A History of Being Prescribed Controlled Substances and Risk of Drug Overdose Death

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Abstract

Objective. The abuse of prescription drugs has increased dramatically since 1990. Persons who overdose on such drugs frequently consume large doses and visit multiple providers. The risk of fatal overdose for different patterns of use of opioid analgesics and sedative/hypnotics has not been fully quantified.

Design. Matched case-control study. Cases were 300 persons who died of unintentional drug overdoses in New Mexico during 2006–2008, and controls were 5,993 patients identified through the state prescription monitoring program with matching 6-month exposure periods.

Outcome Measures. Death from drug overdose or death from opioid overdose. Exposures were demographic variables and characteristics of prescription history. Crude and adjusted odds ratios (AOR) were calculated.

Results. Increased risk was associated with male sex (AOR 2.4, 95% confidence interval [CI] 1.8–3.1), one or more sedative/hypnotic prescriptions (AOR 3.0, CI 2.2–4.2), greater age (AOR 1.3, CI 1.2–1.4 for each 10-year increment), number of prescriptions.
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(AOR 1.1, CI 1.1–1.1 for each additional prescription), and a prescription for buprenorphine (AOR 9.5, CI 3.0–30.0), fentanyl (AOR 3.5, CI 1.7–7.0), hydromorphone (AOR 3.3, CI 1.4–7.5), methadone (AOR 4.9, CI 2.5–9.6), or oxycodone (AOR 1.9, CI 1.4–2.6). Patients receiving a daily average of >40 morphine milligram equivalents had an OR of 12.2 (CI 9.2–16.0).

Conclusions. Patients being prescribed opioid analgesics frequently or at high dosage face a substantial overdose risk. Prescription monitoring programs might be the best way for prescribers to know their patients’ prescription histories and accurately assess overdose risk.

Key Words. Opioid; Analgesic; Prescriptions; Abuse; Safety; Pain Management

Introduction

The rate of death from drug overdose in the United States has more than doubled since 1999 [1] impelled largely by an increase in overdoses involving prescribed controlled substances, especially opioid analgesics and sedative/hypnotics [2–8]. Morbidity has increased along with mortality: the number of people sent to the emergency department because of the nonmedical use of opioid analgesics or benzodiazepines roughly doubled between 2004 and 2008 [9].

Medical examiners who investigate such pharmaceutical deaths suggest that most involve drug diversion and/or drug abuse [5,10–12]. A study in West Virginia showed a large role for prescription drug abuse: 63% of people dying from pharmaceutical overdoses had taken one or more drugs for which they did not have a prescription; 21% had prescriptions for controlled substances from five or more physicians in the year prior to death; and 16% also had illicit drugs such as heroin and cocaine contributing to their deaths [10].

Despite the continuation of an epidemic of drug overdoses for more than a decade, researchers know little about how people treated with controlled substances and dying from an overdose are different from other patients treated with similar drugs. One study based on electronic medical records shows that patients receiving 100 or more morphine milligram equivalents (MME) per day face an 8.9-fold (95% confidence interval [CI] 4.0–19.7) increase in overdose risk compared with patients being treated at lower dosages and had an annual overdose rate of 1.8% [13]. A second study of people on chronic opioid therapy showed greater risk of adverse drug events such as overdoses with higher dosage and more days of supply of opioids [14]. A study of 15- to 24-year-olds in Australia illustrates that the numbers of prescriptions for abusable drugs and doctor visits in the year prior to death can predict risk of an overdose from an illicit drug [15].

Providers are now increasingly being warned about the hazards of prescribing controlled substances, especially opioid analgesics, and are cautioned about overestimating their benefits [16–18]. Without better risk information, however, providers have difficulty identifying the highest-risk patients and making risk–benefit calculations when prescribing such drugs. Similarly, health plan managers, prescription drug monitoring programs, and insurers do not have validated “flags” to identify patients who are at high risk of serious outcomes such as overdoses and therefore might benefit from special interventions such as management by a pain specialist, restriction to single providers, and/or referral to substance abuse treatment.

For this study, our goal was to identify characteristics of treatment with controlled substances that were associated with fatal overdoses in the patient population. We also separately examined such characteristics among patients dying from overdoses involving opioid analgesics.

