Drug Saf (2018) 41:787–795
https://doi.org/10.1007/s40264-018-0660-4

ORIGINAL RESEARCH ARTICLE

Comparative Rates of Mortality and Serious Adverse Effects Among Commonly Prescribed Opioid Analgesics

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Published online: 26 March 2018

Abstract

Introduction The epidemic of prescription opioid overdose and mortality parallels the dispensing rates of prescription opioids, and the availability of increasingly potent opioid analgesics.

Objective The common assumption that more potent opioid analgesics are associated with higher rates of adverse outcomes has not been adequately substantiated. We compared the rate of serious adverse events among commonly prescribed opioid analgesics of varying potency.

Methods Serious adverse events (SAEs; defined as death, major medical effect, or hospitalization) resulting from exposure to tablets containing seven opioid analgesics (oxycodone, hydrocodone, morphine, hydromorphone, oxymorphone, tapentadol, and tramadol) captured by the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program were evaluated from 2010 through 2016. Rates of SAEs were adjusted for availability through outpatient dispensing data and regressed on morphine milligram equivalents (MME).

Results There were 19,480 cases of SAE during the 7-year study period. Hydrocodone and oxycodone contributed to 77% of SAE cases. Comparing rates of outcome by relative potency, a hierarchy was observed with hydromorphone (8.02 SAEs/100 kg) and tapentadol (0.27 SAE/100 kg) as the highest and lowest rates, reflecting a 30-fold difference among individual opioid products. SAE rate and potency were related linearly—SAEs increased 2.04 per 100 kg drug dispensed for each 1-unit rise in MME ($p = 0.004$). Linear regression of SAE/100 kg drug dispensed and drug potency identified that MME comprised 96% of the variation observed. In contrast, potency did not explain variation seen using other study denominators (prescriptions dispensed, dosage units dispensed, and the number of individuals filling a prescription).

Conclusions and Relevance Potency of a prescription opioid analgesic demonstrates a significant, highly positive linear relationship with exposures resulting in SAEs per 100 kg drug dispensed reported to poison centers. Potency should be carefully considered from both individual provider and public health perspectives.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40264-018-0660-4) contains supplementary material, which is available to authorized users.

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Key Points

The total amount of prescription opioid analgesics dispensed from retail pharmacies has a strong relationship with clinically significant adverse outcomes reported to poison centers.

There is a 30-fold difference in adverse outcomes reported to poison centers among commonly prescribed opioid analgesic tablets, with much of the difference in variation explained by the relative drug potency.

1 Introduction

The current burden of misuse and abuse of prescription opioids in the United States has reached epidemic proportions. Over a 15-year period, the total number of prescriptions for opioids dispensed at US retail pharmacies tripled [1]. The majority of prescriptions emanate from primary care physicians, internists, dentists, and orthopedic surgeons [2]. Increasing opioid availability was mirrored by rising nonmedical use [3] and overdose morbidity and mortality [4], as well as increased social and healthcare costs with an estimated annual total economic burden of US$78.5 billion in the US for 2013 [5].

Numerous factors likely contribute to the current epidemic; however, it has been suggested that drug availability may influence abuse behavior [6]. Not surprisingly, increasing opioid prescription rates correlate with increased diversion and a rise in the magnitude of opioid-related mortality [7]. While hundreds of opioid-containing products of varying formulations are available by prescription, the vast majority (85%) dispensed from US retail pharmacies contain either hydrocodone or oxycodone [2]. Expectedly, the burden of overdose deaths is highest in the category containing these products—the natural and semisynthetic opioids [8]. While parallel increases in availability of opioid analgesics and their associated negative outcomes have been observed [9], drug-specific characteristics and formulation are not completely understood and are of particular interest.

1.1 Goals of This Investigation

While it is commonly presumed that increasing potency among opioid analgesics is linked to higher rates of adverse outcomes, this claim has not been fully substantiated. Potency has been shown to predict ED visits for drug abuse utilizing the Drug Abuse Warning Network (DAWN) database and IMS Health pharmacy dispensation estimates [10]. However, little work has been done to establish comparative rates of clinical morbidity and mortality among opioid analgesics. Poison center (PC) surveillance data can provide insight into this question as they track exposure and outcomes for commonly prescribed opioid formulations. We hypothesized that major outcomes in PC cases occur at different rates among commonly prescribed opioid analgesics, and are a function of drug potency.

2 Methods

2.1 Study Design and Setting

This retrospective observational study reviewed cases of prescription opioid exposures reported to US PCs participating in the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program. The study period was a convenience sample spanning 84 months from January 1, 2010 through December 31, 2016.

