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Research Article

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Fatal Toxicity Index, Total Prescriptions per Death, a Unique View of Medical Examiner Deaths and Prescription Monitoring Data

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Abstract

Introduction: *This study is the first of its kind in the United States to report a fatal toxicity index (FTI) of prescription drugs commonly implicated in deaths to quantify the dangers of prescription drugs. Death rates for the top fourteen schedule II-IV drugs implicated in overdoses were examined as deaths per million pills dispensed to a large county population over a one-year period to derive a fatal toxicity index (FTI), which is an indicator of the level of toxicity in accidental prescription-related overdose deaths. Medical Examiner data used to understand the prescription drugs, co-prescribing of multiple prescriptions, illicit drugs and alcohol in deaths.*

Methods: *This retrospective, descriptive analysis examined all accidental prescription-related deaths (n=247) as determined by the San Diego Medical Examiner (ME) investigation during 2015. Data were analysed by age, sex, individual prescription drugs and combinations of prescription drugs. Prescribing data were obtained from the CURES reporting system, California's prescription drug monitoring system. The CURES data in combination with ME data were used to derive an FTI for each of the selected drugs.*

Results: *Approximately 57% (n=140) of the 247 prescription-related deaths in 2015 were among men with an average age of 48(SD=14.4). Of all single prescription deaths, the majority involved opioids (n=31; 67.4%). Over two-thirds of all deaths involved two or more substances with the most common contributory drugs being oxycodone (n=57, 23%), alprazolam (n=39, 15.8%), and morphine (n=36, 14.6%). Hydrocodone provided the largest quantity of prescribed pills (55,378,292) but accounted for only 12 percent of all accidental prescription deaths (n=30). Of all drugs examined hydrocodone had the lowest FTI (0.54 deaths per million pills dispensed). Drugs with the highest FTI included chlordiazepoxide (40.03), fentanyl (35.75) and methadone (9.1).*

Conclusions: *Focus on the prescription drug epidemic has been on opioids however, data suggest that drugs from various classes are represented in deaths. A multi-drug approach and study of top prescription related deaths should be considered when working to promoting safe prescribing and to reduce accidental overdoses.*

Keywords: Prescription, Medications, Deaths, Fatal Toxicity Index, Medical Examiner

Introduction

This study is the first to report a fatal toxicity index (FTI) of prescription drugs commonly implicated in accidental overdose deaths, demonstrating a unique approach in the evaluation of prescription safety by comparing prescription drug monitoring data of number of pills dispensed to number of medical examiner cases of accidental overdose. Drug overdose is the leading cause of accidental death in the United States with over 63,600 deaths in 2016, a 21.4% increase from 2015 [1,2]. The epidemic has been largely fuelled by opioids, both prescription and illicit. Opioids were involved in over 66% of drug related deaths nationally in 2016 with over 40% attributed to prescription opioids. The increase in the rate of deaths due to prescription opioids has slowed but the number of deaths continue to rise annually. Deaths involving prescription opioids increased by 10% between 2015 to 2016 [3]. The slowing rate has been attributed to increased awareness of risks associated with opioids, formulation of abuse-deterrent prescription opioids and state level efforts to reduce inappropriate opioid prescribing [4,5].

In response to the epidemic, preventative measures have been taken to address the growing epidemic of prescription drug related deaths. Preventative measures have largely focused on changing prescriber practices. The development of Prescription Drug Monitoring Programs (PDMP) has allowed physicians to address patient care with consideration of prescriptions from other providers. In California, the Controlled Substance Utilization Review and Evaluation System (CURES 2.0) is the designated PDMP that currently

receives about 1 million prescription entries per week and monitors about 128,000 prescribers and 151,000 dispensing pharmacies [6]. At the time of this study, prescribers of controlled drugs were not mandated to register with CURES and did not regularly check the database prior to writing a prescription for a controlled drug, unless suspicion was high [7,8]. Physician registration drastically increased following the passing of Senate Bill 209 requiring all physicians to be registered with the system by July 2016.

In San Diego County, which has an estimated population of 3.3 million people, drug overdose is the leading cause of accidental death with 510 drug related deaths in 2015, of which 247 (48%) involved prescription drugs [9,10]. A previous study examining accidental prescription-related overdose deaths in San Diego County reported 254 deaths in 2013, showing slightly fewer deaths compared to the current 2015 data but illustrates the ongoing problem [11]. Of the 254 deaths, 80% of prescription-related overdose deaths involved a combination of multiple prescription drugs [11].