Methods

The study design was a matched, case-control comparison. We defined a case patient as a resident of New Mexico more than 10 years old who died of an unintentional drug overdose in New Mexico between October 1, 2006 and March 31, 2008 and had at least one record in the New Mexico Prescription Monitoring Program (PMP) within the 6 months prior to death. The New Mexico Office of the Medical Investigator (OMI), the state’s centralized medical examiner agency, identified case patients. The OMI is authorized to investigate unnatural deaths in New Mexico and is contracted to investigate many such deaths occurring in tribal jurisdictions within the state. OMI forensic pathologists determine whether a death is due to a drug overdose based on the circumstances of the death, the death scene, medical records, an autopsy, and quantitative toxicologic evaluation. Drug overdoses include those due to licit and illicit drugs, either alone or in combination with alcohol. In a subset analysis focusing on deaths caused at least in part by prescription opioids, cases were restricted to those dying of overdoses of non-heroin opioids, alone or in combination with other drugs. During the study period, the OMI routinely tested suspected drug overdose deaths with an opioid panel that included codeine, dihydrocodeine, hydrocodone, hydro- morphine, methadone, morphine, oxycodone, and oxymorphone. Buprenorphine and fentanyl could be analyzed by special request. Where morphine was the only opioid listed as a cause of death, the death was excluded from the subset analysis of opioid deaths because the morphine might have been a metabolite of heroin.

The New Mexico PMP collects information on all prescriptions dispensed in the state for drugs in Schedules II, III, or IV and carisoprodol using proprietary software (Optimum Technologies, Columbus, OH, USA). The PMP does not capture methadone doses dispensed in opiate treatment programs or prescriptions filled in other states. It also does not require reporting from military, Veterans Administration, or Indian Health Service facilities or in-clinic dispensing. However, the PMP does capture prescriptions from mail-order pharmacies for New Mexico residents. Data
routinely collected by the PMP were retasked for this study. We used 2 years of PMP data from April 1, 2006 through March 31, 2008 to analyze at least 6 months of prescription records prior to the earliest date of death. The prescription records provided the patient’s sex and age and identifiers for patients, prescribers, and dispensers. Prescription records also included details about the drug prescribed: the National Drug Code [19], which encoded the drug name, strength, dosage form, and formulation; the quantity and number of days supplied; and the date filled.

To ensure complete prescription histories for this study, we first identified all prescriptions dispensed to each patient in the PMP database using The Link King, version 6.4 (Camelot Consulting, Olympia, WA, USA), a public-domain, combined deterministic and probabilistic linkage software package (http://www.the-link-king.com) [20]. We excluded names that appeared to apply to health care facilities or animals. We used name, sex, date of birth, and street address as recorded on the prescriptions for the linkage. Visual review of a sample of 475 records by a linkage epidemiologist indicated that false-positive linkages by this method were minimal (<3%), so all linkages were included.

We next used the same variables to link the case persons to their PMP records. Finally, for each case, we randomly selected 20 controls from all New Mexico residents more than 10 years old in the PMP file with at least one prescription during the 6 months prior to the date of death of the matched case (the “reference date”). No other matching variables were employed. Twenty controls were used to avoid small cell sizes for rare exposures among controls. We excluded controls with missing age.

We selected exposure variables from previous work identifying risk factors associated with diagnoses of opioid abuse [21,22] or risk factors generally thought to indicate inappropriate use of controlled substances [23–26]. Exposure variables included sex and age and the numbers of prescriptions, prescribers, and pharmacies. Refills were counted as separate prescriptions. We also examined a history of any prescriptions for six categories of controlled substances: opioid analgesics, sedatives/hypnotics, stimulants, anabolic steroids, cannabinoids, and mixed-substances: opioid analgesics, sedatives/hypnotics, and antagonists (whether or not the drug also had agonist activity). The sedative/hypnotic category included nonopioid depressants, such as benzodiazepines, barbiturates, and carisoprodol.

We focused additional attention on opioids and sedative/hypnotics because of their frequent involvement in drug overdose deaths. We examined the number of opioid analgesic and sedative/hypnotic prescriptions, a history of overlapping opioid or sedative prescriptions, and a history of any one of 15 base opioid compounds (including tramadol). We defined overlapping prescriptions as those in the same category of drug that overlapped by 25% or more of the days prescribed [26]. Finally, we calculated the dosage of opioid prescribed in MME per day [27] in three different ways. The single peak dosage was the highest amount per day in any single opioid prescription. The total peak dosage was the highest dosage per day at any time during the exposure period after summing dosages from all overlapping opioid prescriptions. The average dosage was the average daily opioid dosage during the entire study period from all opioid prescriptions combined. For regression analysis, we categorized each measure of daily dosage into 0–40, >40–120, and >120 MME/day.

