported even at high doses in clinical trials [21–24]. Beyond ecologic studies and clinical trials, several patient-level observational studies have provided insight into opioid analgesic use in routine clinical practice [25–34]. Direct comparison between these studies is difficult because of variations in whether deaths due to illicit drugs and suicide were included, which opioids were considered in the exposure, and whether relative effect measures included opioid unexposed individuals in the reference group. Most provide little to no information on the gradient of risk above 200 mg per day of morphine equivalents because these studies treat all higher doses the same, despite the fact that medicine is routinely prescribed above this level [35]. None reported the extent to which the dose-dependent effect may be influenced by co-prescribed benzodiazepines, a well-established risk factor for respiratory depression [36–38].

For reasons that are unclear, the notion has become entrenched that 100 or 120 mg per day of morphine equivalents is a "high dose" of opioid and is associated with an inflection point of risk for overdose, despite varying definitions of how average daily dose is calculated. Dose ranging within epidemiologic studies has been limited due to sample size considerations [25–31]. The tendency of the scientific community to settle on 100 mg as a threshold for risk is not arbitrary, but rather may be explained by the psychological phenomenon of digit preference (e.g., preferentially choosing numbers that end in 5 or 00), within the broader concept of

heaping [39], and the ease of risk communication. To address this limitation, a prospective cohort study among North Carolina residents was undertaken to quantify population-based rates of dose-dependent overdose mortality without an a priori threshold. Patterns of clinical opioid analgesic utilization, focusing on prescribers, prescriptions, and patients, with attention to opioid substance and formulation type were first described. It was also hypothesized that the dose-dependent risk of mortality associated with opioid analgesics could partially be explained by additional attributable risk from exposure to concurrently prescribed benzodiazepines.

Methods

Study Design

The analysis was structured as a prospective population-based cohort study of all NC residents alive in 2010. Exposure was defined as having received a dispensed prescription of an opioid analgesic for use in 2010. The outcome was overdose death (both unintentional and undetermined intent) involving opioid analgesics.

Data Sources

The North Carolina Controlled Substances Reporting System (CSRS) is a state-mandated prescription monitoring program operating since 2007. CSRS data are generated when prescriptions for a controlled substance are dispensed at pharmacies in North Carolina, with electronic systems that capture patient data (name and birthdate), 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 managed by the NC Division of Mental Health, Developmental Disabilities and Substance Abuse Services (DMHDDSAS). Due to federal regulations and state laws, the CSRS does not include prescription 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 overdoses, supplemented with detailed electronic records from the Office of the Chief Medical Examiner (OCME). All deaths that occurred in North Carolina are certified by trained medical examiners or attending physicians. Postmortem serum toxicological analyses are 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 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.

Data Linkage

Linkage between mortality and CSRS data were conducted deterministically. For each overdose decedent, prescriptions dispensed in the 365 days prior to death were identified using the first five letters of the last name and date of birth, confirmed by matching the first name,

full last name and date of birth as recorded on the death certificate.