To understand the prescription drug epidemic, it is important to identify what drugs are most frequently implicated in overdose deaths as well as to understand the role of combination drug use [11]. It is estimated that combination drug use explains between 40% - 60% of increases in drug deaths over recent years, yet there is little literature reporting on combination drug use due to a lack of reliable information on drugs involved in overdose deaths [12]. In addition to frequency of fatal poisonings caused by specific pharmaceuticals, consumption figures of drugs are useful in assessing their relevance in overdose deaths. A useful measure of relative drug toxicity is the fatal toxicity index (FTI), which is calculated by relating the number of deaths associated with a specific drug to the drugs estimated consumption figure over the same area and time [13,14]. Previous studies reporting FTIs have been published for various pharmaceutical drug classes such as antidepressants, benzodiazepines, street drugs and methadone, with little literature documenting FTIs for multiple drug classes involved in fatal overdoses [14-19].

The overall objective of this study was to provide information on the relative toxicity of pharmaceutical drugs commonly identified in overdose deaths, which may be used by physicians to inform prescribing decisions, as well as, to inform safe prescribing practices and policies. Additionally, to better understand differences in relative toxicity between drugs, medical examiner data was used to assess the contributions of combinations of prescription drugs, illicit drug use and alcohol in accidental prescription-related deaths. There were no identified studies in the United States reporting FTIs of pharmaceutical drugs involved in overdose deaths at the time of the current study, making it difficult to draw comparisons.

Methods

This is a retrospective, descriptive analysis comparing all accidental prescription-related deaths from January 1, 2015, to December 31, 2015, as determined by a San Diego Medical Examiner (ME) investigation, with the total number of prescriptions and pills dispensed in the county in 2015. Prescription data were obtained from the California PDMP, CURES (Controlled Substance Utilization Review and Evaluation System) database. A database was created that included all deaths in San Diego County from the period of January 1, 2015, until December 31, 2015, with the cause of death attributed to accidental prescription drug intoxication. The database included deaths involving prescription drugs that were mixed with over-the-counter (OTC) drugs, alcohol, or illicit drugs. Deaths deemed to be suicides were excluded from the database.

Medical Examiner Data

The San Diego County ME's office follows Government Code Section 27941, which states that an investigation is to be conducted for all unnatural deaths including homicides, suicides, accidents, deaths in custody, and certain infectious diseases [20]. Additionally, all deaths clearly related to trauma and deaths known or thought to be due to alcohol or drug intoxication must be reported to the ME office [20]. All accidental deaths deemed primarily caused by prescription drugs, as determined by the San Diego ME, were evaluated. The toxicology reports for these deaths were reviewed. The top fourteen Schedule II-IV prescription drugs identified in deaths were selected for analysis. These drugs were oxycodone, alprazolam, hydrocodone, methadone, fentanyl, clonazepam, tramadol, morphine, temazepam, chlordiazepoxide, carisoprodol, diazepam, zolpidem, and oxymorphone.

Toxicological Testing

Specimen Collection

All specimens analysed toxicologically were collected at autopsy at the San Diego County Medical Examiner's Department. Peripheral blood (utilized for drug confirmation and quantitation) was drawn from the common iliac veins (blood returning from the leg and visually identified in the pelvis at autopsy) and stored in standard glass tubes containing sodium fluoride (100 mg) and potassium oxalate (20 mg). Central blood (utilized for drug of abuse screening) collected into identical glass tubes. Specimens were stored at 4ºC until analysed. All toxicological analyses were generally completed within six weeks of specimen collection.

Toxicological Screening

At a minimum, toxicological screening regimen included screening for simple volatile compounds, and drugs of abuse. Peripheral blood was screened for alcohol and volatile compounds with headspace gas chromatography-flame ionization detection (GC-FID) [21]. Central blood was screened for a 13 drugs of abuse panel by enzyme linked immunosorbent assay (ELISA: cocaine metabolite, opiates, methamphetamine, amphetamine, benzodiazepines, cannabinoids, fentanyl, synthetic cannabinoids, oxycodone, methadone, zolpidem, carisoprodol, and buprenorphine) (Immunalysis Inc., CA). Additionally, if requested by the forensic pathologist in cases expected of drug abuse or toxicity, an alkaline drug screen by gas chromatography-mass spectrometry (GC-MS) following solid phase extraction was performed for common therapeutic medications [22].