In preliminary analysis, we noted strong correlations both among the variables for total numbers of prescriptions, prescribers, and pharmacies, and measurements of daily opioid dosage, and among the variables for the extent of sedative/hypnotic use. Therefore, to minimize the problems of collinearity and multi-collinearity, we began the multiple regression model with the variables with the strongest association with the outcome as measured by the likelihood ratio chi-square statistic: total number of prescriptions and having at least one sedative prescription. Associations between death from unintentional drug overdose and the exposures were expressed as crude odds ratio (OR) and as adjusted odds ratio (AOR) generated by conditional logistic regression for matched sets (SAS PROC PHREG, SAS Institute, Inc., Cary, NC, USA). The referent group for each OR was patients without the indicated exposure.

The New Mexico State University Institutional Review Board and the New Mexico Board of Pharmacy approved this study. Access to personal identifiers in PMP data was restricted to one of the authors (NS) and a linkage epidemiologist contracted by the New Mexico Department of Health.

The Centers for Disease Control and Prevention and the New Mexico Department of Health funded the study.

Results

During the 18-month study period, 300 deaths meeting the case definition occurred among 730,381 patients in the PMP—27.4 per 100,000 patients per year. Among these patients, we identified 5,993 matched controls (after excluding seven with missing age).

Among case patients, 58.0% were men, 95.7% were white, 43.3% were Hispanic, and 93.7% were between 21 and 60 years of age. People 41–60 years of age represented 59.4% of case patients and 37.9% of control patients, whereas people more than age 60 represented 5.6% of case patients and 26.4% of control patients. Persons under age 21 were similarly under-represented among the cases (Table 1). In the crude OR, risk of overdose death was associated with younger age, although the highest age-specific OR (not shown) were among the middle-aged (Table 2). The nonlinear relationship with age required adding a quadratic term, age-squared, to the model.
The association between risk and the continuous variables of number of prescriptions, prescribers, and opioid daily dose was graded, but risk leveled off at the highest levels (Figures 1–3). Six controlled substance prescriptions during 6 months quadrupled the risk of overdose deaths (Figure 1). The ORs for single peak prescriptions did not increase until dosage exceeded 20 MME/day (Figure 2). The ORs increased thereafter and tended to level off above 200 MME/day no matter which method of calculation of daily dose was used. Among cases prescribed opioids, 34.2% had average daily dosages above 60 MME/day; 23.6% had dosages above 120 MME/day, and 17.3% had dosages above 200 MME/day. The corresponding figures for controls were 4.4%, 3.0%, and 2.1%. Finally, risk increased as soon as patients exceeded a single prescriber (Figure 3). Among case patients, 66.3% had seen two or more prescribers; 43.0% had seen three or more; and 13.7% had seen six or more. The corresponding figures for controls were 28.3%, 9.3%, and 0.6%.

Among the 300 deaths, 119 qualified for the secondary analysis of deaths caused by opioids, excluding those attributed to morphine, which might have been a metabolite of heroin. The variables associated with the unadjusted risk of an opioid-related overdose death were similar to those in the primary analysis (data not shown). In the adjusted subset analysis, the risks for specific opioids were generally higher than those in the final model of the primary analysis. Buprenorphine, in contrast, was no longer a significant contributor to the model.

Having at least one prescription for a sedative/hypnotic was a stronger risk factor than having an opioid prescription. Overlapping opioid or sedative/hypnotic prescriptions were strongly associated with risk. Risk of overdose death increased with the number of prescriptions, prescribers, and pharmacies. When compared with persons with lower opioid dosages or no opioid prescriptions, risk was greater at daily opioid dosages above 40 MME, especially for average daily dosages at this level. The OR for an average daily dose of more than 40 MME/day was 12.2 (95% CI 9.2–16.0). Risk was not significantly increased for any of the opioids weaker than morphine (codeine, meperidine, or propoxyphene). Other opioids at least as strong as morphine (buprenorphine, methadone, hydromorphone, fentanyl, morphine, oxycodone, and hydrocodone) all had significant associated risk. Other variables not significantly associated with increased or decreased risk of overdose death (not shown) were having a prescription for the less-frequently prescribed opioids butorphanol, dihydrocodeine, oxymorphone, pentazocine, or tramadol, or having a prescription for any stimulant, cannabinoid, anabolic steroid, or mixed-type drug.

