Prescription drug overdoses: A review

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Abstract

Problem. Overdoses involving prescription drugs in the United States have reached epidemic proportions over the past 20 years. Methods. This review categorizes and summarizes literature on the topic dating from the first published reports through 2011 using a traditional epidemiologic model of host, agent, and environment. Results. Host factors include male sex, middle age, non-Hispanic white race, low income, and mental health problems. Agent risk factors include use of opioid analgesics and benzodiazepines, high prescribed dosage for opioid analgesics, multiple prescriptions, and multiple prescribers. Environmental factors include rural residence and high community prescribing rates. Discussion. The epidemiology of prescription drug overdoses differs from the epidemiology of illicit drug overdoses. Incomplete understanding of prescription overdoses impedes prevention efforts. Summary. This epidemic demands additional attention from injury professionals.

1. Introduction

The year 1992 marked the nadir in unintentional injury mortality rates in the United States in the Twentieth Century (National Safety Council, 1999). The age-adjusted rate was 33.2 per 100,000 people in 1992. Rates began to increase in 1993 and reached a peak of 40.0 per 100,000 in 2007. Most of the increase in injury mortality since 1992 was because of an increase in unintentional poisoning mortality (Paulozzi, Ballesteros, & Stevens, 2006). The increase in poisoning death rates has been because of increasing drug overdose death rates. Drug overdose deaths now constitute 9 out of 10 poisoning deaths. Drug overdose and drug abuse are major, growing public health problems (Paulozzi, Jones, Mack, & Rudd, 2011).

Drug overdoses have historically not been seen as a public health problem. Instead, they have been viewed as a substance abuse or law enforcement issue (Paulozzi, 2007). This has changed in recent years as most drug overdoses have become associated with licit pharmaceuticals such as opioid analgesics and psychotherapeutic drugs. Overdoses can be viewed as a type of injury resulting from chemical energy and can be addressed by traditional approaches to injury prevention such as Haddon's matrix (Haddon, 1970). They can also be seen as classical epidemiologic concerns such as epidemics with risk factors associated with host, agent, and environment. This review will take this epidemiologic approach to prescription drug overdoses.

2. Time trends

The first report of an increase in drug poisoning mortality was made in 1998 by the National Center for Health Statistics (Fingerhut & Cox, 1998). It noted that poisoning mortality increased 25% from 1985 to 1995, with all of the increase associated with drugs. It indicated that “opiates” were a major contributor to the increase but could not distinguish between heroin and prescription opioids based on the coding scheme in use at the time. Beginning in 1999, deaths were coded by the new, Tenth Revision of the International Classification of Diseases, which allowed a distinction between licit and illicit opiates/opioids. Shortly thereafter, first reports of an increase in prescription opioid deaths were published by individual states, North Carolina and Maine (Sanford, 2002; Sorg & Greenwald, 2002). A later report on an increase in drug poisoning in 11 states noted that more deaths were due to prescription than illicit opioids such as heroin from 1999–2000 (Centers for Disease Control and Prevention [CDC], 2004).

National drug poisoning rates increased steadily after 1999 (Paulozzi, Budnitz, & Xi, 2006). Deaths rates from poisoning, and then drug poisoning, passed motor vehicle traffic crash mortality rates in 2008 and 2009 respectively (Fig. 1). The increase in drug poisoning has been driven by prescription drugs, especially prescription opioid analgesics, since at least 1999 (Fig. 2). The increase in health outcomes associated with prescription drugs has been associated with a dramatic increase in the use of such drugs (Gu, Dillon, & Burt, 2010). The increase in use of opioid analgesics has been uninterrupted since 1999 (Fig. 3).

Among emergency department (ED) visits involving drug misuse or abuse tracked by the Drug Abuse Warning Network, pharmaceuticals...
surpassed illicit drugs over the past decade. By 2009, there were roughly 1.1 million ED visits involving the nonmedical use of pharmaceuticals, including roughly 350,000 involving opioid analgesics (Office of Applied Studies Substance Abuse and Mental Health Services Administration, 2011) (Fig. 4).