Confirmation and Quantitation

When detected by the above screening procedures, all drugs were confirmed and quantified in peripheral blood by previously described analytical procedures. Opioids were confirmed by gas chromatography-mass spectrometry (GC-MS), fentanyl by GC-MS, carisoprodol / meprobamate by GC-MS, benzodiazepines and zolpidem by high performance liquid chromatography with photodiode array detection (HPLC-DAD), and methadone and tramadol by a specific gas chromatography-nitrogen phosphorus detection (GC-NPD) procedure [23-27].

Prescription Data

Prescription data were obtained from CURES, California's PDMP. The drugs entered into the California PDMP database include all Schedule II-IV medications. Data are obtained from pharmacy information and uploaded into the state system. All major pharmacies have the software necessary to comply with the regulation (SB 809) that requires data be uploaded within a week of dispensing the prescription [7]. Prescriptions obtained from inpatient hospital pharmacies, the Veterans Administration, military hospitals, methadone clinics, and out-of-state pharmacies are not included in the CURES system. A PDMP inquiry was run to obtain the number of prescriptions and pills dispensed in San Diego County during 2015 for the top fourteen Schedule II-IV prescription medications identified in deaths.

Data Analysis

Descriptive Statistics

Demographic information obtained from ME reports to calculate distributions of age, gender, and race of the study population. Drug frequencies calculated using ME data to identify the top prescription drugs most commonly identified in overdose deaths. Contribution of illicit drugs, alcohol, and additional prescription drugs in overdose deaths calculated using information from ME reports and reported for the top 14 Schedule II-IV prescription drugs identified.

Fatal Toxicity Index

An FTI calculated for each of the fourteen schedule II-IV drugs selected for analysis, expressed as deaths per million pills dispensed. Previous studies have measured drug consumption by prescriptions dispensed, defined daily doses (DDD), or kilograms [14]. Given the variations in numbers of pills dispensed for each prescription written, drug consumption measured by the number pills dispensed for each of the schedule II-IV prescription drugs during the 2015 calendar year. FTIs were calculated by dividing the number of deaths attributed to each drug (numerator) by the total number of pills dispensed in San Diego County during 2015 (denominator) to be expressed as deaths per million pills dispensed. The reported FTIs are reflective of deaths involving multiple substances. FTIs calculated for single-drug deaths have the advantage of being able to ascertain which drug was responsible for death but given that the majority of overdose deaths involve a combination of substances, single-drug FTIs may underestimate the relative toxicity of specific drugs [17]. The morphine equivalents or prescription strength were not considered in this calculation as seven of the 14 drugs were non-opioids. Ninety-five percent confidence intervals (CI) calculated based on an exact Poisson distribution. The data analysis for this paper was generated using SAS software. The San Diego State University IRB review board as exempt approved the research.

Results

Demographics

The San Diego County ME Office reported 247 accidental prescription-related deaths in 2015. The total cohort of 247 included 57% males, with an average age of 48.3(SD=14.4) and age range of 18 to 83 years in Table 1.

Table 1: Demographic Characteristics of Decedents of Accidental Prescription Related Deaths in San Diego County, California 2015

Characteristic		Total Deaths	Percent
Gender			
	Male	140	56.7
	Female	107	43.3
Age Range			
	15-24	19	7.7
	25-34	31	12.5
	35-44	32	12.9
	45-54	58	23.7
	55-64	86	34.8
	65+	21	8.4
Race/Ethnicity Group			
	Non-Hispanic White	184	74.5
	Hispanic	33	13.5

	Black	18	7.3
	Asian	6	2.4
	Native American	3	1.2
	Other	3	1.2

Number of Deaths by Drug Implicated in Overdose

Of all substances involved in overdose deaths, oxycodone was involved in 23.1% (n=57) of deaths followed by alprazolam (15.8%, n=39), diazepam (15%, n=37), morphine (13.1%, n=36), hydrocodone (12.1%, n=30) and methadone (12.1%, n=30) in Figure 1.

