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Systematic Review

Patient Characteristics and Outcomes in Unintentional, Non-fatal Prescription Opioid Overdoses: A Systematic Review

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Background: Opioid overdose continues to be a significant and growing cause of preventable mortality and morbidity. Studies suggest that unintentional, non-fatal overdose from prescription opioid analgesics constitutes a large portion of total overdose events. The societal burden associated with these events is a frequently overlooked public health concern.

Objectives: To evaluate unintentional, non-fatal prescription opioid overdoses, including the identification of risk factors, societal burden, and knowledge gaps where further study is warranted.

Study Design: Systematic review of the literature for unintentional, non-fatal opioid overdose.

Methods: Preferred reporting items for systematic reviews and meta-analyses guidelines were used in constructing this systematic review. To determine the scope of the existing literature, a systematic search was conducted using the MEDLINE, CINAHL, PsycINFO, and Web of Science databases.

Results: This systematic review analyzes 24 articles (21 retrospective descriptive analyses, 2 prospective analyses, one phase III trial, and one meta-analysis). Articles were reviewed by authors and relevant data examined. Results show that opioid overdose morbidity is significantly more prevalent than mortality and sequelae of non-fatal events should be studied in more detail.

Limitations: The limitations of this systematic review include the range of study populations and opioids discussed and the broad and variable definitions of "opioid overdose" in the literature.

Conclusion(s): Opioid overdose morbidity and mortality is seen across the entire spectrum of inpatient and outpatient use with significant numbers of adverse events occurring in population segments not identified by high risk indicators. Increased physician awareness and a multi-modal approach could help mitigate the overdose epidemic while maintaining effective pain control for patients.

Key words: Prescription, opioid, accidental drug overdose, unintentional overdose, drug poisoning, fentanyl, oxycodone, hydrocodone, methadone, oxymorphone, hydromorphone

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The number of prescription opioid-related deaths has grown dramatically in the United States, with 4,000 reported in 1999 and 14,800 reported in 2008, over a 3-fold increase (1). The total number of deaths from drug poisoning closely approached traffic collisions in 2008 and surpassed them in 2009 as the leading cause of unintentional injury deaths in the United States (1,2). Prescription opioid medications account for approximately 40% of all drug poisonings (1). According to the Centers for Disease Control, in 2013, 16,235 deaths were due to prescription opioid overdose (3) as compared to

8,260 deaths from heroin (4). At least 13,486 (83%) of the prescription opioid overdose fatalities were unintentional (17% were intentional or undetermined) (4). This rise in opioid-related deaths follows a similar rise in prescribing patterns for opioid medications (5,6). After the medical community proposed pain as the fifth vital sign in 1996, prescriptions for opioid analgesics increased 7 fold over the next 4 years (6). In 2010, total sales of opioid analgesics were equivalent to 710 mg morphine-equivalent doses per person in the United States (5,6).

A multi-pronged response to this public health emergency has ensued. Responses include changes in FDA opioid regulation, FDA revision of opioid labeling relating to safety, adoption of new risk evaluation and mitigation strategies for opioid products with increased risk for abuse and life-threatening respiratory depression, tighter control of opioid prescribing practices by government, and revisions of controlled substance prescribing guidelines by state medical boards (7). For example, the Drug Enforcement Administration (DEA) announced in 2014 rescheduling of hydrocodone-combination products from Schedule III to Schedule II (8). There have been aggressive changes to policies in Florida that regulate pain clinics as well as stricter enforcement and monitoring of inappropriate physician prescribing and pharmacist dispensing that has resulted in the revocation of pain medication dispensing privileges from physicians' offices and substantial consequences to Florida pharmacies, respectively (9). In addition, non-profit, community-based pilot programs such as Project Lazarus in North Carolina (10) and the Overdose Prevention Project of Prevention Point Pittsburgh in Pennsylvania (11) have implemented programs focused on decreasing fatalities due to prescription opioid overdose. Despite these substantial government and public health initiatives, including state enactment of prescription drug monitoring programs, FDA approval of abuse-deterrent opioid products, and DEA initiatives to curb inappropriate opioid prescribing, as well as similar harm reduction efforts (12,13), opioid overdose continues to be a significant and growing cause of preventable mortality and morbidity in the United States (US).

Published articles on prescription opioid overdose have largely focused on the epidemiology and characteristics associated with fatal opioid overdose events (14,15). However, studies suggest non-fatal overdose events from prescription opioid analgesics constitute a much larger portion of total overdose events (16-18).

Progression to death during an opioid overdose emergency is usually not immediate as sedation generally precedes life-threatening opioid-induced respiratory depression (19-21). Understandably, fatal outcomes have garnered much public attention; however, the societal burden caused by morbidity associated with non-fatal prescription opioid-related overdose is an often overlooked, and potentially growing, public health concern.

This systematic review evaluates unintentional, non-fatal prescription opioid overdoses, including the identification of risk factors, societal burden, and knowledge gaps where further study is warranted.

Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used in constructing this systematic review (22). To determine the scope of the existing literature, a systematic search was conducted using the MEDLINE, CINAHL, PsycINFO, and Web of Science databases. Results were filtered to include articles published between January 1, 1999, and July 14, 2014, in English about human subjects. MEDLINE was searched first using the MESH terms "Drug Prescriptions," "Analgesics," "Opioid," "Prescription Drug Misuse," "Medication Errors," and "Drug-Related Side Effects and Adverse Reactions," along with the following key words: drug prescription, prescription, opioid analgesics, opioid, opiate, fentanyl, oxycodone, hydrocodone, methadone, codeine, oxymorphone, hydromorphone, prescription drug misuse, accidental drug overdose, accidental overdose, unintentional overdose, overdose, medication errors, inappropriate prescribing, adverse drug event, adverse drug reaction, drug toxicity, and drug poisoning. Corresponding topic headings and the same key words were used to search the additional databases. Inclusion and exclusion criteria (Table 1) were applied to the titles and abstracts of identified articles by 2 independent authors. Discrepancies were discussed and resolved by consensus.