Exposure Definition

For prescription data, Figure 1 depicts the data cleaning process. A total of 54,825,930 records for dispensed prescriptions were available for 2009 through 2011. First, 1,094,717 records were removed corresponding to prescriptions dispensed to non-NC residents, records with unknown or missing drug names, and
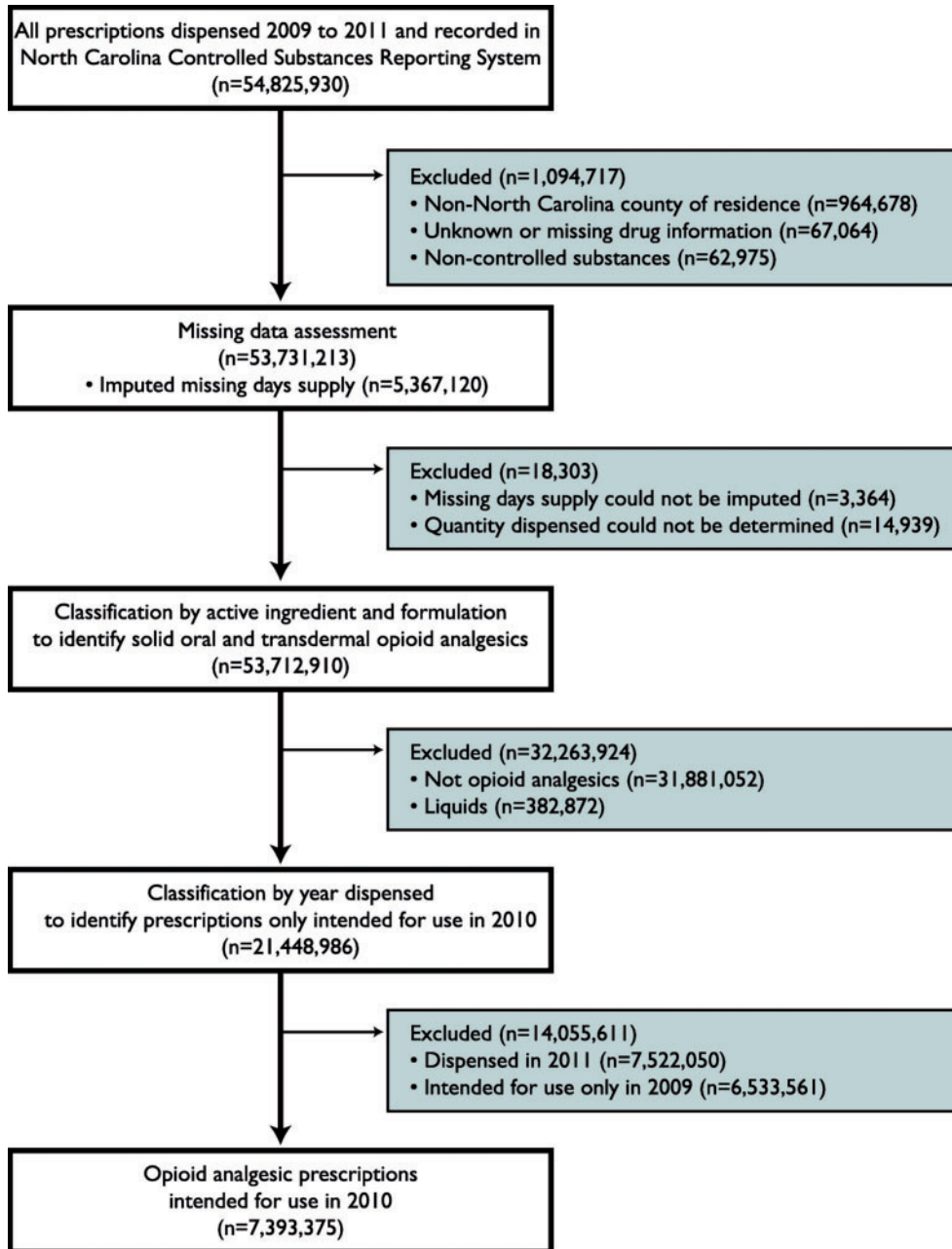

Figure 1 Data cleaning steps for prescription data used in study. Numbers in figure represent the unique count of prescription records included or excluded at each data cleaning step.

noncontrolled substances. Person-days were calculated using a measure referred to as "days supply." Days supply is a legally required prescription element defined by the prescriber, noted on the prescription, and incorporated in a field of the CSRS. Days supply was truncated to 182 days for 1,228 (0.002%) prescriptions for opioid analgesics of greater duration because these illogical values fell outside of DEA rules for controlled substances dispensing. Days supply was imputed for 5,369,748 prescription records (10%) 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, which encompasses strength, formulation, active ingredient and manufacturer. Some records were excluded because the quantity dispensed could not be determined (n = 18,303; 0.033%) because this was a necessary field for calculating daily opioid exposure.

Next, 21,448,986 prescriptions were positively identified for solid oral or transdermal opioid analgesics labeled for acute and chronic pain containing codeine, hydrocodone, hydromorphone, fentanyl, methadone, morphine, oxycodone, and oxymorphone. The active ingredient, milligram strength, and formulation type (e.g., extended-release/immediate-release, and solid oral/patch/liquid) were determined by matching to NDC number. To maximize inclusion of data with incorrect or missing NDC numbers, a natural language processing regular expressions-based parser was run on the drug name field to determine the active ingredient and formulation, created using natural language processing via Perl Regular Expressions. Discrepant records were individually adjudicated to determine the correct classification using the FDA's Orange Book as a reference. The total process resulted in the identification of 7,393,375 prescription records for opioid analgesics.