3. Host factors

3.1. Demographics: sex, age, race, ethnicity, education/income

Sex has a complex relationship with the problem of drug overdoses. Among users of illicit drugs, more men than women die of overdoses (Paulozzi, Jones, et al., 2011) and are seen in EDs (Office of Applied Studies Substance Abuse and Mental Health Services Administration, 2011). More men go into substance abuse treatment, and more men self-report illicit drug use (Substance Abuse and Mental Health Services Administration, 2010b). For prescription drugs, however, although more men die of overdoses (Paulozzi, Jones, et al., 2011), rates of ED visits for nonmedical use are roughly equal (Office of Applied Studies Substance Abuse and Mental Health Services Administration, 2011). More men self-report nonmedical use (Substance Abuse and Mental Health Services Administration, 2010b), yet more women are prescribed drugs prone to abuse (Rao & Schappert, 2006; Simoni-Wastila, Ritter, & Strickler, 2004).

Generally, rates of fatal overdose are lower at the extremes of age, despite the fact the young children are experiencing increasing numbers of pharmaceutical exposures reported to poison centers (Bond, Woodward, & Ho, 2012). Fatal overdose rates are highest among people 45–54 years old, for both unintentional and suicidal overdoses and those of undetermined intent (Fig. 5). The age distribution varies somewhat by major type of drug (Fig. 6), with the highest rates for heroin deaths in the 25–34 years age group.

Rates of overdose by race and ethnicity vary by drug (Fig. 7). African Americans and Hispanics are less likely to be prescribed any drugs (Gu et al., 2010), including controlled prescription drugs (Centers for Disease Control and Prevention, 2006), and are less likely to report nonmedical use of prescription pain relievers (Substance Abuse and Mental Health Services Administration, 2011a). American Indians/Alaska Natives report the highest rates of nonmedical use of pain relievers. The relationship of overdose risk to socioeconomic status, income, or education is not well studied. People who are eligible for Medicaid are more likely to be prescribed opioid analgesics (Rao & Schappert, 2006) and more likely to experience prescription drug overdoses (Coolen, Best, Lima, Sabel, & Paulozzi, 2009). Oxycodone overdose death rates have been higher in lower income districts (Rintoul, Dobbin, Drummer, & Ozanne-Smith, 2011). Rates of ED visits for drug-related poisoning of any intent decrease steadily with increasing median household income in the patient zip code (Xiang, Zhao, Xiang, & Smith, 2011).

3.2. Clinical risk factors: chronic pain, mental health, substance abuse, obesity

Individuals who overdose on prescription drugs typically have a higher prevalence of medical conditions for which those drugs are prescribed. For example, 50–80% of people dying of prescription opioid poisoning use (Substance Abuse and Mental Health Services Administration, 2011). Rates of ED visits for drug-related poisoning of any intent decrease steadily with increasing median household income in the patient zip code (Xiang, Zhao, Xiang, & Smith, 2011).


Fig. 3. Opioid analgesic death rates and sales, U.S., 1999-2010. National Vital Statistics System (99-09); Automated Reports Consolidated Orders System (99-10); crude rates per 10,000 population for kilograms of OPR sold.

Fig. 4. Drug-related emergency department visits by type of visit, U.S., 2004-2009. Source: Drug Abuse Warning Network.
Opioid analgesics are derivatives of opium, or synthetic drugs with similar properties, that possess the ability to reduce pain. Although opioids have a powerful analgesic effect, the body becomes adapted to them and the person using them becomes physically dependent on them. Some opioids, especially methadone and buprenorphine, are also used medically in replacement therapy for people who have become dependent on heroin or other opioid analgesics.

The opioid analgesic morphine is roughly equivalent to heroin in its affinity for the pain receptors in the brain. Opioid analgesics as strong as or stronger than morphine currently available in the United States include buprenorphine, butorphanol, fentanyl, hydrocodone, hydromorphone, oxycodone, oxymorphone, tapentadol, and levorphanol. Weaker opioids include codeine, meperidine, pentazocine, and tramadol. Most opioids are short-acting, requiring dosing every 3–4 hours. Some short-acting opioids formulated in special ways to extend their release time ("extended-release opioids") became available in the 1990s (e.g., fentanyl patches in 1992 and OxyContin® in 1996). Methadone is the only opioid

not more likely to be treated for that pain with opioid analgesics (Toblin, Mack, Perveen, & Paulozzi, 2011). They are also more likely to have psychiatric problems (Simon et al., 2006). In addition, both obesity and chronic opioid use are risk factors for sleep apnea (Epstein et al., 2009; Webster et al., 2011), so they might have an additive effect.