Results

Literature Search

The systematic search identified 1,034 articles, 123 of which met the inclusion criteria after eliminating duplicate articles (Fig. 1). Applying inclusion and exclusion criteria to the full text of the 123 articles resulted in exclusion of 65 articles (Table 2). An article with an incomplete study was excluded as well as 3 articles on

Table 1. *Search strategy inclusion and exclusion criteria.*

Inclusion	Exclusion
Unintentional event	Intentional harm
Prescription opioids	Heroin
Non-fatal overdose or poisoning or toxicity requiring admission to hospital or naloxone administration	Fatal overdose or poisoning or toxicity

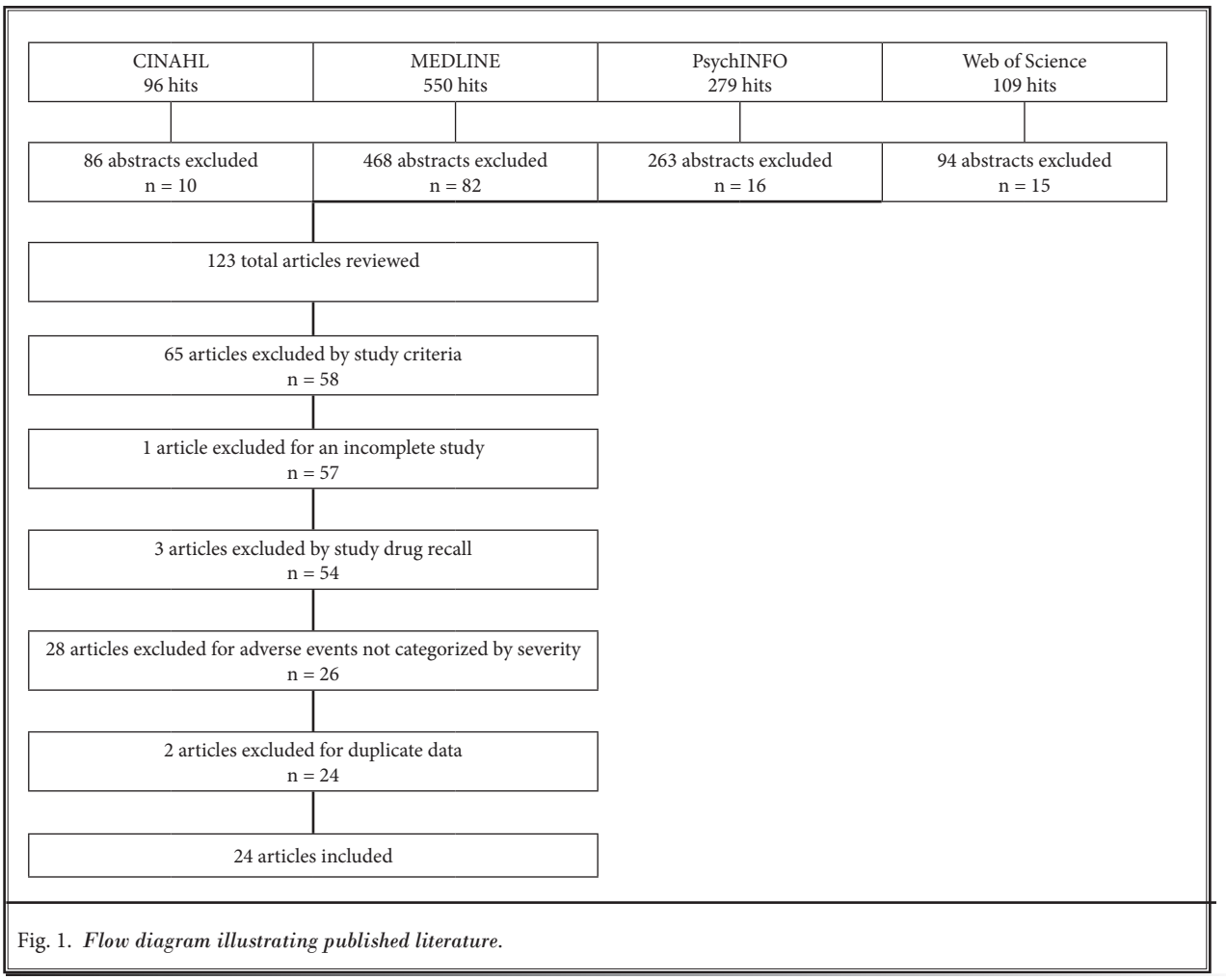

Fig. 1. *Flow diagram illustrating published literature.*

study drugs recalled for toxicity. Adverse events not categorized by severity resulted in exclusion of 28 articles. An additional 2 articles were excluded for duplicate data (Table 2). This review therefore analyzes 24 articles, the characteristics of which are described in Table 3.

Morbidity and Mortality of Severe Opioid-Related Adverse Events

The systematic search revealed national data displaying a sharply increasing number of prescription opioid-related overdose emergency department visits and hospital admissions from 1993 to 2010. Between 1997 and 2005 the number of prescription opioid-related overdose non-fatal events were 7 times the number of deaths (17). In 2009, a total of 293,184 estimated emergency department visits were related to prescription opioid overdose (23). From 2004 to 2008 total emergency department visits due to non-medical use of opioid prescriptions increased 111% from 144,600 to 305,900 (24).