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 2010. In tablet form, methadone is used for chronic pain management, and as a liquid for management of opioid dependence; methadone was included in the ER category for consistency with regulatory classification [40].

Because of differences in potencies between opioids, clinicians may 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. Although legitimate concerns exist about the safety and accuracy of these tables in routine clinical practice, they serve as a convenient tool for epidemiologic research. To have comparable results with previous studies, the conversion ratios suggested by CDC [41] were used to calculate milligrams of morphine equivalents (MME): 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). 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 prescriptions. Days supply was proportionally limited, under the assumption of linearity, for prescriptions written in 2009 for use in 2010, as well as prescriptions written in late 2010 for use at least in part in 2011. Benzodiazepine exposure status was dichotomized as having received dispensed benzodiazepines in the 365 days prior to death or end of the study.

Outcome Definition

Residents who died in 2010 were included if the underlying cause-of-death in vital statistics 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. The outcome was defined as any overdose where at least one of the eight opioid substances was deemed by the medical examiner to be involved in *primary* (the drug was at a concentration sufficient to have caused the death alone regardless of other drugs detected) or *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) roles. Cases were not included 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. 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.

Prescriber Utilization Metric

Using data from the North Carolina Health Professions Data System [42] the number of potential controlled substance prescribers was defined 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 [43]. The proportion of all potential prescribers who wrote dispensed prescriptions for opioid analgesics was calculated by dividing the number of unique NC-registered DEA numbers 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).

Statistical Analysis

This 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 [44]. Individuals without a prescription record for an opioid analgesic in the CSRS contributed unexposed person-days for all of 2010.

Person-time exposed and unexposed to opioids were accrued in calendar year 2010 or in the 365 days prior to overdose death. 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 die of an overdose. 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 introducing selection bias during follow-up that would result from censoring the outcomes of those who changed treatment [45].

MME-stratified incidence rates and 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 [46–48]. An independent structure was assigned after initial inspection of the covariance matrix. Standard errors were calculated using the Huber-White robust variance method [49], 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. Named linkage was conducted by North Carolina Division of Public Health officials under government surveillance authority.

Results

Opioid Analgesic Prescribing Patterns

A total of 2,182,374 North Carolina residents received one or more prescriptions for opioid analgesics for use in 2010, representing 22.8% of the total population. The frequency distribution of average daily dose across the population showed that the vast majority of patients received less than 200 mg of morphine equivalents, Figure 2. The most commonly dispensed opioid was hydrocodone (70% of all opioid analgesic patients), followed distantly by oxycodone (39%), Figure 3. 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). 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, or 11.6% of all opioid prescriptions were in ER form.

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. Opioid analgesics were the most commonly prescribed type of controlled substance, but 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 prescribed extended-release opioids 40.0% (n = 12,939), compared to immediate-release opioids 88.5% (n = 28,649).

Only 61,879 patients (2.8%) received more than 150 mg average daily MME. Of these, 24.9% (n = 15,430) 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 long-term high-dose therapy (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. Females (n = 234) comprised 37.2% percent of decedents, and the median age for both sexes was 43 years (interquartile range: 32–51 years). The most common pharmaceutical opioids involved in overdose deaths were: oxycodone, methadone, hydrocodone and fentanyl, Figure 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).