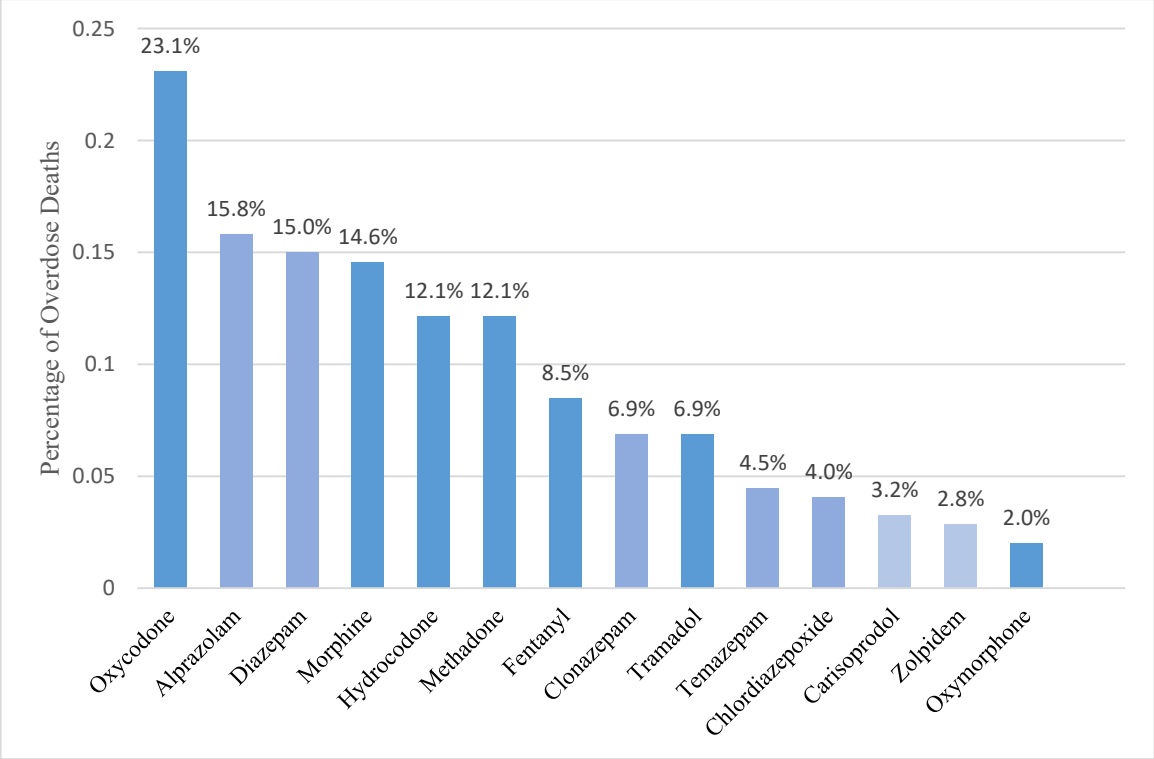

Figure 1: Top 14 Substances Identified in Unintentional Overdose Deaths, San Diego County, 2015

Prescription Data

With 848,814 prescriptions dispensed in 2015, hydrocodone was the most frequently prescribed schedule II-IV drug in San Diego County followed by oxycodone with 431,345 prescriptions dispensed in 2015. Table 2 Oxycodone prescriptions were about half of those dispensed for hydrocodone, yet oxycodone was identified in almost double the number of deaths. Following oxycodone, the next highest prescriptions were for alprazolam (317,643), tramadol (281,912), zolpidem (277,017), clonazepam (163,982), and morphine (113,185) were the most frequently prescribed scheduled II-IV drugs in San Diego County during 2015.

Table 2: Drug Prescribing in San Diego County for top 14 Schedule II-IV Controlled Substances Implicated in Accidental Prescription Related Overdoses, 2015

Opioid Analgesics		
	Number of Rx.	**Number of Pills**
Hydrocodone	848,814	55,378,292
Oxycodone	431,345	33,946,098
Tramadol	281,012	20,470,048
Morphine	113,185	7,528,880
Fentanyl	35,136	587,400
Methadone	27,500	3,298,801
Oxymorphone	7,763	569,428
Benzodiazepines		
Alprazolam	317,643	16,477,129
Clonazepam	163,982	9,554,256
Diazepam	112,522	4,914,026
Temazepam	75,647	2,862,833
Chlordiazepoxide	7,554	249,798
Sedative/Muscle Relaxants		
Zolpidem	277,017	9,043,168
Carisoprodol	66,318	4,645,231

Fatal Toxicity Index

Deaths per million pills dispensed were highest for chlordiazepoxide (40.03 per million pills dispensed), fentanyl (35.75 per million pills dispensed), methadone (9.10 per million pills dispensed), oxymorphone (8.78 per million pills dispensed) and diazepam (7.53 per million pills dispensed). Results of FTI calculations are presented with the drugs separated by drug classes in descending order of FTI in Table 3 & Figure 2.