Table 2. *Characteristics of studies considered for exclusion.*

Author		Reason for Exclusion
Campbell et al (2014)		Study not completed
Amari et al (2011) Barreto et al (2011) Becker et al (2013) Bekjarovski et al (2012) Beno et al (2005) Bigal et al (2009) Blanco et al (2013) Bjorn et al (2009) Bond et al (2012) Casati et al (2009) Carvalho et al (2013) Chou et al (2014) Cohen et al (2003) Cote et al (2000) Currie et al (2011) Dalleur et al (2000) Darnall et al (2012) Dassanayake et al (2012) De Cuyper et al (2013) Degenhardt et al (2006) Denison et al (2011) Duh et al (2010) Elwood et al (2011) Fareed et al (2011) Fibbi et al (2012) Fischer et al (2014) Fishman et al (2009) Frei et al (2010) Gugelmann et al (2012) Hemptstead et al (2014) Hersh et al (2007) Hudec et al (2004) Jann et al (2014)	Koeppe et al (2013) Kuehn et al (2010) Lee et al (2009) Liu et al (2009) Lloyd et al (2011) Marshall et al (2012) Maxwell et al (2011) McCarthy et al (2012) McWhirter et al (2012) Morgan et al (2010) MMWR 60(43) (2011) MMWR 61(1) (2012) MMWR 61(26) (2012) MMWR 62(26) (2013) Myers et al (2003) Paulozzi et al (2012) Pergolizzi et al (2011) Porucznik et al (2011) Rajpa et al (2013) Reisfield et al (2013) Roxburgh et al (2011) Sims et al (2007) Soderberg et al (2013) Sowa et al (2014) Stoermer et al (2003) Webster et al (2012) White et al (2009) Whiteside et al (2013) Wolff et al (2012) Wong et al (2013) Xian et al (2012) Zacny et al (2012)	Not relevant to study criteria
Afshari et al (2005) Badalamenti et al (2012) Hawton et al (2011)		Opioid no longer used due to toxicity
Baldini et al (2012) Ballantyne et al (2012) Bennett et al (2014) Blackwell et al (2009) Birnbaum et al (2013) Blackwell et al (2009) Boockvar et al (2009) Braden et al (2010) Brands et al (2008) Colburn et al (2012) Degenhardt et al (2006) Green et al (2011) Hartung et al (2007) Havens et al (2011)	Ivanova et al (2013) Jenkins et al (2011) Jones et al (2012) Manchikanti et al (2012) McNeely et al (2006) Neale et al (2000) Passik et al (2011) Paulozzi et al (2014) Rich et al (2011) Schifano et al (2005) Schuman-Olivier et al (2013) Seal et al (2012) Silva et al (2013) Walley et al (2013)	Adverse events not categorized by severity
Adaw et al (2010) Fine et al (2010)		Duplicate data

Table 3. Characteristics of studies considered for inclusion.

Article	Study Design	Study Year(s)	Total Opioid Exposures, Morbidity & Mortality
Bailey et al (2009)	Retrospective descriptive analysis	2003-2006	9179 total person exposures 1353 total AEs, 43 severe AEs, 8 deaths
Berling et al (2013)	Case series	2001-2011	137 severe AEs
Bonar et al (2014)	Cross-sectional survey	2008-2009	326 total person exposures 94 severe AEs
Bunn et al (2010)	Retrospective descriptive analysis	2001-2007	794 severe AEs (540 unintentional), 11 deaths 402 additional cases not specified with amount of deaths involved
CDC (2010)	Retrospective descriptive analysis	2004-2008	305,900 total nonmedical ED visits in 2008 (111% increase from 2004) 72,700 admitted to the hospital
CDC (2012)	Retrospective descriptive analysis	2002-2011	34 (19%) children, 14 (5.6%) adults respiratory depression 3 (1.7%) children, 2 (0.8%) adults respiratory arrest 42 (25.6%) children, 47 (21.4%) adults moderate to major event 3 deaths (2 adults, 1 teen) 120 (48.6%) admitted to hospital
Coben et al (2010)	Retrospective descriptive analysis	1999-2006	129,025 hospitalizations (increase from 8,815 in 1999 to 22,907 in 2006)
Dunn et al (2010)	Retrospective Cohort	1997-2005	9940 total person exposures 51 total AEs, 34 severe AEs (8 unintentional), 6 deaths
Dy et al (2007)	Retrospective descriptive analysis	1998-2004	638 total person exposures 336 severe AEs, 6 deaths
Fulton-Kehoe et al (2013)	Retrospective descriptive analysis	2004-2010	408 severe AEs, no deaths (96 overdose, 312 AEs not defined as overdose)
Inocencio et al (2013)	Retrospective descriptive analysis	2009	Estimated 402,453 severe AEs, 16,205 deaths
Lovborg et al (2012)	Prospective analysis	2008-2009	Totals not separated
Man et al (2004)	Cross-sectional survey	1999-2000	135 total person exposures 296 severe AEs (involving 76 persons)
Meyer et al (2014)	Literature review	N/A	N/A-review
Modarai et al (2013)	Ecological study	1997-2010	Opioid sales, ED Overdose visits and unintentional overdoses correlate with rural areas and regions of poverty in NC
Morton et al (2010)	Prospective audit	2007-2008	10,726 total pediatric inpatient exposures 14 severe AEs, 1 death
Nalamachu et al (2011)	Combined analysis of three double-blind, placebo-controlled, and two open-label studies	N/A	1160 total person exposures 925 total AEs, 136 severe AEs, 6 deaths 11 overdoses-all resolved satisfactorily 611 total AEs, 15 severe due to FBT treatment (5 studies combined)
Oviedo-Jokes et al (2009)	Open-label, phase 3, randomized, controlled trial	2005-2008	251 total person exposures 79 severe AEs (involving 54 persons), 1 death
Shadnia et al (2012)	Retrospective case series	2008	100 total person exposures 100 severe AEs, 0 deaths
Tormoehlen et al (2011)	Retrospective case series	1994-2007	1634 total AEs, 172 severe AEs, 15 deaths
Unick et al (2013)	Retrospective descriptive analysis	1993-2009	Prescription overdose rate rose from 1.92 to 14.85 Death rate rose from 0.8 to 0.38 per 100,000
Wisniewski et al (2008)	Retrospective descriptive analysis	1995-2002	ED visits for oxycodone increased 5.6 fold ED visits for morphine increased 1.16 fold ED visits for hydrocodone increased 1.6 fold
Yoon et al (2014)	Retrospective descriptive analysis	2010	6769 non-weighted & 33,726 weighted unintentional prescription opioid overdose hospitalizations
Zosel et al (2013)	Retrospective descriptive analysis	2007-2009	8866 total person exposures 6896 total AEs, 462 severe AEs, 20 deaths