Of 2,182,374 patients prescribed opioids, 478 overdose deaths were reported (0.022%). The rate of overdose deaths per 10,000 patients with one or more opioid prescription per year (in black, Figure 3) was lowest for codeine (0.2 per 10,000 patients) and hydrocodone, and highest for morphine, fentanyl, and oxymorphone. The opioid substance-specific rates per 10,000 patients generally followed the proportion of prescriptions written for ER formulations indicated for chronic pain, and did not follow the clinical potency as closely. The exception was oxymorphone which had 54 deaths per 10,000
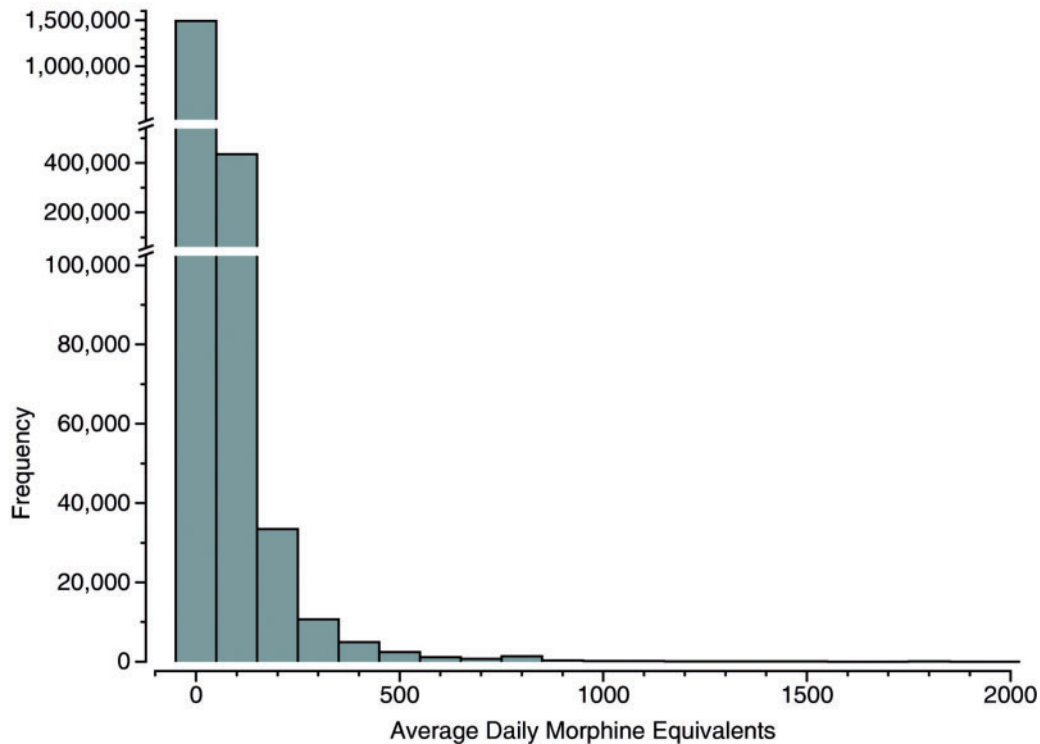
Figure 2 Distribution of average daily morphine equivalent dose. Histogram depicting average daily dose of opioid analgesics in terms of morphine equivalents (n = 2,182,374 patients).

patients, despite only being prescribed to 0.5% of opioid analgesic patients.

Half of all decedents (51%, n = 244) had a prescription for an active current opioid analgesic on the day of death, ostensibly meaning they were under the care of a NC prescriber. 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.

Dose-Dependent Overdose Risk

There were 2,181,847 person-years of opioid analgesic exposure accrued during the study period. Incidence rates appeared to increase gradually, and stayed elevated beyond 200 mg/day MME, Figure 4 and Table 1. No distinct threshold was observed at 100 mg/day MME or 120 mg/day MME.

The percent of all opioid analgesic recipients who were also prescribed a benzodiazepine in the past year was 80.0% (n = 1,747,166). Benzodiazepines were determined to be involved by medical examiners in 61.4% (n = 386) of overdose deaths involving opioid analgesics. Rates of overdose death were about ten times higher among those receiving benzodiazepines and opioids

concurrently (7.0 per 10,000 person-years, 95 percent CI: 6.3, 7.8), compared to only opioid analgesics (0.7 per 10,000 person years, 95 percent CI: 0.6, 0.9), Figure 5. 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.

Discussion

This study reports findings from the largest known prospective cohort study of opioid analgesic use in routine medical practice. While there may be a place for high-dose opioid formulations in modern medicine, previous research provided little insight on risks above 100 MME. These results extended the knowledge of the relationship between opioid analgesic use and mortality by clarifying dose-specific risks at higher doses. 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.