2.2 Data Source

2.2.1 Opioid-Related Exposures and Medical Outcomes

The RADARS System is a non-profit prescription drug abuse and misuse surveillance program and a part of the Rocky Mountain Poison and Drug Center, a division of the Denver Health and Hospital Authority. The RADARS Poison Center Program comprises 50 PCs accredited by the American Association of Poison Control Centers. These PCs provide poison management advice for 48 states, which includes over 90% of the US population. Each center receives spontaneous calls from caregivers, patients, and healthcare providers regarding potentially toxic exposures. PC specialists trained in toxicology assist in the care of the individual and document numerous aspects of each case, including medical outcome and the place where individuals with an exposure-related call are managed. In a case with multiple drug exposures, priority (or rank) of each substance is recorded by relative contribution to the patient's clinical condition at the discretion of the PC specialist, with the acknowledgement that drug–drug interactions would be assessed by individual specialists. Participating PC records are uploaded to a central database where case review and quality control are conducted, and exposure mentions are recorded for analysis. Quality control includes a review of exposure reasons, removal of identifying information, and to verify exposure substances [11]; however, the exposure

is self-reported and not systematically confirmed with laboratory testing. The data extraction process has been previously described (supplemental appendix reference).

2.2.2 *Opioid Dispensing*

National outpatient pharmacy dispensing data were obtained from the National Prescription Audit Plus maintained by IMS Health (Danbury, CT, USA now known as IQVIA, Research Triangle Park, NC, USA), a common data source used in health services research for opioid research [12–14]. Data are obtained electronically from outpatient pharmacies for every fill of a prescription medication. Approximately 90% of all retail pharmacies are included in the sample [15] and a proprietary projection methodology is used to extrapolate for the entire US. In this analysis, we used national estimates of kilograms dispensed, prescriptions filled, number of dosage units dispensed, and number of individuals filling prescriptions for opioid analgesics.

2.3 Definitions

Serious adverse event (SAE) was a composite outcome including death, hospitalization, or 'major effect.' The medical outcome of 'major effect' is recorded when the patient had life-threatening symptoms or significant residual disability resulting from the exposure [16].

2.4 Methods and Measurements

All cases regarding exposures to a prescription opioid medication in tablet form and resulting in death, major medical effect, or hospitalization were included for analysis. Schedule II opioid analgesics were included for analysis given their high abuse potential and risk of severe psychological or physical dependence. Tramadol (schedule IV) was included to expand the range of potency for comparison. Fentanyl was excluded due to its primary parenteral route of administration. Codeine was excluded because RADARS did not monitor it during the entirety of the study period.

2.5 Outcomes

The primary outcome of this study was SAEs as a result of exposure to tablets containing seven commonly prescribed opioid analgesics: oxycodone, hydrocodone, morphine, hydromorphone, oxymorphone, tapentadol, and tramadol. No distinction was made between formulation (e.g., extended or immediate release, abuse deterrent formulation, etc.) of each individual opioid in this study, but has been examined previously [17]. Route of administration for exposures was not examined; however, prior work has evaluated effect of relative risk of non-oral routes of opioid administration among the RADARS dataset [18].

2.6 Analysis

Rates of primary outcome were derived using four denominators: 100,000 grams dispensed, 100,000 prescriptions filled, 100,000 dosage units dispensed, and 100,000 individuals filling prescriptions. Linear regression was performed with rate of SAEs regressed on morphine milligram equivalents (MME), with strength of relationship reported as R^2 value. Relative opioid potency was estimated using the CDC conversion chart estimating MME [19]. To evaluate the relative contribution among exposure to multiple products, a sensitivity analysis was performed by restricting analysis to cases of exposure to a single product (one opioid product without any other opioid or non-opioid co-ingestants).

3 Results

3.1 Characteristics of Study Subjects

There were 64,538 cases reported to PCs during the study period where one of the index opioids was mentioned. Of all cases with exposure to one or more index opioids, 19,480 cases (30.1%) met criteria for SAEs. Among cases resulting in SAEs, 52.5% were male, and 78.1% of patients were between the ages of 20–59 years (Table 1).

3.2 Main Results

There were 19,480 cases involving an opioid of interest associated with an SAE during the 84-month study period, of which 148 were associated with death, 2955 with a major medical effect, and 18,713 with a hospitalization (Table 2). Hydrocodone ranked first in each category and was involved in 49% of all opioid-related deaths reported to PCs. Dispensing estimates of each of the seven opioid products are reported in Table 3. Hydrocodone represented the most prescriptions, dosage units dispensed, and number of individuals filling a prescription, while oxycodone had the largest mass of drug dispensed. The rate of death, major medical effect, or hospitalization varied substantially (0.27–8.02 SAEs per 100 kg dispensed) depending on the individual opioid exposure (Table 4).