ED=Emergency department, AE=Adverse event, N/A=Not applicable, FBT=Fentanyl buccal tablet

In a 2004 – 2008 study, approximately one-quarter of nonmedical overdose cases were admitted to the hospital (24) and in a 2009 study this proportion increased to one-third (23). Prescription opioid overdose hospitalization rates climbed sharply from approximately 2 per 100,000 people to almost 15 per 100,000 people during 1993 – 2009 (25). While this study revealed that death rates also increased from 0.08 to 0.38 per 100,000 (25), these rates were considerably lower than the rates for non-fatal events. Total prescription opioid overdose events rose from 8,815 hospitalizations in 1999 to 22,907 hospitalizations in 2006 (26) and an estimated 180,106 hospitalizations in the year 2009 (23). Hospital discharges related to unintentional prescription opioid overdose totaled 33,726 in 2010, more than 27% of all unintentional drug poisonings that year (27).

Studies in this review indicate that harm to children from prescription opioids has also increased. For example, study data from the Indiana Poison Control Center from 1994 to 2007 showed a significant increase in calls to the poison control center regarding adolescents overdosing on opioids after the Joint Commission for Accreditation of Health Care Organizations (JCAHO) pain management standards went into effect on January 1, 2001 (28). In this study, prescription opioid overdose events occurred in 172 cases of 1,634 prescription opioid-related exposures (10.5%). Additionally, non-fatal prescription opioid-related overdoses were 11.5 times more frequent than deaths relating to prescription opioids. Of the 172 cases of prescription opioid overdose, 51 (30%) occurred before and 121 (70%) occurred after the JCAHO initiative. Calls to the Indiana Poison Control Center were 2.84 times (95% CI: 2.06, 3.91) more likely to involve adolescents who developed medical complications with opioids after the JCAHO initiative compared to before the JCAHO initiative, a significant increase. Similarly, after the JCAHO initiative, calls involving adolescents were 3.03 (95% CI: 2.20, 4.18) times more likely to have an opioid-related medical complication compared to before the JCAHO initiative.

This systematic review identified a broader study of adolescents focused on prescription abuse and misuse which utilized data from 45 RADARS Poison Control Centers from 2007 to 2009 (29). Prescription opioid overdose events occurred in 462 (6.7%) of 6,896 cases with reported adverse effects. Importantly, non-fatal adverse effects (462) occurred 23 times more than death (29). Almost 30% of cases were treated in an acute care health facility and 50% of these cases were admitted to the hospital.

Studies included in this systematic review indicate that younger children are also directly affected by prescription opioids. Bailey et al (30) found negative effects of prescription opioids on children less than 6 years of age in a study of data from 11-40 Poison Control Centers collected from 2003 to 2006. Prescription opioid overdose events occurred in 43 cases of 9,240 identified prescription opioid exposures. Non-fatal cases (43) occurred 5 times more than death (8)(30).

Over 86% of intentional exposures occurred in the adolescent's own home (29). Sites of exposure also included another's residence (3.2%) or school (3.5%)(29). This was similar in cases from children under 6 years of age, where 92% of exposures occurred in the child's own home and 6% occurred in another's residence (30).

Economic Impact

Studies identified in this review reveal the increased economic impact of prescription opioid overdose. From 1999 to 2006 the average length of stay for a prescription opioid overdose hospitalization was 3 days (26) and in a separate 2009 study, 4 days (23). In a study of oxycodone admissions to a toxicology unit from 2001 to 2011, the length of stay was on average 18 hours, compared to a 15 hour average for all other toxicology admissions (31). The length of stay increased further if a naloxone bolus was administered (combined pre-hospital and emergency department data) with a median stay of 21 hours. Patients requiring naloxone infusion had a median length of stay of 36 hours (31) suggesting that naloxone administration in a hospital setting is likely a surrogate for opioid overdose event severity and associated increased economic burden.

In 2009, the average direct total cost of a prescription opioid overdose event was $4,255, while the average direct cost for emergency department treatment was $1,967 (23). This correlates to an annual cost of approximately $1.76 billion for US prescription opioid poisonings (23). The estimated indirect cost for each prescription opioid overdose was $34,285. The estimated annual total U.S. indirect costs for poisoning by all opioids was $18.2 billion in 2009 (23).

In a study of methadone-related hospitalizations from 2001 to 2007, the most frequent expected payer source was self-payment in patients aged 15 – 34 years with almost a quarter of all cases in the study being self pay (32). Medicare and Medicaid were billed for over 50% of all methadone-related hospitalizations of patients over age 35 years and Medicare was the most frequent payer. The total charges for inpatient hospi-

talizations related to methadone toxicity events in this Kentucky study was $19,053,910 for 1,207 cases, which is an average of almost $16,000 per admitted patient (32).

Associated Risks for Prescription Opioid Serious Toxicity and Overdose

Prescribing Patterns and Dose of Opioid Medications

Several studies identified in this systematic review relate risks associated with prescribing patterns and dose of opioid medications. As the rate of prescribing of opioids increases, there is a significant correlation with growth in self-reported, non-medical use and opioid-related emergency department visits (33). As the availability of prescription opioids increases within a community, a concomitant rise in unintentional exposures in young children occurs (30). This study found a positive correlation between zip codes of retail pharmacies prescribing opioids and an increase in prescription opioid exposures in young children in the same zip code (30). Persons who did not recently receive a prescription for an opioid were one-fifth as likely to experience a serious prescription opioid overdose while any opioid use resulted in an 8.4-fold increase for a serious event (17).