4. Agent (drug) factors

4.1. Prescription drugs in general

Prescription drugs as a group offer advantages to people using drugs for nonmedical reasons over street drugs such as heroin or cocaine. Users can be reasonably certain that they do not contain contaminants. Their strength is assured because of the oversight on the manufacturing process, thus lessening the risk of taking more than or purchasing less than the expected amount. In contrast, the purity of heroin purchased on the street is highly variable. Prescription drugs offer a wide but well-documented variety of effects on mood and awareness, which cannot be said for various forms of designer drugs. They also have the advantage of greater legal and social acceptability. Possession alone is not a crime as long as prescription drugs are obtained by prescription, and they can be readily obtained without having to interact with criminals selling street drugs (Inciardi, Surratt, Kurtz, & Cicero, 2007).

4.2. Opioid analgesics

Opioid analgesics have increased risk of fatal overdoses (Degenhardt et al., 2010). It might also be because people who are abusing opioids often prefer to combine them with benzodiazepines to moderate or enhance the desired effects of the opioids.

People who are regular or dependent users of heroin and other opioids have increased risk of fatal overdoses (Degenhardt et al., 2010). Conversely, people who are just finishing substance abuse treatment or being released from incarceration are at increased risk of overdose. This increased risk might be because they have lost their tolerance for their usual doses, at least judging from the heroin literature (Warner-Smith, Darke, Lynskey, & Hall, 2001).

One study has suggested that people who die of overdoses are more likely to be obese (Centers for Disease Control and Prevention, 2005). Obese people are more likely to report chronic pain but are more likely to be obese (Centers for Disease Control and Prevention, 2005). Obese people are more likely to report chronic pain but are more likely to be treated for that pain with opioid analgesics (Toblin, Mack, Perveen, & Paulozzi, 2011). They are also more likely to have psychiatric problems (Simon et al., 2006). In addition, both obesity and chronic opioid use are risk factors for sleep apnea (Epstein et al., 2009; Webster et al., 2011), so they might have an additive effect.
that is intrinsically long-acting, requiring dosing only two or three times a day for pain (Smith, 2008).

All opioid analgesics have a depressant effect on respiration and have been associated with some overdose deaths and ED visits. However, the most recent information indicates that oxycodone, methadone, and hydrocodone are found most commonly among such health outcomes. Increased risk for adverse outcomes per prescription or per morphine milligram equivalent has been found for opioids stronger than morphine. Increased risk is also associated with the extended-release forms compared with their immediate-release versions. Evidence for this is based on reports of key informants (Cicero, Inciardi, & Munoz, 2005; Cicero, Surratt, Inciardi, & Munoz, 2007), admissions to treatment for abuse of OxyContin® (Hays, Kirsh, & Passik, 2003), emergency department visit rates (Braden et al., 2010; Dormitzer, 2008), and overdose death proportions and rates (Dhala et al., 2009; Paulozzi, Kilbourne, et al., 2012; U.S. Department of Justice, 2002). Methadone is both stronger than morphine and has a particularly long and variable half-life. It also has potentially dangerous interactions with benzodiazepines and is therefore considered among the most risky of opioid analgesics (Cicero et al., 2007; Webster et al., 2011).

4.3. Benzodiazepines

Benzodiazepines such as valium and alprazolam are drugs used primarily for the relief of anxiety. They have been available for at least 50 years, but their use has increased markedly over the past 15 years (Belouin, Reuter, Borders-Hemphill, & Mehta, 2008). Their long-term use can result in physical dependence, and they are frequently abused (Substance Abuse and Mental Health Services Administration, 2010a). Like opioids, they have a depressant effect on the central nervous system and therefore can cause respiratory depression at high doses. They are frequently found in combination with opioid analgesics in postmortem toxicology, but they rarely are identified as the only drug involved (Hall et al., 2008).

4.4. Other types of prescription drugs

Muscle relaxants such as carisoprodol are prescribed with increasing frequency, often in concert with other drugs in the treatment of musculoskeletal pain such as back pain. Carisoprodol is frequently associated with abuse and adverse health outcomes (Forrester, 2011; Owens et al., 2007) and as a result was added to the list of controlled substances by the Drug Enforcement Administration in 2011. Sleep aids, e.g., zolpidem (Ambien®) are a fourth category of prescription drugs prone to abuse and diversion (Hajak, Muller, Wittchen, Pittrow, & Kirch, 2003) and are frequently involved in drug-related deaths (Florida Department of Law Enforcement, 2010).