Comparing rates of outcome by relative potency, a hierarchy was observed with hydromorphone (8.02 SAEs/100 kg of drug dispensed) and tapentadol (0.27 SAE/100 kg of drug dispensed) as the highest and lowest rates, reflecting a 30-fold difference among individual opioid

Table 1 Age and gender distribution of exposures with serious adverse event, January 2010 to December 2016

Age (year)	Male		Female		Unknown		Total	
	N	%	*N*	%	*N*	%	*N*	%
<5	4	0.04	3	0.03	0	0	7	0.04
5–12	30	0.29	17	0.18	0	0	47	0.24
13–19	1269	12.40	661	7.15	0	0	1930	9.91
20–29	2877	28.11	1857	20.10	0	0	4734	24.30
30–39	1969	19.24	1868	20.21	3	60.00	3840	19.71
40–49	1549	15.14	1870	20.24	1	20.00	3420	17.56
50–59	1547	15.12	1674	18.11	0	0	3221	16.53
60–69	685	6.69	854	9.24	0	0	1539	7.90
70–79	179	1.75	282	3.05	0	0	461	2.37
≥80	45	0.44	81	0.88	0	0	126	0.65
Unknown	80	0.78	74	0.80	1	20.00	155	0.80
Total	10,234	100.00	9241	100.00	5	100.00	19,480	100.00

Table 2 Poison center cases of opioid analgesic exposure involving the outcomes of death, major medical effect, or hospitalization, January 2010 to December 2016

	Death	Major medical effect	Hospitalization	Serious adverse event
Hydrocodone	72	951	7736	7872
Oxycodone	57	1154	6801	7121
Tramadol	7	526	3070	3280
Morphine	14	316	1547	1600
Hydromorphone	2	106	638	667
Oxymorphone	9	184	554	613
Tapentadol	0	14	93	97
Total[a]	148	2955	18,713	19,480

[a]Total is not the sum of each row because exposures could involve more than one substance

Table 3 Nationwide US retail pharmacy prescription dispensing data associated with commonly prescribed opioid analgesics, January 2010 to December 2016

Drug name	Grams dispensed	Dosage units dispensed	Prescriptions dispensed	Individuals filling a prescription
Tramadol	952,211,554	18,834,509,219	253,874,705	163,296,621
Oxycodone	409,898,810	29,327,106,594	374,948,749	235,067,690
Hydrocodone	408,114,891	52,067,289,663	795,628,769	520,693,179
Morphine	153,535,539	4,153,778,010	57,855,630	31,358,043
Tapentadol	35,289,898	411,876,991	5,676,783	3,409,587
Oxymorphone	11,117,615	551,588,068	7,822,288	3,947,931
Hydromorphone	8,315,540	1,733,149,581	19,849,615	11,906,016

products. The relation of SAE rate and potency was linear with an increase of 2.04 cases (death, major medical effect, or hospitalization) per 100 kg of drug dispensed for each 1 unit change in MME ($p < 0.001$). Linear regression of SAE/100 kg of drug dispensed and drug potency (Fig. 1a) revealed that 96% of the variation was accounted for due to MME. In contrast, prescriptions dispensed, dosage units dispensed, and the number of individuals filling a prescription identified only 42%, 38%, and 33% of variation, respectively (Fig. 1b–d). Association between potency and individual rates of death, hospitalization, and major medical effect are reported in Table 4 and Fig. 2. There was a stronger association between potency and rate of hospitalization ($R^2 = 0.96$) and major medical effect ($R^2 = 0.83$), compared with death ($R^2 = 0.43$).

Table 4 Rate of death, major medical effect, hospitalization, or SAE (composite outcome) for commonly prescribed opioid analgesics, January 2010 to December 2016

Opioid drug	Morphine milligram equivalents (MME)	Rate of outcome per 100,000 grams dispensed (95% CI)			
		Death	Major medical effect	Hospitalization	Serious adverse event
Hydromorphone	4	0.02 (<0.01–0.09)	1.28 (1.04–1.54)	7.67 (7.09–8.29)	8.02 (7.42–8.65)
Oxymorphone	3	0.08 (0.04–0.15)	1.66 (1.42–1.91)	4.98 (4.58–5.42)	5.51 (5.09–5.97)
Oxycodone	1.5	0.01 (0.01–0.02)	0.28 (0.27–0.30)	1.66 (1.62–1.70)	1.74 (1.70–1.78)
Hydrocodone	1	0.02 (0.01–0.02)	0.23 (0.22–0.25)	1.90 (1.85–1.94)	1.93 (1.89–1.97)
Morphine	1	0.01 (<0.01–0.02)	0.21 (0.18–0.23)	1.01 (0.96–1.06)	1.04 (0.99–1.09)
Tapentadol	0.4	0 (0–0.01)	0.04 (0.02–0.07)	0.26 (0.21–0.32)	0.27 (0.22–0.34)
Tramadol	0.1	<0.01 (0–<0.01)	0.06 (0.05–0.06)	0.32 (0.31–0.33)	0.34 (0.33–0.36)

SAE Serious adverse event—composite outcome resulting in death, hospitalization, or meeting criteria for major medical effect as defined by the American Association of Poison Control Centers coding manual [16]. *MME*—the number of milligrams of a drug needed to cause analgesia equivalent to 1 mg of morphine [19]