Table 3: Fatal Toxicity Index for Top Drugs Involved in Accidental Prescription-Related Overdoses, San Diego County 2015

Opioid Analgesics				
	Total number of pills dispensed	**Total number of deaths**	**Deaths per million pills dispensed**	**95% confidence interval**
Fentanyl	587,400	21	35.75	22.1, 54.60
Methadone	3,298,801	30	9.10	6.1, 13.0
Oxymorphone	569,428	5	8.78	2.85, 20.5
Morphine	7,528,880	36	4.78	3.35, 6.62
Oxycodone	33,946,098	57	1.68	1.27, 2.18
Tramadol	20,470,048	17	0.83	0.48, 1.33
Hydrocodone	55,378,292	30	0.54	0.37, 0.77
Benzodiazepines				
Chlordiazepoxide	249,798	10	40.03	19.2, 73.6
Diazepam	4,914,026	37	7.53	5.30, 10.40
Temazepam	2,862,833	11	5.59	3.19, 9.08
Alprazolam				
16,477,129	39	2.37	1.68, 3.42	
Clonazepam	9,554,256	17	1.78	1.04, 2.85
Sedative/Muscle Relaxants				
Carisoprodol	4,645,231	8	2.15	1.03, 3.96
Zolpidem	9,043,168	7	0.74	0.31, 1.59

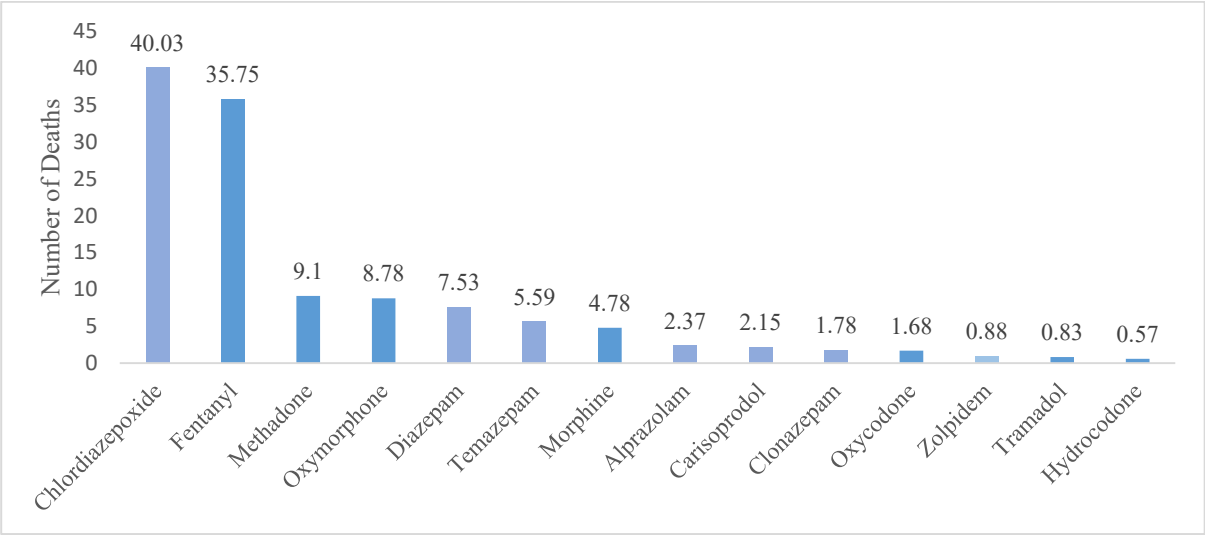

Figure 2: Fatal Toxicity Index for Top Drugs Involved in Unintentional Overdoses, San Diego County 2015

Combinations of Drugs Involved in Accidental Prescription Related Overdose Deaths

Accidental prescription-related deaths that involved combinations with illicit drugs, alcohol, and OTC drugs shown in Table 4. Of the 247 deaths, 211 (85.4%) were found to have multiple drugs on autopsy, whereas 36 (14.6%) had only a single drug on autopsy. Among the multi-drug deaths, the average number of concomitant substances was 3.0 with a range of 1 to 10 drugs.