Overdose mortality rates rose gradually at lower doses, and increased gradually at doses greater than 200 mg average daily MME. Like previous studies, a dose–

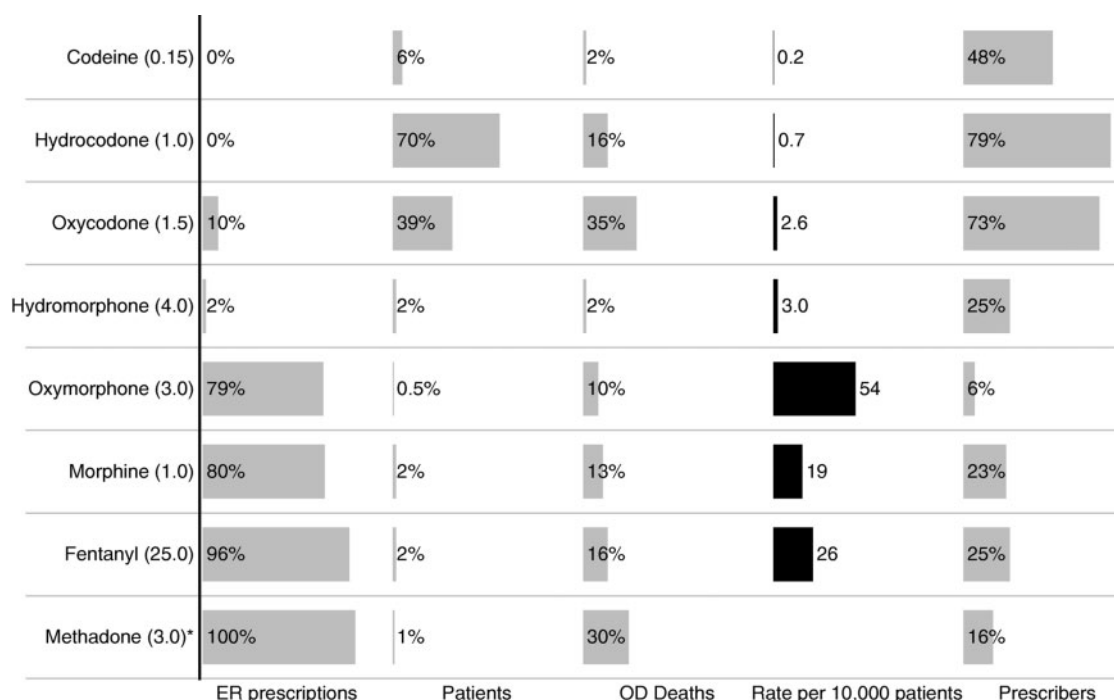|	ER prescriptions	Patients	OD Deaths	Rate per 10,000 patients	Prescribers
Codeine (0.15)	0%	6%	2%	0.2	48%
Hydrocodone (1.0)	0%	70%	16%	0.7	79%
Oxycodone (1.5)	10%	39%	35%	2.6	73%
Hydromorphone (4.0)	2%	2%	2%	3.0	25%
Oxymorphone (3.0)	79%	0.5%	10%	54	6%
Morphine (1.0)	80%	2%	13%	19	23%
Fentanyl (25.0)	96%	2%	16%	26	25%
Methadone (3.0)*	100%	1%	30%		16%

Figure 3 Percents of prescribers, prescriptions, patients receiving opioid analgesics, and overdose deaths, by active ingredient and formulation type. 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. Column 1 represents the percent of total opioid analgesic prescriptions (column 2) that were extended-release or long-acting formulations (n=858,118), by active opioid ingredient. The denominator for column 2 is the total number of unique recipients of opioid analgesics (n = 2,182,374). The denominator for column 3 is the number of deaths involving opioid analgesics in a primary or additive role (n = 629), and column 4 is the rate of overdose deaths per 10,000 patients per year expressed with the number of unique opioid analgesic patients as the denominator. The denominator for column 5 is all licensed clinicians in North Carolina including doctors, nurse practitioners, physician assistants, and clinical pharmacists (n = 32,361). * Methadone rate is not presented because methadone involved in overdose deaths is not differentiated by formulation in medical examiner data, and include mentions of methadone in tablet form (pain management) as well as liquid (management of opioid dependence).

response relationship between MME and mortality risk was observed, but there is new evidence that the shape of the curve is not linear. Unlike previous studies, there was no meaningful inflection of the incidence rate at 100 mg/day average daily MME [25]. However, there appeared 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. Theoretically, opioid tolerance may be part of the explanation. 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.