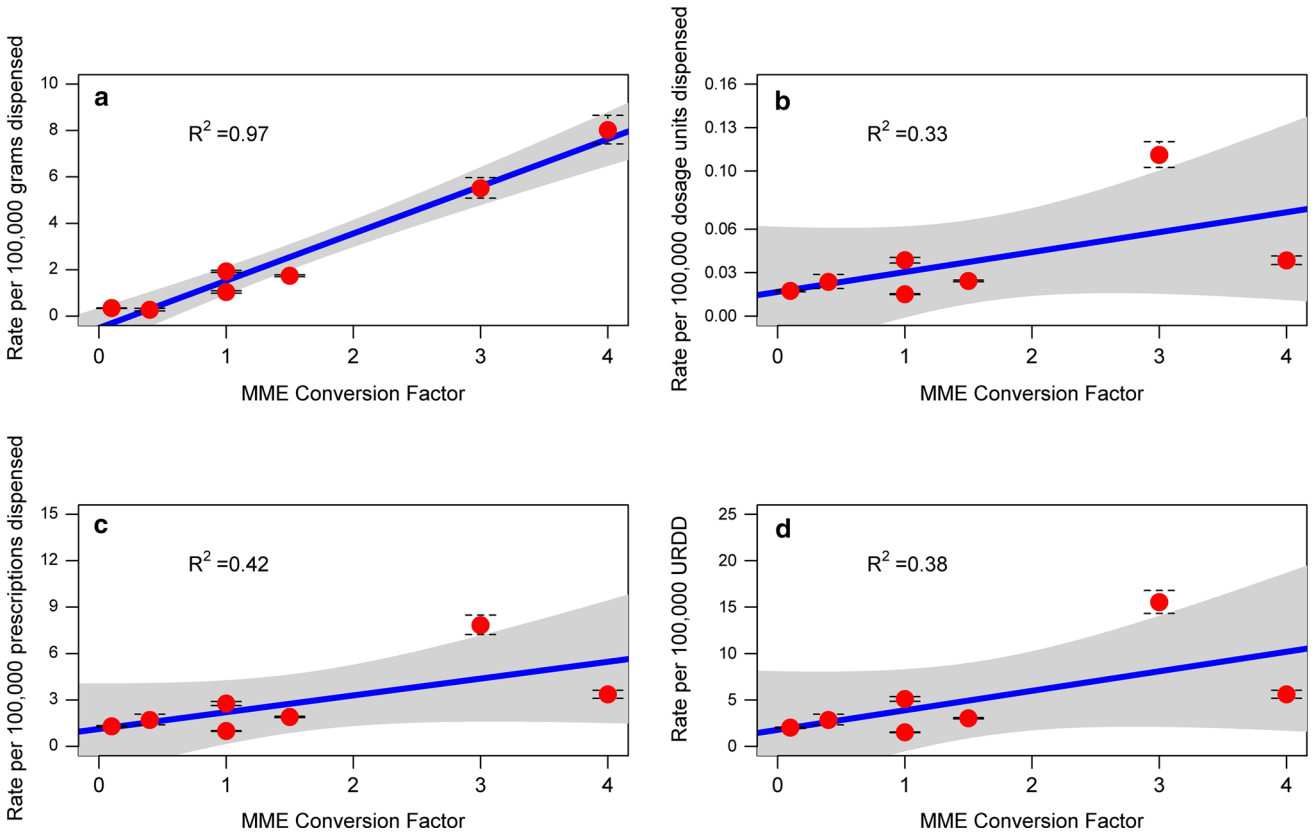

Fig. 1 a–d Correlation of serious adverse event rate and relative opioid potency, January 2010 to December 2016. Grey areas indicate 95% CI range. Serious adverse event—composite outcome resulting in death, hospitalization, or meeting criteria for major medical effect as defined by the American Association of Poison Control Centers coding manual [16]. *MME* morphine milligram equivalents, *URDD* unique recipients of dispensed drug

A sensitivity analysis was performed by restricting analysis to the 7169 cases of single product exposures (accounting for 36.8% of cases resulting in SAE), yielding a similar pattern of SAE rate and potency to drug dispensation but weaker correlation (R^2 values of 0.91, 0.21, 0.25, 0.24 for grams dispensed, dosage units dispensed, prescriptions dispensed, and individuals filling a prescription, respectively).