4.5. Route of administration

Studies of people who use heroin suggest that injection of the drug is a risk factor for overdose compared with sniffing or smoking (Brugal et al., 2002). Most prescription opioids have good oral absorption (Smith, 2008) and are taken orally during nonmedical use, although almost all can be crushed for snorting or dissolved for injection. For example, among people reporting nonmedical use of OxyContin® in the past month, only 27% reported ever using a needle to inject any drug (Purdue Pharma, 2008). This is in contrast to heroin, which has poor oral absorption, making injection a more cost-effective option. Nonetheless, a substantial minority of prescription overdose deaths involve nonmedial routes of use (Hall et al., 2008), and heavier users might be more likely to use nonmedical routes of administration than the average nonmedical user. One third of people entering treatment for non-heroin opioid abuse, for example, report smoking, inhalation, or injection of drugs (Substance Abuse and Mental Health Services Administration, 2011b).

4.6. Sources

The providers of prescription drugs used in overdoses and in nonmedical use are a mix of medical and nonmedical sources. Among nonmedical users of opioid analgesics aged 12 or greater, most report getting them for free from a friend or relative; few bought from a dealer. However, most of the friends or relatives got them from a single doctor (Substance Abuse and Mental Health Services Administration, 2011a). Among high-risk individuals entering methadone treatment, the most common source is a dealer (Parrino, 2011). Among people dying of prescription overdoses, half or more obtained one or more drugs without a prescription (Hall et al., 2008; Lanier, 2010; Whitmire & Adams, 2010). Among young children with exposures to opioids reported to poison centers, most find a discarded pill or an open container left by someone in their home (Bailey, Campagna, & Dart, 2009).

4.7. Dose, duration, overlap

Significant positive associations have been noted between risk of overdose and daily prescribed dosage of opioid analgesics (Bohnert et al., 2011; Dunn et al., 2010; Paulozzi, Kilbourne, et al., 2012). Similar associations with overdose risk have been found with the number of prescriptions for opioids or controlled substances and the number of days prescribed (Paulozzi, Kilbourne, et al., 2012). Multiple sources in terms of different prescribers and different pharmacies are also markers of increased risk. Combinations of opioids and benzodiazepines are also associated with risk (Dunn et al., 2010).

5. Environmental factors

5.1. Place of death

According to death certificates, just over half of drug overdose deaths occur at home, roughly a quarter occur in a medical facility, and about one in six occur in some other known location (Table 1). However, the place of death varies by the type of drug involved, with death involving illicit drugs such as heroin and cocaine occurring more often in nonresidential, nonmedical locations and people dying of those drugs being more likely to make it to a medical facility before dying. This suggests that overdoses from illicit drugs might be more likely to occur in public places or in the presence of witnesses who can get emergency medical care for the patient.

Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical facility</th>
<th>Home</th>
<th>Hospice/nursing home</th>
<th>Other</th>
<th>Unknown</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>28.2</td>
<td>42.7</td>
<td>0.4</td>
<td>26.7</td>
<td>2.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Heroin</td>
<td>21.9</td>
<td>45.0</td>
<td>0.3</td>
<td>32.3</td>
<td>0.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Other opioid</td>
<td>19.1</td>
<td>59.3</td>
<td>0.5</td>
<td>19.6</td>
<td>1.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Methadone</td>
<td>19.3</td>
<td>57.3</td>
<td>0.5</td>
<td>20.9</td>
<td>1.9</td>
<td>100.0</td>
</tr>
<tr>
<td>Other synthetic narcotic</td>
<td>18.5</td>
<td>62.8</td>
<td>0.5</td>
<td>16.6</td>
<td>1.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>20.9</td>
<td>57.5</td>
<td>0.6</td>
<td>19.3</td>
<td>1.6</td>
<td>100.0</td>
</tr>
<tr>
<td>All Drugs</td>
<td>24.2</td>
<td>53.1</td>
<td>0.7</td>
<td>20.1</td>
<td>1.9</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Note: Deaths might involve more than one drug type, so some deaths might be in more than one column. Drug overdose deaths are defined by ICD-10 codes: X40-44, X60-64, and Y10-14. “Other opioid” deaths are those with the ICD-10 code T40.2, which includes opioids such as oxycodone, hydrocodone, and morphine. Methadone deaths are coded with T40.3. Other synthetic narcotic deaths are assigned the code T40.4 and included drugs such as fentanyl.
5.2. Rural–urban residence

Overdose rates also vary by urban–rural county type based on data from death certificates. When the analysis is restricted to the white population in 16 states with centralized medical examiner systems—to avoid confounding by death certification process and race–noncore nonmetropolitan counties had the highest opioid analgesic overdose death rates in 2008 (Fig. 8). In contrast, the highest death rates for heroin occurred in large central metropolitan counties. Similarly, pharmaceutical deaths occurred at higher rates in more rural counties of West Virginia (Hall et al., 2008). Oxycodone deaths are over-represented in rural areas of Victoria, Australia (Rintoul et al., 2011). Rates for ED visits related to poisoning from any drug were 179–233/100,000 in metropolitan/micropolitan counties versus 684/100,000 in other counties (Xiang et al., 2011). Prescription abuse is most common in rural and small urban communities (Cicero et al., 2007).