A surprising finding was that benzodiazepines had been prescribed in the previous year to eight-out-of-ten patients receiving opioid analgesics, despite widespread clinical knowledge of the risk of respiratory depression and electronic access to a controlled

substances prescription monitoring program. This is in comparison to 5% of the adult US population receiving benzodiazepines [50]. A recent study among Medicaid patients in Washington state found that 44.5% of methadone poisoning decedents and 48% of other opioid poisoning decedents had sedative (e.g., benzodiazepine) prescriptions in the month before death [34]. Another recent study among United States military veterans found that 27% of patients who received opioid analgesics also received benzodiazepines, and that 49% of overdose decedents had concurrent opioid analgesic and benzodiazepine prescriptions [51]. The differences between studies are likely due to time definitions used. The risk of respiratory depression from concurrent benzodiazepine and opioid analgesic use is widely known in clinical settings, and increased mortality risk has been documented among drug users [37]. Cross-sectional mortality surveillance studies [52] have also noted the presence of benzodiazepines among overdose deaths; one study found that benzodiazepines were involved in 78.5% of deaths involving
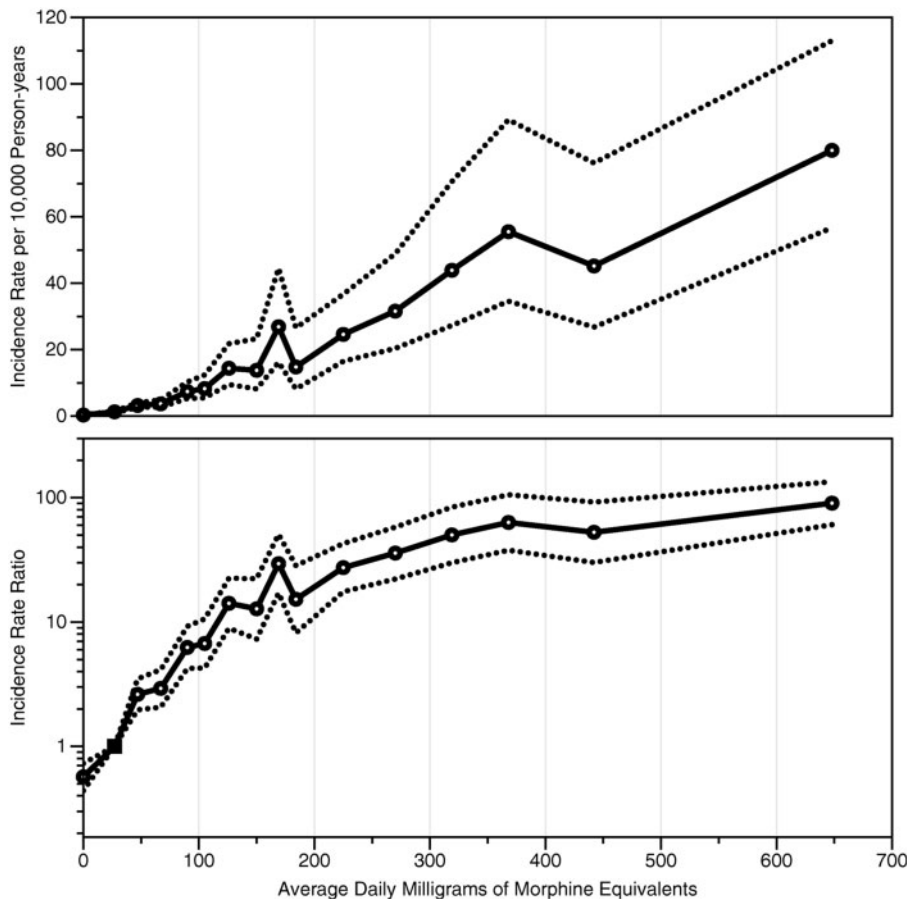
Figure 4 Incidence rates and incidence rate ratios for overdose deaths involving opioid analgesics, by average daily milligrams of morphine equivalents. The incidence rate appears to be distinctly elevated at doses greater than 200 mg average daily MME, top graph. Dotted lines are the bounds of the 95 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.

psychotherapeutic drugs. However, there is limited information as to how commonly the two central nervous system depressants are coprescribed in large population samples. This situation differs considerably from opioid analgesic efficacy clinical trials that exclude patients with psychiatric diagnoses for conditions routinely treated with benzodiazepines (e.g., anxiety, etc.) in the United States.