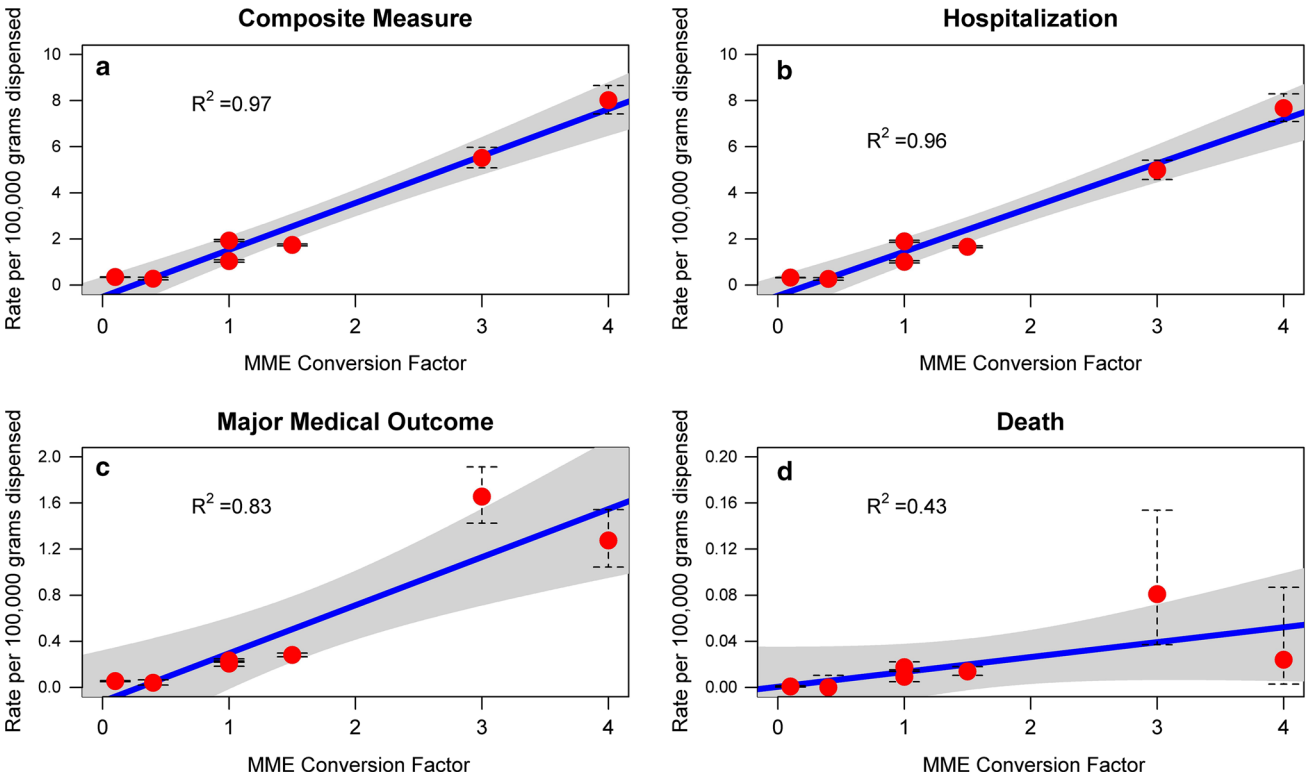

Fig. 2 a–d Correlation of drug dispensation and relative opioid potency by outcome, January 2010 to December 2016. Grey areas indicate 95% CI range. Serious adverse event—composite outcome resulting in death, hospitalization, or meeting criteria for major medical effect as defined by the American Association of Poison Control Centers coding manual [16]. *MME* morphine milligram equivalents

4 Limitations

PCs capture reported incidents associated with opioid use, representing only a small portion of total adverse events from opioid use, and are subject to reporting bias. Estimating the fraction of all cases reported to, and factors that predict PC involvement is challenging. Early work using PC surveillance data sets suggested poor capture of toxicological fatalities [20]; however, subsequent work has demonstrated a strong relationship between deaths associated with PC cases and deaths reported by coroners and medical examiners on death certificates [21]. A recent analysis of methadone poisonings using RADARS suggested that cases were predictive of deaths despite the limited capture among PCs [22].

Another limitation is that the sources of opioids, whether obtained from diversion or from pharmacy dispensation, were unknown. Further, reported exposures were not confirmed cases and there is no quantitative verification of any opioid exposure. It is unknown if patients were hospitalized because of opioid-related exposure or because of additional effects of other possible co-ingestants. While our sensitivity analysis attempted to address this issue, the PC data cannot attribute causality.

This analysis reports a composite outcome of clinically relevant, yet disparate severity. The relatively small sample size of cases resulting in death and major medical effect limit our interpretation. The majority of cases reported to PCs meeting criteria for inclusion in this analysis were hospitalizations. As such, this individual outcome may weight the outcome disproportionately (as evidenced by Fig. 2). Additionally, the route of administration is unknown. Pharmacokinetic properties of individual opioids vary substantially based on route of administration (e.g., enteric, inhalation, or injection) and portend substantially different risk of mortality [23].

Methadone was not included in our analysis due to the potential for misclassification bias. For the exposure, dispensing data from IMS Health do not include methadone dispensed onsite for treatment of opioid dependence in federally regulated addiction treatment clinics, which would have resulted in an undercount in the denominators of rate calculations. Similarly for the outcomes, the accuracy of differentiating between formulations of methadone used in pain versus addiction is unknown in PC data. Previous analysis by our research group has examined rates of methadone calls to PCs in detail [22].

5 Discussion

Among commonly prescribed opioid analgesics, we found wide variability in the number of SAEs involved in PC cases, ranging from hydrocodone (7872) to tapentadol (97). When adjusting SAEs for total drug dispensing in kilograms, the rate of SAEs was highest for hydromorphone (8.02/100 kg) and lowest for tapentadol (0.27/100 kg), representing a 30-fold difference. The descending rank order was hydromorphone, oxymorphone, hydrocodone, oxycodone, morphine, tramadol, and tapentadol. A highly linear correlation was observed when comparing rates of SAEs and opioid analgesic potency with 96% of the variation observed due to MME alone.