The study by Dunn et al (17) indicated that as prescription opioid dose escalates, the risk of prescription opioid overdose increases. Compared to persons taking opioid doses from 1 – 19 mg morphine-equivalent daily dose (MEDD), those persons taking 20 – 49 MEDD, 50 – 99 MEDD, and ≥ 100 MEDD had a 1.2, 3, and 11-fold increased risk of prescription opioid overdose, respectively (17). MEDD is the parenteral morphine equivalent of a non-morphine opioid, which is derived using a standard conversion table. Persons receiving the highest opioid doses compared to the lowest dose persons were current smokers (40.0% vs. 28.0%), had a treatment history of depression (32.0% vs. 25.9%) or substance abuse (13.7% vs. 5.3%), and were male (48.4% vs. 39.5%) (17). However, the majority of overdoses occurred among patients receiving low to moderate dose regimens, due to the amount of patients receiving lower opioid dosages. There were 7 non-fatal opioid overdose events for each fatal opioid overdose identified in the study (12% were fatal).

Opioid overdoses at dosages well below 100 MEDD have also been documented (17). Fulton-Kehoe et al (34) found that prescribed opioid doses were below the flagged dosage of 120 MEDD used by Washington State guidelines for 72% of opioid poisoning events and 70% of opioid adverse effect events. The median dose was 75 MEDD. In addition, the majority of opioid poisonings and opioid adverse effects did not occur in chronic prescription opioid users (defined as having ≥ 90 days' supply of opioid medications during the year before the opioid event occurred) (34).

Specific Opioid Medications

Studies in this systematic review identify oxycodone, hydrocodone, and methadone prevalence in overdose events. From 2004 to 2008, emergency department visit rates were highest for oxycodone, hydrocodone, and methadone during the entire study period, with total oxycodone emergency department visits increasing from 41,700 to 105,200, which is 34.4% of 2008 emergency department drug poisoning visits (24). In adolescent prescription opioid exposures from 2007 to 2009 in the RADARS system, hydrocodone was reportedly involved in 5,232 cases (47.7%), oxycodone in 2,471 cases (22.5%), and tramadol in 1,752 cases (16%). Hydrocodone was involved in more intentional exposures by adolescents than any other drug (29).

Methadone poisonings, in particular, rose 400% from 1,703 hospitalizations in 1999 to 5,362 hospitalizations in 2006 (26). Methadone had the largest increase in hospitalizations over the study period in comparison with other prescription opioids, sedatives, and tranquilizers (26). Other opioid prescription-related hospitalizations rose steadily as well, from 7,742 in 1999 to 17,545 in 2006 (26). In a Kentucky study from 2001 to 2007, methadone inpatient hospitalizations increased by 21 every year, even though prescriptions decreased slightly from 27 to 21 per 1,000 population. Half of the methadone-related hospitalizations were related to unintentional poisonings (32). Significant increases in calls to the Indiana Poison Control Center involving methadone occurred after the JCAHO pain management standards were implemented in 2001, while cases involving codeine and propoxyphene decreased (28). Methadone had the highest percentage of major effects (5.0%) on outcomes in children under 6 years of age, compared to other opioid analgesics (30).

In a study of opioid poisonings and adverse effects in a workers' compensation system, events due to hydrocodone occurred in 47% of opioid poisonings and 47% of opioid adverse events, whereas events due to oxycodone were 57% and 56%, respectively (34). Ingestion of sustained release (SR) oxycodone formulations was associated with a lower Glasgow Coma Score and increased use of naloxone compared to immediate

release (IR) oxycodone ingestion (31). Sixteen of 20 patients who ingested oxycodone presented with prolonged QT interval and had electrocardiograms before event, after event, or upon discharge that showed normal QT lengths, suggesting oxycodone involvement in prolonging the QT interval (31). However, torsades de pointes was not associated with the prolonged QT interval(31).

A review of 5 studies examining the safety of fentanyl buccal tablets revealed a much higher morbidity compared to mortality (35). A total of 925 adverse events were recorded from the study population (n = 1,160) who received one or more doses of fentanyl buccal tablets. Serious morbidity occurred 136 times while 6 deaths were recorded (35). In another study, fentanyl had a significant rate of moderate (10.1%) and major (3.8%) effects in young children (30).

Buprenorphine exposures in young children in RADARS data showed that 68% resulted in an adverse effect, 2 to 3 times the rate of any other prescription opioid studied (30). Major (4%) and moderate (20%) effects were associated with these buprenorphine exposures. Minor effects were defined as "the patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient." Moderate effects were defined as "more pronounced, more prolonged or more of a systematic nature than minor symptoms," but not life-threatening. Major effects were defined as "life threatening or resulted in significant residual disability or disfigurement." All other prescription opioid exposures resulted in major effect rates between 0% – 1.9% except fentanyl (3.8%) and methadone (5%). Almost 30% of buprenorphine exposures resulted in a major effect compared to 2% of the buprenorphine plus naloxone exposures (30). In a separate study, respiratory depression due to buprenorphine was seen in 34 children less than 5 years of age (19.0%) and respiratory arrest in 3 (1.7%). Respiratory depression was also seen in 14 adults (5.6%), and respiratory arrest in 2 (0.8%) (36).

Tramadol was identified among drugs with the highest preventable adverse events in one inpatient study (37). In a study of 100 individuals with tramadol overdose and seizures, a mean tramadol dose of 1,100 mg was associated with a single episode of seizure and a mean tramadol dose of 2,000 mg was associated with recurrent seizures (38). Recurrent seizure occurrence was not dose dependent and vital signs were similar in the single and recurrent seizure groups. Seven of the cases were unintentional whereas 93 occurred due to intentional overdose, and no fatalities occurred within the 100 patient study population. Nearly all patients had only one seizure (n = 93), while a few had 2 seizures (n = 4), 3 seizures (n = 2), or 4 seizures (n = 1). Data on adverse events (e.g., number of seizures or dosage) by intent was not provided in this study.