In the AOR, male sex, age and age-squared, and the number of prescriptions remained significant, as did a history of most of the stronger opioids and of a sedative/hypnotic prescription.

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Among the 300 deaths, 119 qualified for the secondary analysis of deaths caused by opioids, excluding those attributed to morphine, which might have been a metabolite of heroin. The variables associated with the unadjusted risk of an opioid-related overdose death were similar to those in the primary analysis (data not shown). In the adjusted subset analysis, the risks for specific opioids were generally higher than those in the final model of the primary analysis. Buprenorphine, in contrast, was no longer a significant contributor to the model.

Much of the population of New Mexico more than 10 years of age, approximately 44%, filled a prescription for a controlled substance in Schedules II–IV during the study period. In the crude analysis, males, middle-aged people, and those who were prescribed either an opioid or a sedative were at increased risk of overdose death, and risk was higher for some opioids than others. Increasing numbers of prescriptions, prescribers, and pharmacies were all associated with higher risk. Risk did not increase further with additional prescriptions, providers, or higher dosages once certain thresholds were reached. Overlapping prescriptions and high daily dosages, markers of potential misuse of controlled substances, were strongly associated with risk of overdose death. We found similar results in the subset with opioid analgesics contributing to death, suggesting that these behaviors were risk factors for overdose irrespective of the type of drugs involved in death.

The findings highlight demographic differences between the prevalence of use of scheduled prescription drugs and the risk of drug overdose. Men are consistently less likely to be prescribed opioid analgesics and benzodiazepines than women [5,28–30], as was seen in the low percentage of men among controls; however, men are more likely to die of prescription drug overdose [3,10]. Both opioid and sedative use increases with age over the lifespan [28,30,31], but people older than age 60 were underrepresented among cases in this study.
This study shows that receiving multiple prescriptions and the behaviors correlated with such a history, such as using multiple prescribers and pharmacies, are markers of overdose risk [15,32] as well as potentially markers of suboptimal medical care [26]. These results are consistent with a study from Maine that showed an increased risk of opioid dependence, abuse, or overdose among persons receiving multiple prescriptions, having multiple prescribers, or using multiple pharmacies [21]. The prevalence of using many providers was relatively low among controls in this study, consistent with a report from Massachusetts researchers, who found that <1% of patients prescribed Schedule II drugs had seen six or more providers or had been to six or more pharmacies within 1 year [24]. This study shows that risk begins to increase, however, even with two prescriptions, providers, or pharmacies within 6 months.