Previous investigations have identified specific opioid analgesics implicated in overdose mortality. Hall reported methadone, hydrocodone, and oxycodone as the opioid analgesics contributing to the greatest number of unintentional overdose deaths in West Virginia, USA [24]. Similarly, a North Carolina cohort identified oxycodone, methadone, and hydrocodone as the worst offenders by number of unintentional overdose deaths [25].

Our findings revealed hydrocodone and oxycodone to be associated with the highest number of cases resulting in SAEs (40% and 37%, respectively) among the studied opioid analgesics, presumably due to their relative abundance and availability. Previous estimates suggest that hydrocodone and oxycodone were the most commonly prescribed opioid analgesics among patients discharged from the emergency department [4], and together account for 85% of all opioid prescriptions dispensed from US retail pharmacies [2]. We report a similar rate of dispensing either hydrocodone or oxycodone (79.6%) among schedule II opioid analgesics included in this study. Interestingly, tramadol accounted for the third most SAEs, despite being the least potent opioid analgesic included in this study. A possible explanation may lie in the additional pharmacokinetic effects of tramadol to inhibit serotonin and norepinephrine reuptake activity, leading to unique toxic effects such as adrenergic hyperactivity, seizures, and serotonin depletion syndrome [26, 27].

We found a robust relationship between relative opioid analgesic potency and rate of SAE per the total amount of the drug dispensed from retail pharmacies. The observed positive linear relationship for increasing potency and rate of outcome was found only for the total amount of drug dispensed (R^2 0.92). Interestingly, denominators of prescriptions filled, tablets dispensed, and individuals filling prescriptions nationally did not behave in a linear fashion and showed weak correlation (Fig. 1, R^2 0.29–0.36) between rate of outcome and potency. A similar pattern of variation has been observed with rates of relative abuse-related ED visits among opioid analgesics when adjusting for several measures of drug availability [28]. There are several possible explanations for this observation. Prescriptions filled and tablets dispensed are heavily influenced by drug formulation, where extended-release products contain a large amount of active drug per unit dispensed compared with immediate-release products that contain a much smaller amount of drug. For example, the category of hydrocodone would include primarily immediate-release products in the range of 5–10 mg compared with morphine extended release, which is composed primarily of extended-release products in the range of 15–200 mg. Thus, hydrocodone has a very large number of prescriptions with small pill size and often small number of doses due to its use primarily for acute, short-term pain control. In contrast, extended-release morphine is often prescribed for a month with a larger number of units for treatment of chronic pain. The profile of each opioid in relation to the proportion of prescribing various tablet strengths and quantities creates large variation. We posit that both prescriptions filled and tablets dispensed involve an important intrinsic difference based on drug formulation (immediate versus extended release), whereas total drug dispensed removes this inconsistency.

The observed correlation with total amount of drug dispensed has important public health implications. Prior work has illustrated a dose–response relationship associated with opioid overdose-related morbidity and mortality. Dose escalation due to tolerance further complicates matters, as higher daily MME doses are associated with an increased risk of opioid overdose morbidity [29] and mortality [30]. Similarly, it is documented that a majority of prescription opioids implicated in overdose deaths are obtained via diversion [25, 29]. Thus, as more prescription opioids are dispensed (and therefore diverted and available for nonmedical use), it is plausible that opportunities for larger dosing become more abundant and imply greater hazard. To mitigate this risk, physicians should prescribe the lowest potency opioid, for the shortest duration, and exhaust non-opioid alternatives in order to minimize opioid needs and adequately manage a patient's pain [31].

While the vast majority (89%) of all toxicologic exposures reported to PCs involved a single product, cases resulting in death frequently involve multiple products (58%) [32]. To better isolate the opioid effect alone, we performed additional sensitivity analyses restricting analysis to cases of single opioid product exposure; the results were similarly robust for grams dispensed (R^2 = 0.91) and poor for other denominators (R^2 = 0.21–0.25), and thus did not alter findings or interpretation.

Epidemiologic data have shown a relationship between prescription opioid sales and opioid-related morbidity and mortality [33]. Paulozzi and Ryan described a linear relationship between total opioid analgesic sales (grams per

100,000 population) and drug poisoning mortality rates (per 100,000 population) among US states [34]. These authors evaluated population-adjusted dispensing and mortality rates and found substantial variability by specific prescription opioid. However, the variation in mortality as explained by each individual drug was limited and other contributing factors, such as potency, were not examined. Dasgupta et al. reported that morbidity associated with non-medical use of opioids is predictable based on potency and prescriptive use [10]. Their model identified higher rates of emergency department 'mentions' associated with opioid abuse sequelae when more potent opioid analgesics were involved. Our findings show a congruent relationship with potency, demonstrating higher rates of important clinical outcomes among more potent opioid analgesics. Our data further solidify the predictability of opioid-associated morbidity and mortality in relation to drug potency.