Co-Ingested Substances

Studies identified in this review show that co-ingested substances also increase the risk for prescription opioid overdose. From 2004 to 2008, 38% of emergency department visits involved single drugs while 62% involved poly-drug events (24). Cocaine and heroin use are significantly associated with opioid overdose (39). Of all prescription-related opioid poisonings in 2009, 29% involved benzodiazepines and 14% involved alcohol (23). Patient populations prescribed medications within opioid treatment programs are at greatest risk of overdose when benzodiazepines and alcohol are combined with opioids (40). Persons prescribed both methadone and diazepam reported the most overdoses and they had the majority of intentional overdoses compared to persons using methadone alone, diazepam alone, or neither prescribed medication (40). Prescription opioid overdose events involved co-ingestants in 44% of cases, while only 0.6% of prescription opioid adverse events involved co-ingestants in a study of workers' compensation cases (34). Seven out of 10 prescription opioid overdose patients who received naloxone treatment reported the use of co-ingestants, such as benzodiazepines or cocaine during that adverse event in one study (41). This same study reported 7 seizures related to the study opioid (diacetylmorphine) with 2 seizures occurring in a patient with a history of epilepsy and the remaining 5 seizures occurring in patients who had used cocaine or benzodiazepines before the seizure (41).

Non-medical Use of Opioid Medications

Studies in this review indicate that nonmedical use of prescription opioids increases a person's risk of a prescription opioid overdose. Substance abuse is strongly related to prescription opioid overdose events (17). A majority of patients actively involved in opioid treatment programs report a significant rate of previous prescription opioid overdose (40). A history of prescription opioid overdose was found significantly more in individuals involved in heavy nonmedical use of prescription opioids with a lifetime history of heroin use and higher reported pain levels (39). Individuals with a lifetime suicide attempt had a higher incidence of prescription opioid overdose

history and heavy nonmedical use of prescription opioids (39,40). Other risk factors in this population were low tolerance as well as poly-drug use (40). Individuals with prior overdose events reported belief that bad luck or drug purity misjudgment were reasons for occurrence of the overdose (40).

Demographic and Co-morbidity Factors

Several risk factors associated with prescription opioid overdose were identified by the studies, including middle age (40 – 49 years of age) (25,34), lack of a high school education (39), recent prescriptions for sedative-hypnotics (17), rural areas (42), and regions of poverty, especially the Appalachian region of the US (32,42). For example, the highest prescription opioid-related hospitalization and fatality rates in Kentucky were observed in the eastern Appalachian region of the state (32), and unintentional drug death-related emergency department visits for opioid overdose and prescription sales of opioids were highest in rural areas of North Carolina, particularly in the Appalachian region (42). Increased poverty in the decedent's county of residence was associated with higher fatality rates due to unintentional pharmaceutical overdoses (32).

General differences between men and women and intentional versus unintentional opioid overdose were also reported. Bipolar disorder in women and depressive disorders in men and women were associated with increased risks for unintentional prescription opioid overdose (27). From 1999 to 2006, men were more likely to be hospitalized with unintentional prescription opioid overdose, whereas women were more likely to be hospitalized with intentional prescription opioid overdose (26). Yoon and colleagues (27) showed a slight majority of female hospitalizations from unintentional prescription opioid overdose, 55% (n = 18,520). Bunn et al (32) reported the majority of unintentional prescription opioid overdoses were in men aged 25 – 34 and women aged 35 – 44 years. Study findings from 1993 to 2009 showed women were more likely to be hospitalized for a prescription opioid overdose for all study years (25,43).

Pregnancy

A review of opioid-related adverse events in pregnant women found an increased risk for fetal cardiac defects (including conoventricular septal defects and hypoplastic left heart syndrome), neural tube defects, gastroschisis, and open neural tube defects (43). Neonatal admissions to the intensive care unit were due to iatrogenic late preterm birth or early birth and were from respiratory complications, hypoglycemia, jaundice, difficulty feeding and, a small percentage (5.6%), from abstinence syndrome. Somnolence occurs in breastfeeding infants of opioid-naïve women treated with opioids for postpartum pain. Concerns relate to the variability in opioid levels in breast milk which can be lethal to infants (43).

Inpatient Opioid Use

In an analysis using MEDMARX, a national medication error reporting database, investigators found that opioid overdose occurred 336 times with 6 deaths in 644 reported harmful errors in 222 inpatient facilities (44). Hydromorphone errors were significantly more likely to be overdoses than other opioids. Many errors, particularly for hydromorphone, but also for other opioids within the study, occurred due to dosing for oral and intravenous forms being interchanged. Fentanyl errors almost exclusively occurred with transdermal patches, with higher rates of omission and underdosing compared with other opioids selected in the study. Meperidine errors were mainly due to incorrect route of administration (intravenous administration of an intramuscular order), and had higher opioid overdose compared with other opioids. Numerous seizures or other central nervous system complications related to meperidine occurred. Oxycodone errors were significantly more likely to be from omission or as wrong drug administration than other opioids. Oxycodone IR and SR formulations were interchanged. Several cases of morphine drips being administered over one hour instead of over a 24 hour period occurred (44).

An identified study of pediatric opioid infusions by Morton and Errera (45) reported one cardiac arrest and 8 cases of respiratory depression requiring naloxone administration out of 10,726 pediatric patients, aged 0 – 18 years receiving opioid treatment in 18 centers, over a study period of 18 months. The incidence rate of respiratory depression was 0.13% (n = 14), 6 without naloxone treatment. Thirteen of the 14 cases involved post-operative opioid treatment (half of all respiratory events occurred in the immediate postoperative setting) and 7 of the cases involved patients who were ≤ one year of age, or patients with significant neurodevelopmental, respiratory, or cardiac comorbidities. Three out of 7 of these very young patients required naloxone compared to 5 out of 7 of the patients who were more than one year old. The cardiac arrest occurred in a neonate with an additional complication of neurocutaneous melanosis and suffered the event 37

hours postoperative and subsequent opioid treatment. All incidences were rare with total adverse events occurring the least (0.29%) in patients aged one month – one year old and most often (0.59%) in patients < one month old (45).