### Table 2  Risk of unintentional drug overdose death by patient risk factors, New Mexico, October 2006–March 2008

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Case Deaths (N = 300)</th>
<th>Control Patients (N = 5,993)</th>
<th>Crude OR (95% CI)</th>
<th>AOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>174 58.0</td>
<td>2,438 40.7</td>
<td>2.0 1.6–2.5</td>
<td>2.4 1.8–3.1</td>
</tr>
<tr>
<td>Prescription history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One or more opioid prescription</td>
<td>257 85.7</td>
<td>4,425 73.8</td>
<td>2.1 1.5–2.9</td>
<td></td>
</tr>
<tr>
<td>Overlapping opioid prescriptions</td>
<td>89 29.7</td>
<td>211 3.5</td>
<td>11.7 8.8–15.7</td>
<td></td>
</tr>
<tr>
<td>One or more sedative prescription</td>
<td>225 75.0</td>
<td>2,281 38.1</td>
<td>4.9 3.7–6.4</td>
<td></td>
</tr>
<tr>
<td>Overlapping sedative prescriptions</td>
<td>85 28.3</td>
<td>212 3.5</td>
<td>11.0 8.2–14.7</td>
<td></td>
</tr>
<tr>
<td>Opioid daily dosage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single peak &gt;40 MME</td>
<td>164 54.7</td>
<td>1,596 26.6</td>
<td>3.3 2.6–4.1</td>
<td></td>
</tr>
<tr>
<td>Single peak &gt;120 MME</td>
<td>89 29.7</td>
<td>310 5.2</td>
<td>7.6 5.8–10.0</td>
<td></td>
</tr>
<tr>
<td>True peak &gt;40 MME</td>
<td>196 65.3</td>
<td>1,800 30.0</td>
<td>4.3 3.4–5.5</td>
<td></td>
</tr>
<tr>
<td>True peak &gt;120 MME</td>
<td>109 36.3</td>
<td>381 6.4</td>
<td>8.4 6.5–10.8</td>
<td></td>
</tr>
<tr>
<td>Average &gt;40 MME</td>
<td>103 34.3</td>
<td>255 4.3</td>
<td>12.2 9.2–16.0</td>
<td></td>
</tr>
<tr>
<td>Average &gt;120 MME</td>
<td>60 20.0</td>
<td>128 2.1</td>
<td>11.3 8.1–15.8</td>
<td></td>
</tr>
<tr>
<td>Type of opioid prescribed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>9 3.0</td>
<td>9 0.2</td>
<td>21.5 8.3–56.0</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>14 4.7</td>
<td>455 7.6</td>
<td>0.6 0.3–1.0</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>25 8.3</td>
<td>72 1.2</td>
<td>7.7 4.8–12.4</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>163 54.3</td>
<td>2,797 46.7</td>
<td>1.4 1.1–1.7</td>
<td></td>
</tr>
<tr>
<td>Hydromorphine</td>
<td>15 5.0</td>
<td>26 0.4</td>
<td>11.8 6.2–22.3</td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>4 1.3</td>
<td>73 1.2</td>
<td>1.1 0.4–3.0</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>22 7.3</td>
<td>34 0.6</td>
<td>13.4 7.8–23.0</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>35 11.7</td>
<td>129 2.2</td>
<td>6.1 4.1–9.0</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>145 48.3</td>
<td>1,345 22.4</td>
<td>3.2 2.5–4.1</td>
<td></td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>32 10.7</td>
<td>478 8.0</td>
<td>1.4 0.9–2.0</td>
<td></td>
</tr>
<tr>
<td>Continuous Variables</td>
<td>Case Mean</td>
<td>Case Median</td>
<td>Control Mean</td>
<td>Control Median</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>44.3 45.5</td>
<td>48.2 48</td>
<td>0.9 0.8–1.0</td>
<td>1.3 1.2–1.4</td>
</tr>
<tr>
<td>Age-squared (years^2)</td>
<td>2,088.5 2,701</td>
<td>2,692.9 2,304</td>
<td>1.0 1.0–1.0</td>
<td>1.0 1.0–1.0</td>
</tr>
<tr>
<td>No. of prescriptions†</td>
<td>13.3 10</td>
<td>3.5 2</td>
<td>1.1 1.1–1.2</td>
<td>1.1 1.1–1.1</td>
</tr>
<tr>
<td>No. of opioid prescriptions†</td>
<td>6.8 5</td>
<td>2.0 1</td>
<td>1.2 1.2–1.2</td>
<td></td>
</tr>
<tr>
<td>No. of sedative prescriptions†</td>
<td>6.0 4</td>
<td>1.3 0</td>
<td>1.2 1.2–1.3</td>
<td></td>
</tr>
<tr>
<td>No. of prescribers†</td>
<td>3.0 2</td>
<td>1.4 1</td>
<td>1.7 1.6–1.9</td>
<td></td>
</tr>
<tr>
<td>No. of pharmacies†</td>
<td>2.4 2</td>
<td>1.2 1</td>
<td>2.3 2.0–2.5</td>
<td></td>
</tr>
<tr>
<td>Single peak opioid dose (mg MME)*</td>
<td>924.2 49.6</td>
<td>55.5 25.0</td>
<td>1.0 1.0–1.0</td>
<td></td>
</tr>
<tr>
<td>True peak opioid dose (mg MME)*</td>
<td>1,086.1 67.5</td>
<td>73.4 26.7</td>
<td>1.0 1.0–1.0</td>
<td></td>
</tr>
<tr>
<td>Average opioid dose (mg MME)*</td>
<td>214.1 12.0</td>
<td>12.9 0.7</td>
<td>1.0 1.0–1.0</td>
<td></td>
</tr>
</tbody>
</table>

* Odds ratio represents an increase of 10 units, e.g., 10 years of age or 10 mg MME.
† Odds ratio represents an increase of one unit, e.g., one more prescription or one more prescriber in the previous 6 months.
MME = morphine milligram equivalents; OR = odds ratio; CI = confidence interval; AOR = adjusted odds ratio.
The strongest association was with number of pharmacies, suggesting that some people might have legitimate reasons for having multiple prescribers or prescriptions, whereas multiple pharmacies might be more often an attempt to conceal drug misuse. The fact that risk levels off at the highest levels of prescriptions and providers suggests that some of these patients might be selling rather than consuming all the drugs they receive. Although some patients might not be taking all the drugs they are prescribed, the high risk associated with relatively large daily doses of opioids is consistent with the daily dosages recorded for overdose decedents or reported by people in treatment for opioid abuse. In Washington State, for example, patients with fatal overdoses had been prescribed a mean daily dose in morphine equivalents of greater than 180 mg [33]. People entering drug abuse treatment in a clinic in Kentucky consumed a mean dose of 181 mg of OxyContin (Purdue Pharma L.P., Stamford, CT, USA) per day [34].