The application of epidemiologic data suggesting that more potent opioid analgesics impart a disproportionate risk of an SAE has clinical importance. A recent 2015 CDC report described marked increases in the strength of opioid analgesics prescribed between 2002 and 2012 [9]. Our study suggests that increasing potency (per one unit MME) correlates with an increase of 1.7 in the rate of SAEs involving a PC, and therefore a smaller number needed to harm (NNH; number of grams dispensed to cause one death, major medical effect, or hospitalization). The conclusions we can draw upon any derived NNHs would be very limited, as individual providers do not prescribe opioids by the kilogram, and PCs capture but a small portion of adverse outcomes related to opioid use, misuse, and abuse. However, mounting evidence that user profiles, total drug dispensation, and potency correlate with clinically significant outcomes suggests that judicious prescribing of opioid analgesics according to clinical guidelines and policies should remain a priority of public health stewardship.

Our results also suggest that adjustments currently used in postmarketing surveillance may not be optimal. The two most common adjustments currently used in analyses used in FDA analgesic advisory committees are prescriptions dispensed and number of dosage units dispensed. However, these measures had poor correlation with the outcomes reported by PCs in our study. In contrast, the total amount of opioid dispensed correlated well. Further work is needed to assess the appropriate adjustments to use in the analysis of postmarketing surveillance data.

6 Conclusions

Several questions remain, particularly regarding various formulations of individual opioid analgesics. Future research may be required as new analgesics come to market that have agonism beyond the μ-opioid receptor pathway. Further, many other drugs like benzodiazepines or gabapentin complicate our understanding of prescription opioid abuse. Future direction for research could elucidate the roles of benzodiazepine co-ingestion, combination drug products, route of administration, and dose–response associated with important clinical outcomes.

In summary, potency of a prescription opioid analgesic demonstrates a significant, highly positive linear relationship with SAEs per 100 kg dispensed that are reported to PCs. Our work suggests that opioid potency should be carefully considered from both individual provider and public health perspectives and supports tighter regulation of more potent opioid drugs.

Author Contributions Conceived and designed the experiments: DM JL GS RD. Performed experiments: GS. Analyzed the data: DM JL GS HO ND RD. Drafted the manuscript: DM JL GS ND RD.

Compliance with Ethical Standards

Ethics approval The Poison Center Program study protocol received its most recent review and approval from the Colorado Multiple Institutional Review Board (COMIRB) on 21 December 2016. In addition, the study protocol was reviewed and approved by the IRB of each participating poison center.

Funding There were no sources of financial assistance that were used to conduct this study or used to assist with the preparation of the manuscript.

Conflict of interest David Murphy, Jacob Lebin, Stevan Severtson, Nabarun Dasgupta, Heather Olsen, and Richard Dart have no conflicts of interest that are directly relevant to the content of this study. It should be noted that most manufacturers of prescription opioid analgesics or stimulants have subscription contracts to receive data from RADARS System. RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado (public hospital for Denver, Colorado). The subscribers receive data, they do not participate in developing the System, participate in data collection or the analysis of the data, nor do they have access to the raw data. No employee of Denver Health has a financial relationship nor receives any payment from any pharmaceutical company.

References

1. Nora D. Prescription Opioid and Heroin Abuse. Presentation included IMS Health, Vector One source data of National Prescription Audit, years 1997-2013, delivered at 2014 Testimony to U.S. Congress, House Committee on Energy and Commerce Subcommittee on Oversight and Investigations. Available at https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/prescription-opioid-heroin-abuse.
2. Volkow N. Characteristics of Opioid Prescriptions in 2009. JAMA. 2011;305(13):1299.
3. U.S. Department of Health and Human Services. Results from the 2013 National Survey on Drug Use and Health: Summary of