Deaths involving combinations with illicit drugs, drug class further stratified alcohol, and OTC prescriptions for each of the 14 prescription drugs included in the study in Table 5. Opioid analgesics were the most predominant class of drugs, contributing to 178 deaths (72.1%). Benzodiazepines were involved in 116 deaths (47%). Opioid and benzodiazepine combinations were identified in 75 deaths (30.4%). Opioids were present in 64.7% of all benzodiazepine deaths. Benzodiazepines were identified in 42.1% of all opioid deaths. Decedents who overdosed on benzodiazepines had a higher co-occurrence of additional prescription drugs (97.3%), illicit drugs (37.1%), and alcohol (20.7%) than decedents who used opioid analgesics (83.8%, 22.5%, 17%) respectively.

Among the 36 single-drug deaths, opioids accounted for 63.4%, of which fentanyl accounted for 22.2% followed by morphine (14%), methadone (8.3%), and hydrocodone (5.3%). Antidepressants accounted for 19.4% of cases of single drug toxicity, of which paroxetine accounted for 5.6% followed by citalopram (2.8%), bupropion (2.8%), amitriptyline (2.8%), and sertraline (2.8%). The remaining deaths due to single drug toxicity were attributed amphetamines (5.6%), benzodiazepines (5.6%), and antipsychotics (2.8%).

Table 4: Accidental Prescription Drug Deaths and Combinations of Other Substances, San Diego County 2015

Substance	Number of Deaths (%) (n=247)
Prescription alone	130 (52.64)
Prescription + Illicit	60 (24.29)
Prescription + Alcohol	35 (14.17)
Prescription + Illicit + Alcohol	13 (5.26)
Prescription + OTC*	5 (2.02)
Prescription + Other	2 (0.81)
Prescription + Illicit + OTC*	2 (0.81)
*OTC=over the counter drugs	

Table 5: Contribution of additional prescription drugs, illicit drugs, and alcohol in accidental overdose deaths San Diego County, 2015

		Percent Contribution		
Contributory Prescription Drug	**Deaths Total (%)**	**Other Prescription Drugs**	**Illicit Drugsa**	**Alcohol**
Opioid Analgesics	178 (72.1)	83.8	22.5	17.0
Oxycodone	57 (23.1)	84.2	21.0	12.2
Morphine	36 (14.6)	75.0	8.3	25.0
Methadone	30 (12.1)	70.0	30.0	6.7
Fentanyl	21 (8.5)	62.0	29.6	4.7
Hydrocodone	30 (12.1)	90.0	16.7	23.3
Oxymorphone	5 (2.0)	100.0	-	-
Tramadol	17 (6.9)	88.2	29.4	5.9
Other opioid analgesics[b]	33 (13.3)	93.9	21.2	15.2
Benzodiazepines	116 (47.0)	97.3	37.1	20.7
Diazepam	37 (14.9)	100.0	48.6	10.8
Alprazolam	39 (15.8)	100.0	41.0	15.4
Chlordiazepoxide	10 (4.0)	100.0	50.0	60.0
Clonazepam	17 (6.9)	100.0	47.1	11.8
Temazepam	11(4.5)	100.0	18.2	-
Other benzodiazepines[c]	33 (13.4)	94.0	36.4	36.4
Sedative/Muscle Relaxants	22 (8.9)	100.0	13.7	9.1
Zolpidem	7 (2.8)	100.0	-	28.6
Carisoprodol	8 (3.2)	100.0	25.0	12.5
Other sedative/				
muscle relaxant	13 (5.3)	100.0	15.4	20.0
Antidepressants	57 (23.1)	87.8	10.5	14.0

a. Illicit drugs include: heroin, cocaine, methamphetamine, MDMA, mirtagynine, cannabinoid, phencyclidine
b. Other Opioids include: codeine, dihydrocodeine, hydromorphone, oxymorphone, opiate
c. Other Benzodiazepines includes: lorazepam, oxazepam, benzodiazepine
d. Other sedative/muscle relaxant includes: zopliclone, meprobamate, methocarbamol, cyclobenzaprine
*Percentages do not add up to 100 because multiple drugs contributed too many of the deaths.

Discussion

This retrospective, observational study examined accidental prescription related deaths in San Diego County during the 2015 calendar year using information available on the medical examiner's report and prescribing information in the California PDMP database, CURES. This study is the first to report a FTI of prescription medications commonly implicated in accidental overdose deaths, offering a unique approach to evaluating the safety of prescription medications. In addition to reporting the absolute number of deaths involving particular drugs, utilizing the FTI quantified risks associated with prescribing particular drugs based on the number of pills dispensed for each of the 14 Schedule II-IV prescription drugs analysed in the study. Drug combinations were evaluated for each of the prescription drugs included in analysis to better understand results of the FTI.