Comparison to Heroin Use

Although excluded from our systematic review as a criterion, several identified articles use heroin as a comparator to demonstrate the prevalence of non-heroin prescription opioid poisoning. Heroin-related poisoning hospitalizations remained relatively constant from 1999 to 2006 (26) and in 2009, approximately 25% of all opioid-related poisonings involved heroin (23). Prescription opioid overdose emergency department visits occurred approximately 3 times more often, and hospitalizations 4.5 times more often as compared to heroin-related poisonings in 2009 (23). This study showed heroin poisoning costs ($440 million) were only 20% of the total direct cost of all prescription opioid-related poisonings (23). Unintentional poisoning by heroin was 2.4 times less than the 33,726 unintentional poisonings from prescription opioids in 2010 (27).

In a UK opioid treatment center study, heroin use was common in persons without prescription medications and in those prescribed either methadone (69%) or benzodiazepines (100%). Heroin was used the least (40%) in the group that used prescription opioids plus benzodiazepines. This group also reported the most deliberate and lifetime overdose events (40).

Prescription opioid abuse and illicit opioid abuse were loosely correlated from 1993 to 2009, and the increase in heroin overdoses near the end of the study period appeared to be linked to the exponential growth of prescription opioid-related overdoses (25). Lag models of one group could predict an increase in the other group's rate the following year. In fact, each addition in prescription opioid overdose hospitalizations increased the subsequent year heroin-related overdoses by a factor of 1.3 ($P < 0.001$) (25). Unick and colleagues (25) suggest that focusing on supply-based interventions simply shifts use from one drug to another, rather than reducing harm.

Naloxone Use

In one identified study, all 10 uses of naloxone for reversal of opioid overdose had resolution of an overdose event without sequelae or hospitalization (41). Bailey et al (30) presented 35 cases involving young children administered naloxone with 34 reporting a positive response and one had no record of response. Berling and colleagues (31) conducted a retrospective review of 65 patients with oxycodone overdose. After admission into a toxicology unit each received naloxone during the adverse events (31). More patients ingesting SR forms of prescription opioids required naloxone infusions when compared to IR formulations or combination IR + SR ingestions (31). In the retrospective analysis of 644 MEDMARX harmful error reports, naloxone was administered in approximately 31% of opioid overdose inpatient cases (6 deaths occurred that were unrelated to naloxone) (44). All 8 children receiving naloxone for respiratory depression in another study had full resolution of symptoms (45).

Discussion

Overdose data for prescription opioids has primarily focused on mortality (14,15) and the heroin-using population (46). The data in this systematic review reveals that non-fatal overdose events from prescription opioid analgesics occupy a much larger portion of total overdose events than does mortality and that these non-fatal events are also primarily unintentional (16,17). A broader understanding of the characteristics, incidence, and risk factors of non-fatal prescription opioid overdose is needed. And yet, in a study of administrative claims data and secondary sources, the total cost for prevention and research comprised only 0.6% of all estimated societal costs due to prescription opioid abuse, dependence, and misuse (47).

Six retrospective descriptive analyses show the significant economic stress placed on the health care system from non-fatal opioid overdoses resulting in hospitalizations, emergency department visits, and emergency medical services transport and care (16,17,23,25-27). These findings were echoed by a 2010 nationwide emergency department sample with 135,971 emergency department visits for opioid overdose, and another more recent study with at least 92,209 emergency department visits (68%) from prescription opioids (18). The investigators found a 1.4% mortality rate (n = 1,864) (18) which corresponds to a non-fatal opioid-related toxicity rate of 98.1%. Several other investigators have found prescription opioid-related overdose admission rates of 55% (18), 53% (48), and 49% (49). Methadone alone demonstrated a 68% admission rate, indicating that methadone has a higher rate of hospitalization compared to other opioid analgesics (18,26,32). Methadone, used for the treatment of pain as well as off-label for the treatment of opioid use

disorders, is inexpensive to health care plans as well as patients and includes flexible dosing regimens (50). Unfortunately, lack of awareness for methadone's safety profile, including long half-life, potential drug interactions, and metabolism have led to increased morbidity and mortality.

However, 2 additional analyses highlight the fact that hospitalizations and emergency department visits are only a portion of the total amount of prescription opioid overdose events that occur each year. In the Fulton-Kehoe et al (34) study, only 56% of each group (opioid poisoning and opioid adverse events) were seen in the emergency department and Zosel et al (29) found roughly 30% of adolescent exposures to prescription opioids received care at a health facility. This suggests that opioid overdose data from emergency department visits and national inpatient discharges may significantly under-represent the amount of harm from prescription opioids in the US.

Four studies address opioid use by children and adolescents (28-30,51). Of young children and adolescents exposed to opioids, almost all exposures occur in their own residence (29,30), and the majority (53%) of exposure to prescription opioids occurs via persons obtaining the medications from friends or relatives (52). The Tormoehlen et al (28) study documented the rise in opioid overdose events after the JCAHO initiative. These studies highlight the importance of educating patients on the risk of opioid overdose with prescription opioids.

The increased rate of prescribing opioids, dose escalation, non-medical use, and co-ingested substances all contribute to increased risk of opioid overdose across varied populations (17,33,39,40). Other variables include opioid overdose at modest dosing levels (34), age (25,34), education (39), and rural location and poverty (32,42). More recent research shows significant risks for opioid overdose associated with mental and mood disorders, circulatory disease, respiratory disease and respiratory failure, chronic pain diagnosis, acute alcohol intoxication and alcohol-related disorders as well as hepatitis (18). The focus on severe risks from prescription opioids must broaden to consider patients that do not necessarily qualify for overdose criteria based on current literature. As the authors state, "Even at modest dosing levels over short time intervals, prescription opioid use can have serious health consequences" (34).