National Findings. Rockville: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality; 2014. Available at https://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.pdf.
4. Center for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, Mortality File. Number and Age-Adjusted Rates of Drug-poisoning Deaths Involving Opioid Analgesics and Heroin: United States, 2000–2014. Atlanta: Center for Disease Control and Prevention; 2015. Available at https://www.cdc.gov/nchs/data/health_policy/AADR_drug_poisoning_involving_OA_Heroin_US_2000-2014.pdf.
5. Florence C, Zhou C, Luo F, Xu L. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. Med Care. 2016;54(10):901–6.
6. Wightman R, Perrone J, Portelli I, Nelson L. Likeability and Abuse Liability of Commonly Prescribed Opioids. J Med Toxicol. 2012;8(4):335–40.
7. Paulozzi L, Kilbourne E, Desai H. Prescription drug monitoring programs and death rates from drug overdose. Pain Med. 2011;12(5):747–54.
8. Rudd R, Aleshire N, Zibbell J, Gladden R. Increases in drug and opioid overdose deaths—United States, 2000–2014. MMWR Morb Mortal Wkly Rep. 2016;64(50–51):1378–82.
9. Frenk S, Porter K, Paulozzi L. Prescription opioid analgesic use among adults: United States, 1999–2012. NCHS Data Brief. 2015;189:1–8.
10. Dasgupta N, Kramer E, Zalman M, Carino S Jr, Smith M, Haddox J, et al. Association between non-medical and prescriptive usage of opioids. Drug Alcohol Depend. 2006;82(2):135–42.
11. Smith M, Dart R, Hughes A, Geller A, Senay E, Woody G, et al. Clinician validation of poison control center (PCC) intentional exposure cases involving prescription opioids. Am J Drug Alcohol Abuse. 2006;32(3):465–78.
12. Compton W, Volkow N. Major increases in opioid analgesic abuse in the United States: concerns and strategies. Drug Alcohol Depend. 2006;81(2):103–7.
13. Jones C, Lurie P, Throckmorton D. Effect of US drug enforcement administration's rescheduling of hydrocodone combination analgesic products on opioid analgesic prescribing. JAMA Intern Med. 2016;176(3):399.
14. Budnitz D, Lovegrove M, Sapiano M, Mathew J, Kegler S, Geller A, et al. Notes from the field: pediatric emergency department visits for buprenorphine/naloxone ingestion—United States, 2008–2015. MMWR Morb Mortal Wkly Rep. 2016;65(41):1148–9.
15. Ritchey M, Tsipas S, Loustalot F, Wozniak G. Use of pharmacy sales data to assess changes in prescription- and payment-related factors that promote adherence to medications commonly used to treat hypertension, 2009 and 2014. PLoS One. 2016;11(7):e0159366.
16. Gummin D, Mowry J, Spyker D, Brooks D, Fraser M, Banner W. 2016 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report. Clin Toxicol. 2017;55(10):1072–254.
17. Iwanicki J, Severtson S, McDaniel H, Rosenblum A, Fong C, Cicero T, et al. Abuse and diversion of immediate release opioid analgesics as compared to extended release formulations in the United States. PLoS One. 2016;11(12):e0167499.
18. Green J, Bucher Bartelson B, Le Lait M, Roland C, Masters E, Mardekian J et al. Medical outcomes associated with prescription opioid abuse via oral and non-oral routes of administration. Drug Alcohol Depend. 2017;175:140–5.
19. Von Korff M, Saunders K, Thomas Ray G, Boudreau D, Campbell C, Merrill J, et al. De facto long-term opioid therapy for noncancer pain. Clin J Pain. 2008;24(6):521–7.
20. Hoppe-Roberts J, Lloyd L, Chyka P. Poisoning mortality in the United States: comparison of national mortality statistics and poison control center reports. Ann Emerg Med. 2000;35(5):440–8.
21. Dart R, Surratt H, Cicero T, Parrino M, Severtson S, Bucher-Bartelson B, et al. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med. 2015;372(3):241–8.
22. Dasgupta N, Davis J, Jonsson Funk M, Dart R. Using poison center exposure calls to predict methadone poisoning deaths. PLoS One. 2012;7(7):e41181.
23. Katz N, Dart R, Bailey E, Trudeau J, Osgood E, Paillard F. Tampering with prescription opioids: nature and extent of the problem, health consequences, and solutions. Am J Drug Alcohol Abuse. 2011;37(4):205–17.
24. Hall A. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA. 2008;300(22):2613.
25. Hirsch A, Proescholdbell S, Bronson W, Dasgupta N. Prescription histories and dose strengths associated with overdose deaths. Pain Med. 2014;15(7):1187–95.
26. Ryan N, Isbister G. Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. Clin Toxicol. 2015;53(6):545–50.
27. Moulis F, Rousseau V, Abadie D, Masmoudi K, Micallef J, Vigier C, et al. Serious adverse drug reactions with tramadol reported to the French pharmacovigilance database between 2011 and 2015. Thérapie. 2017;72(6):615–24.
28. Secora A, Trinidad J, Zhang R, Gill R, Dal Pan G. Drug availability adjustments in population-based studies of prescription opioid abuse. Pharmacoepidemiol Drug Saf. 2016;26(2):180–91.
29. Dunn K. Opioid prescriptions for chronic pain and overdose. Ann Intern Med. 2010;152(2):85.
30. Gomes T, Mamdani M, Dhalla I, Paterson J, Juurlink D. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med. 2011;171(7):686–91.
31. Dowell D, Haegerich T, Chou R. CDC guideline for prescribing opioids for chronic Pain—United States, 2016. MMWR Recomm Rep. 2016;65(1):1–49.
32. Mowry J, Spyker D, Cantilena L, Bailey J, Ford M. 2012 Annual report of the american association of poison control centers' national poison data system (NPDS): 30th annual report. Clin Toxicol. 2013;51(10):949–1229.
33. Fischer B, Jones W, Urbanoski K, Skinner R, Rehm J. Correlations between prescription opioid analgesic dispensing levels and related mortality and morbidity in Ontario, Canada, 2005–2011. Drug Alcohol Rev. 2013;33(1):19–26.
34. Paulozzi L, Ryan G. Opioid analgesics and rates of fatal drug poisoning in the United States. Am J Prev Med. 2006;31(6):506–11.