Opioids and benzodiazepines were the most prevalent drug classes identified in the prescription-related overdose deaths. While opioids have been identified as a main driver of the current epidemic, benzodiazepine related overdose deaths increased 5-fold between 2001-2014, with co-prescribing of opioids implicated in 49-54% of deaths [11,28-30]. Many benzodiazepines are prescribed for anxiety and insomnia although they are not first line agents in treatment. In this study, opioid and benzodiazepine combinations were identified in 30.4% of all deaths. Apart from the increased risk of accidental overdose death in patients receiving both opioids and benzodiazepines, these patients also have worse health outcomes, increased utilization of healthcare resources and higher rates of mental health co-morbidity [29,31].

A few potential confounding factors should be mentioned prior to interpreting results of the FTIs. It is important to consider the

possibility that prescription drugs with higher FTIs are prescribed to populations at a higher inherent risk for accidental overdoses, resulting in an overestimation of toxicity. Patient characteristics such as age, gender and co-occurring medical conditions and drugs prescribed to at-risk groups, specifically, drugs prescribed in the treatment of substance use disorders (e.g. chlordiazepoxide) all potentially influence the resulting FTI [13]. Patients receiving treatment for substance use disorders are at a disproportionately higher risk for accidental overdoses, potentially increasing the FTI of these drugs [13]. With consideration to the population most commonly prescribed certain drugs, an elevated FTI might be a better reflection of substance misuse within the patient population rather than an inherent greater toxicity in overdose [32]. Despite the potential confounding factors, previous studies have concluded that inherent toxicity is a critical factor of pharmaceutical drugs with a high FTI [13,33]. Additionally, combination drug use was evaluated for each of the 14 prescription medications and should be considered when interpreting results of the FTI.

Among opioid analgesics, oxycodone, morphine, hydrocodone, methadone, fentanyl and tramadol accounted for the greatest number of deaths. However, once standardized by the number of pills dispensed our data shows the drugs with the greatest FTI are fentanyl, methadone, oxymorphone, and morphine. Of all opioids, Methadone, fentanyl and tramadol had the most frequent concomitant use of illicit drugs. The FTI does not account for prescription strength thus; the higher FTIs may be associated with higher morphine equivalents per pill.

Methadone, a drug used primarily in the treatment of addiction and withdrawal symptoms of opioids, primarily heroin, has been increasingly contributing to overdose deaths in recent years [34]. It should be considered that while opioid treatment programs (OTPs), also known as methadone clinics, can access PDMP data, they are restricted by law from reporting to PDMPs (Title 42, part 2 of the Code of Federal Regulations). Because of this, we might not be capturing the majority of methadone prescriptions dispensed, leading to an inflated FTI. Given the high co-occurrence of illicit drug use and additional prescription drugs in methadone related deaths as well as, the known abuse potential of the drug, the FTI is likely reflective of a risky patient-population as the drug is used in the treatment of opioid addiction. Allowing OTPs to upload prescribing data into the CURES system would grant doctors access to patient prescribing information, potentially reducing co-prescribing of prescription drugs known to interact with methadone.

Fentanyl, a synthetic opioid 50 to 100 times more potent that morphine has been increasingly involved in opioid overdose deaths since 2013 largely due to illicitly manufactured fentanyl in the heroin market [35]. Over recent years, the San Diego ME office has been adjusting reporting procedures for deaths involving fentanyl to differentiate prescription fentanyl from illicit [10]. Because of this, fentanyl's large FTI may be reflective of the rise in illicit fentanyl rather than prescription fentanyl as we are unable to account for illicit fentanyl supply with CURES data. Similar to methadone, fentanyl had a high co-occurrence of illicit drug use and additional prescription drugs identified in deaths potentially indicating drug misuse within the population.

Of special interest, our data shows tramadol in the top 14 Schedule II-IV prescription drugs most commonly identified in accidental overdose deaths for 2015 as well as, the third most commonly prescribed opioid in San Diego County. Tramadol identified as having a high co-occurrence of illicit drug use and additional prescription drugs, potentially indicating drug misuse among the population. Tramadol, a synthetic opioid drug, prescribed with the false assumption that it is safer or less addictive than other opioids. Originally a non-scheduled drug, tramadol was reclassified by the DEA as a schedule IV-controlled substance in 2014 following evidence of rising abuse and potential for adverse effects [36]. A recently published study shows that this change had minimal effects on providers prescribing practices, with the main impact being that tramadol can now be viewed as a part of the CURES system as a schedule IV drug [37].