The underlying prevalence of chronic pain and the availability of treatment should also be considered. The authors of a telephone-based study of North Carolina households reported that approximately 10% of adults suffered from chronic disabling back pain [53]. 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 [54]. While "access to care" is a commonly described concern in pain management, there is no accepted way 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 [55]. 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, that 40.0% had prescribed an ER opioid was higher than expected. This study also found 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 at an Advisory Committee based on commercially available data [56] (and in line with utilization patterns from other high-income countries [57]). 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 overdose risk.

Many ER opioid analgesics have approved single unit doses greater than 100 mg/day MME. There is limited

Table 1 Incidence rates and ratios for overdose deaths involving opioid analgesics, by average daily milligrams of morphine equivalents

	Deaths	Person-Years	n	Rate per 10,000 Person-Years	95% Confidence Interval	Incidence Rate Ratio	95% Confidence Interval
Unexposed	151	3,554,850	7,377,860	0.34	0.29, 0.40	0.57	0.44, 0.73
>0 to 39.9 mg/day	98	1,305,835	1,305,969	1.3	1.0, 1.5	1	
40 to 59.9 mg/day	90	457,227	457,322	3.2	2.6, 4.0	2.6	2.0, 3.5
60 to 79.9 mg/day	47	213,816	213,868	3.7	2.7, 4.9	2.9	2.1, 4.1
80 to 99.9 mg/day	34	72,448	72,483	7.4	5.3, 10.3	6.2	4.2, 9.2
100 to 119.9 mg/day	23	45,536	45,559	8.3	5.5, 12.4	6.7	4.3, 10.6
120 to 139.9 mg/day	22	20,699	20,721	14.4	9.5, 21.8	14.1	8.9, 22.5
140 to 159.9 mg/day	14	14,586	14,599	13.8	8.2, 23.3	12.8	7.3, 22.4
160 to 179.9 mg/day	15	6,769	6,784	26.9	16.2, 44.5	29.5	17.1, 50.7
180 to 199.9 mg/day	11	9,604	9,615	14.8	8.2, 26.6	15.2	8.2, 28.4
200 to 249.9 mg/day	24	11,653	11,678	24.6	16.5, 36.7	27.4	17.5, 42.8
250 to 299.9 mg/day	20	7,406	7,425	31.6	20.4, 48.9	35.9	22.2, 58.0
300 to 349.9 mg/day	17	4,495	4,512	43.9	27.3, 70.6	50.2	30.0, 84.0
350 to 399.9 mg/day	17	3,563	3,580	55.5	34.6, 89.2	63.2	37.8, 105.7
400 to 499.9 mg/day	14	3,527	3,541	45.2	26.8, 76.2	52.7	30.1, 92.2
500 to 5,000 mg/day	32	4,684	4,718	80.0	56.7, 113.0	90.4	60.7, 134.6
Total	629	5,736,696	9,560,234				

Figure 5 Incidence rate ratios for overdose deaths involving opioid analgesics, by benzodiazepine prescription status. 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 log10 scale. Average daily MME are plotted at the midpoint of the each category range; the last point includes 500 through 5,000 mg/day.
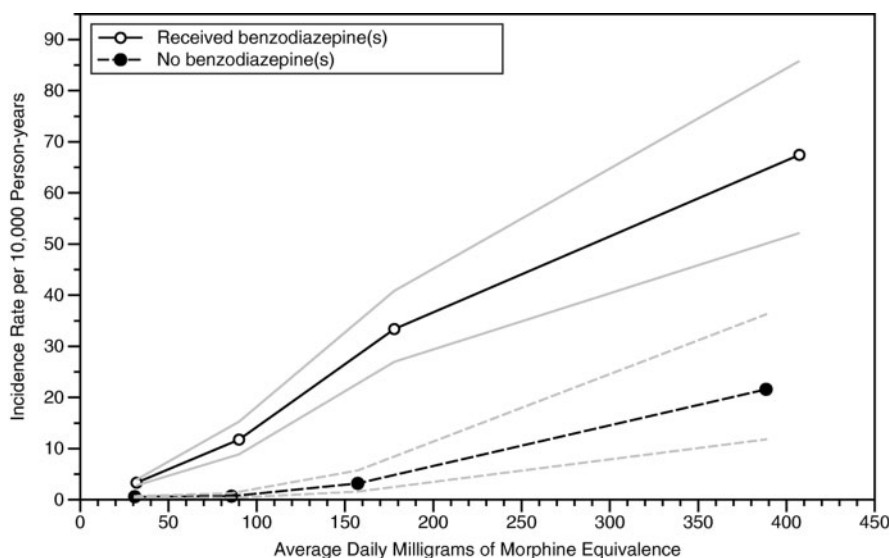
information from general practice settings to guide clinical decisions at these higher doses. The increase in the 160–179.9 mg/day MME interval represents risk from the most commonly prescribed dose strengths of the fentanyl patch. Methods for calculating MME which do not take into account overlapping prescriptions (e.g., total mg MME for all prescriptions divided by the sum of days supply) underestimate the risk in this specific category. Therefore, it is critical to account for overlapping prescriptions, and justifies taking a person-time approach to MME calculation with intent-to-treat principles.