5.3. Other geographic factors

Aside from urban–rural character of place of residence, other poorly defined factors related to place of residence appear to be risk factors. For example, some rural states such as North Dakota have overall low drug overdose death rates, while others such as West Virginia have among the highest of rates. This might be related to differences in income levels between states, with poorer states having greater mortality increases in recent years (Paulozzi, Jones, et al., 2011). Differences in rates of drug distribution and drug marketing practices have been offered as alternative explanations (Paulozzi, Jones, et al., 2011; Paulozzi & Ryan, 2006; VanZee, 2009).

6. Limitations of data

6.1. Reporting bias

Because prescription drug overdoses are stigmatized and might involve legal liability, family members and health care providers might be inclined to attribute them to other problems when a death occurs (Shai, 1994). Individuals experiencing nonfatal overdoses also might be less likely to seek care because they expect disapproval or legal consequences. Therefore, fatal and nonfatal overdose rates are probably underestimates, especially in comparison to mechanisms of injury that are public and difficult to conceal, such as motor vehicle crashes.

6.2. Incomplete information and lack of detail

Drug overdose data are frequently nonspecific, even within medical records (Pollack, Holmgreen, Lui, & Kirk, 1991). Patients might not know which drugs they took; toxicology testing might only indicate broad drug categories. Administrative records might not capture all the detail in medical records. Coding of data on such records often lumps drugs into broad categories (Fingerhut & Cox, 1998). Health care providers frequently miss the signs of drug abuse or fail to record them in medical records (Katz et al., 2003).

6.3. Timeliness

National mortality data on drug overdoses is becoming timelier but is still roughly two years behind events. In general, the smaller the jurisdiction, the more timely is the information. For example, state mortality data are typically available a year earlier than national mortality data.

6.4. Populations at risk

Assessments of overdose risk by demographic or clinical variables ideally use measures of exposure to the drugs as denominators rather than general population counts (Dasgupta et al., 2006). However, exposure-based measures are difficult to obtain. Even insurance claims do not capture all persons using prescription drugs without a prescription or all persons who paid cash for their drugs.

7. Discussion

Available literature indicates that the epidemiology of prescription drug overdoses, summarized in Table 2, differs from the epidemiology of illicit drug overdoses. In particular, prescription overdoses appear to have the greatest impact on non-Hispanic white populations in rural areas, and appear to be obtained far more often from friends or relatives than from strangers such as drug dealers. The availability of prescription drugs from pharmacies located in close proximity to end users in even the smallest of communities and the widespread use of prescription drugs for medical purposes are important factors that distinguish prescription from illicit drugs and shape the patterns of nonmedical usage of prescription drugs in fundamental ways.

Literature on prescription drug overdoses is accumulating rapidly. Nonetheless, important gaps in research exist. Very little good research is available to quantify the benefits of use of the prescription drugs involved in overdoses (Ballantyne & Shin, 2008). Therefore, clinicians have difficulties weighing the risks of use of drugs such as opioid pain relievers against their benefits. In addition, little research exists on the impact of interventions being made to address this problem. Because of the recent emergence of the problem and the absence of systematic evaluation of the effects of intervention efforts, the data available are insufficient to make firm recommendations about effective strategies.
problems with accurate information on the problem identified above, much less is known about both risk factors and prevention measures compared with other prominent injury mechanisms such as motor vehicle crashes. Adding to the body of literature regarding prescription drug overdoses is critically important, however, given the epidemic nature of the problem.

The challenge for the next 20 years will be developing a better way to anticipate the potential social costs from new or expanded applications for pharmaceuticals prone to abuse, because pharmaceuticals are likely to continue to be a more important cause of overdose than illicit drugs. The current system of testing pharmaceuticals in clinical trials, which excludes people with substance abuse or other mental health problems and closely monitors the use of a drug, cannot accurately predict the consequences in a nonexperimental setting. A more realistic test, perhaps involving a community trial, must be developed. In addition, we need to develop more timely ways to detect problems resulting from the misuse of pharmaceuticals shortly after their marketing. These tasks will be an important part of the work of clinical and public health experts in the interface between pharmacoepidemiology and injury prevention.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry.

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