Following oxycodone, morphine was the most commonly identified opioid on ME toxicology reports. Some physicians have expressed interest in prescribing morphine in lieu of hydrocodone due to allegedly less euphoric effects. Results of the FTI calculations show morphine as 9-fold more toxic than hydrocodone in accidental overdose suggesting that morphine might not be a safer alternative to hydrocodone. Additionally, morphine prescriptions and pills dispensed were one-seventh as much than those for hydrocodone, but morphine identified in a greater number of deaths than that of hydrocodone. The morphine equivalents prescribed with oxycodone and morphine are typically higher than those prescribed for hydrocodone.

Among benzodiazepines, alprazolam, diazepam, clonazepam, temazepam, and chlordiazepoxide accounted for the greatest number of deaths. When standardized by number of pills dispensed, our data shows benzodiazepines with the greatest FTI are chlordiazepoxide, diazepam, temazepam, and alprazolam. Of all benzodiazepines, diazepam, alprazolam, chlordiazepoxide and temazepam had the greatest concomitant use of illicit drugs.

Chlordiazepoxide, a benzodiazepine most commonly prescribed in the treatment of alcohol withdrawal, had the highest FTI of all prescription drugs under investigation as well as, the greatest co-occurrence of illicit drug use and additional prescription drugs identified in deaths. The elevated FTI influenced by the patient population being at a higher risk of death due to their underlying disease state and addiction.

Alprazolam accounted for the greatest number of benzodiazepine deaths and prescriptions as well as, showed a high co-occurrence of illicit drug use and additional prescription drugs identified in deaths. Alprazolam (Xanax), a highly addictive benzodiazepine

used primarily in the treatment of anxiety disorders, remains the most commonly prescribed benzodiazepine in the U.S. despite high rates of misuse and literature documenting greater toxicity in overdose in comparison to other benzodiazepines [38,39]. Alprazolam has a limited indication of use to a few weeks for panic disorder and contraindicated for long-term use as serotoin-norepinepherine reuptake inhibitors (SSRIs) are considered first-line agents for anxiety disorders [38]. This known information, in combination with, the high FTI and number of alprazolam related deaths warrants reason for concern in continuing the use of this drug at such high levels.

Limitations

The study had several limitations. Results of the analyses are population-based conclusions and limited in their generalizability as the study compares rates within the same population and is unable to account for potential confounders such as existing medical conditions, substance abuse, and the varying dose-strength formulations of prescription medications included in the study. The PDMP system does not include prescriptions filled by military hospitals, methadone clinics, and out-of-state clinics, and online and illegal prescriptions. The San Diego Veterans Administration did not upload prescribing data into the CURES system until 2016. The ME toxicology reports did not always include all OTC drugs, not all illicit drugs are detectable, and some may not have been tested for by the ME. On 15 ME reports, the toxicology report stated "opiate" without a specific drug name and on 28 ME reports, the toxicology report stated "benzodiazepine" without a specific name. The calculated FTIs are based on the number of pills dispensed as a marker for drug consumption and we are unable to control for varying strengths, dosages, and preparations of each drug under investigation. Fentanyl, a synthetic opioid 50 to 100 times more potent than morphine, can be prescribed as patches or pills and we were unable to account for these adjustments with the prescribing information from CURES. Some of the drugs included have illicit markets and this study did not correlate whether deaths were attributed to the prescribed drugs in CURES. Additionally, the analyses were unable to account for movement of drugs outside the county. A previous study examining prescription related deaths found that only 40% of deaths correlated to a recent prescription found in CURES [11].

Conclusions

The focus of the epidemic in the US has been on opioids, yet our study findings suggest that drugs from various classes are overrepresented in accidental prescription-related deaths. Working towards reducing the number of prescription related deaths requires safe prescribing practices not just of opioids but benzodiazepines, sleep aids, and a reduction in the co-prescribing of multiple CNS depressants. In addition to the absolute number of overdose deaths from prescription drugs, it is important to consider combination drug use. The FTI with consideration to combination drug use can provide valuable information to physicians on the relative toxicity and ranking of prescription drugs in overdose deaths. Medical examiner data and PDMP reports offer a wealth of information and can be used as a guide for safe prescribing. Further studies are warranted to look into the top drugs implicated in prescription related deaths and findings should be considered when working towards promoting safe prescribing and reducing accidental overdoses. Future research should take into consideration the dose-strength relationship when calculating FTIs.

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