Comparing to the most similar published study to ours, the range of 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. 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 (Figure 3) from both studies were strikingly similar in shape (e.g., Figure 2 in Paulozzi et al.), although the current study provides greater resolution at higher doses.

It is important to consider that patients at higher doses, especially those on stable for long periods of time, may be chronic pain patients under the care of a physician. Of course, the possibility exists that some higher dose patients may be diverting opioids or exhibit drug-seeking behavior.

Given that 24% of decedents had no prescription opioid analgesic history in the year preceding death, it is clear that some of the drugs used in overdose deaths are obtained through social sharing outside of sanctioned medical use. This is similar to the 26% and 16% of methadone and other opioids overdose decedents, respectively, not having opioid prescriptions in a Washington state Medicaid study [34]. We found that half of all North Carolina overdose decedents had an active prescription at the time of death, similar to Washington findings of 59% among methadone overdose decedents and 43% among other opioid overdose decedents in the week prior to death [34]. The 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 [58–60].

The study has limitations. First, the statistical 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 shortly after the initiation of therapy. Previous duration of therapy was also not taken into account. 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 but in their infancy [61], as well as changes in formulation of one opioid analgesic [62]. All studies relying on medical examiner or vital statistics data are subject to limitations about ascribing causality for the involvement of drug substances [63,64]. Medical examiner determination of death inherently contains an element of subjective clinical judgment. By excluding deaths were an opioid was simply present, we attempt to mitigate some of the effects of this source of bias. As with the other studies on this topic, the possibility exists that patients obtained opioid analgesics from other states or from outside medical distribution channels. Similarly, the assumption was made that patients on average took the entire dispensed prescription as instructed. Therefore the actual exposure may have differed somewhat from that prescribed.

Another limitation stems from the fact that many high dose IR opioids contain acetaminophen, and overdose deaths may have occurred from hepatic injury [65]. According to North Carolina vital statistics data, there were 18 deaths in 2010 among all residents that were possibly related to acetaminophen toxicity (ICD-10 codes: K71.1, Y45.5, Y10, X40, T39.9, T39.1), with acknowledgment that there may be underreporting of cases and diagnostic suspicion bias which would cause the opioid component of a combination analgesic to be singled out for causal attribution. Only two of these deaths included codes consistent with overdose, but both were deemed to be suicides and were not included in our study. Therefore, the relative contribution of hepatic toxicity appears to be low.

The greatest limitation of this study stems from the 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 may necessitate higher doses. Even though no additional covariate information was available to adjust for the likelihood of receiving treatment, the importance of describing opioid prescribing in a large population-based observational study has the benefit of offering insight into routine medical practice that has broad policy implications.

Deaths involving opioid analgesics result from 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 [58,66]. 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 were thus not controlled for in this study.

Future directions for study will include duration of time on opioid therapy and the specific type and dose of benzodiazepines involved in overdose deaths.

Conclusion

This study is the largest population-based cohort study published to date. It quantifies the dose-response relationship between opioid prescribing and overdose mortality, especially at higher doses than previously examined. 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. 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 dangerous, yet common, situations created by ignoring known drug interactions at the point of care. There is also a need to objectively understand and quantify what benefits patients receive from ER versus IR opioid analgesics.

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