The articles identified in this systematic review show a prevalence of oxycodone, hydrocodone, and methadone overdose events. In adolescents, hydrocodone was involved in the highest number of intentional exposures, followed by oxycodone and tramadol (29). In the Coben et al (26) study, methadone had the largest increase in hospitalizations over the study period. Additionally, this review suggests fentanyl, buprenorphine, and tramadol are associated with increased reports of opioid overdose events (30,35,37,38).

Two identified articles presented data on inpatient opioid use, citing overdose complications due to a change in dosing from oral to intravenous, different drug formulations, or time allotted for drug administration (44,45). Neither of these inpatient overdose studies included information on what, if any, processes or procedures were in place to help prevent the medication errors or adverse events. For example, pharmacists often conduct quality reviews on prescription orders and have information technology systems in place to help flag potential prescribing or medication errors. Pharmacists are also an integral part of ensuring proper opioid dosing, titration, route of administration, and rotation from one opioid to another, which has been shown to be a challenge among some healthcare practitioners (HCPs). For example, in a 2012 study, after educating HCPs on proper use of conversion tables, a significant minority of HCPs continued to incorrectly convert opioid dosages (53). Opioid conversion calculators may vary widely, and may not convert dosages in relation to available formulations or for conversion from one method of administration to another, which can cause underdosing or overdosing (53). Overreliance on published equianalgesic conversion tables was found to be an important contributor to opioid-related mortality, especially when converting to methadone from another opioid. This may be due to inadequate HCP education on proper conversion, in addition to the proliferation of guidelines which are inconsistent on opioid rotation recommendations, conflation of equianalgesic tables, and inherent limitations within the tables themselves (53,54). With the increased trend in prescribing opioid treatment for pain management, focusing primarily on clinical guidelines may not be sufficient to mitigate the risks of overdose, death, and other adverse events (55).

Mitigating risks of severe events due to prescription opioids should cover the entire continuum of patients receiving prescription opioids, not just those persons that may be perceived to be at a higher risk (34). Objectively examining the risk in each patient is advisable due to the increasing number of patients within lower risk populations experiencing severe adverse events and the larger total impact this group has on health care.

The Fulton-Kehoe et al (34) study found the majority of adverse events occurring in individuals who were not considered chronic opioid users, defined as having ≥ 90 days' supply of opioid medications during the year before the opioid event occurred. In a recent study of a commercial claims database, daily users continued to represent less than half of all prescription opioid users who had been taking opioids over the entire 3 years of the study period (56). Two studies found opioid overdoses at dosages well below a 100 mg MEDD level (17,57). In addition, more than 21% of direct and nearly 84% of indirect opioid abuse are from prescription opioids obtained through a single physician (52). Even when considering mortality, 60% of all deaths occur from the 90% of the population who obtain their opioid analgesics from a single physician source who is prescribing within guidelines (16). Together, these findings question the standard practice of using chronic opioid use individuals as the determinant subpopulation for studies involving opioid analgesics. With such a large proportion of the US population using opioid analgesics for treatment of pain, and increasing numbers of prescription opioid-related emergency department visits, opioid overdoses will continue to occur in high volumes at all dose ranges. The focus on severe risks from prescription opioids must broaden to consider patients that do not necessarily qualify for overdose criteria based on current literature.

Five identified articles mention naloxone use in the inpatient treatment of opioid overdose. Naloxone has also been discussed in several observational studies in community and home settings and has been found to "rescue" overdose victims (10), to potentially decrease misuse and abuse (58), and increase abuse-related treatment program admissions (59) in a primarily illicit use population (60,61). Increased public access to naloxone, educating the public, and promoting Good Samaritan laws are key goals of the National Drug Control Strategy for mitigating opioid overdose (62) and are part of the recommendations from the American Medical Association and the Substance Abuse and Mental Health Services Administration (SAMHSA) Opioid Overdose Toolkit's Strategies to prevent overdose deaths (51,63).

Limitations

The findings reported here must be viewed with several limitations in mind. First, the majority of studies are retrospective descriptive analyses reporting on different US and non-US study populations and opioids. Studies were examined individually and presented under headings that group the information in an accessible way. No direct comparisons between studies were made. Second, there is a lack of universal terminology for describing an opioid overdose event which can be defined as a life-threatening adverse event from an opioid exposure (32), drug poisoning (64), toxicity (53), or life-threatening opioid-induced respiratory depression (65). In this systematic review, the term "opioid overdose" included any serious, life-threatening adverse event occurring in response to opioid exposure as manifested by central nervous system and/or respiratory depression.

Conclusion

Opioid overdose morbidity is significantly more prevalent than mortality, and sequelae of toxic events should be studied in more detail. Increased risk of morbidity occurs with: (i) increased opioid availability in the community, (ii) increased dosage, (iii) use of methadone, (iv) nonmedical use, dependence, and illicit drug use, (v) aberrant behaviors, (vi) past suicide attempt, (vii) decreased or lower tolerance, (viii) lack of education, (ix) middle age, (x) poverty, (xi) presence of mental health disorders, (xii) medical comorbidities, and (xiii) co-ingestants. Although abuse-deterrent formulations have been approved, there is no overdose-safe prescription opioid available to date. Opioid overdose morbidity and mortality is seen across the entire spectrum of patient use with significant numbers of adverse events occurring in population segments not identified by high risk indicators. Increased physician awareness of this epidemic as well as additional education on life-threatening opioid-induced respiratory depression that can occur in any patient using opioids as opposed to patients suspected of suffering from an opioid use disorder, as well as the availability of take-home naloxone could help mitigate the overdose epidemic while maintaining effective pain control for patients.

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