The increased risk found in this study for persons receiving more than 20 MME/day at any one time is similarly consistent with another study. That study reported a small, nonsignificant increase in risk of serious overdose events with dosages from 20 to 49 MME/day, and a moderate, significant risk increase with dosages from 50 to 99 MME/day when compared with dosages <20 MME/day [13]. Other studies have also reported an association between high opioid dosage and risk of overdose [14,35,36]. Interestingly, in one early report, Portenoy in 1986 argued that the chronic use of opioids for noncancer pain was safe [37]. These claims were based at least in part on the experience of patients with a median daily dose less than 20 MME. Therefore, having a single prescription with daily dosages less than 20 MME for an adult probably does not, on average, correspond to a significant risk of drug overdose by itself. This would not be true if the patient was using multiple opioid prescriptions or combining opioids with sedative/hypnotics. At the other extreme, a single prescription for more than 120 MME/day does correspond to a high overdose risk, and the need for such dosage should be clearly documented before a patient receives it. Some guidelines recommend specialty consultation or increased clinical vigilance with such patients [38,39].

The high OR for buprenorphine (21.5, 95% CI 8.3–56.0) should be interpreted with caution. Although a buprenorphine prescription history was associated with fatal overdose, buprenorphine itself was not necessarily involved in overdose death.
the overdoses. Buprenorphine has a low risk of overdose [40], and is prescribed on an outpatient basis for treating opiate abuse, especially in nonurban communities in New Mexico that have serious heroin problems but limited access to methadone treatment programs. Its high OR in the full dataset might reflect an elevated risk of overdose among heroin users in spite of or after release from treatment [41]. The lack of an association between buprenorphine and overdose risk in the subset of opioid-related deaths might be because the subset included few of those heroin deaths in nonurban areas.

In contrast, methadone dispensed by opiate abuse treatment programs is not reported to the New Mexico PMP and is not approved for office-based substance abuse treatment. Therefore, the methadone exposures in this study are probably prescriptions for pain rather than for treatment of substance abuse. The significant OR for methadone is consistent with evidence that methadone as an analgesic is more risky than other opioid analgesics [42]. Similarly, hydromorphone was associated with greater rates of emergency department visits per prescription in the 1990s [43] and is preferred by people who abuse drugs [44], while hydrocodone, which had only a weak association with overdose, has lower rates of overdose compared with other opioids nationally [45] and lower attractiveness [44].

Figure 3 Unadjusted association of number of prescribers per patient with risk of unintentional drug overdose death, New Mexico, October 2006–March 2008. Note: The full range of number of prescribers per patient was divided into intervals 1, 2, 3, 4–5, 6–9, and 10–30 prescribers. The X coordinates are the mean number of prescribers within each interval. The Y coordinates are the OR corresponding to those mean values. For example, the mean number of prescribers for the 4–5 prescriber interval was 4.4, and the corresponding OR was 3.5. The referent was persons with one prescriber.

This study has several limitations. Prescription history was associated with risk of overdose, but frequent use of controlled substances might also have been associated with other risk factors for overdose such as use of illicit drugs or mental illness. Particular prescription patterns are therefore a marker of risk but not necessarily a direct cause of overdose. In fact, the drugs prescribed were not necessarily the causes of the overdoses. A small fraction of patients may not have been correctly linked to all their prescription records and may have been incorrectly linked to prescription records for other people. Prescription drug use might have been underestimated if persons filled prescriptions with erroneous identifying information, used the prescriptions of other people, filled prescriptions at facilities not required to report to the PMP, or were out of state for some of the exposure period. Conversely, some persons may have filled their prescriptions, but never used the medication. All the medical residents at the University of New Mexico used a single Drug Enforcement Agency (DEA) number, so the number of different prescribers per patient is probably underestimated. We do not know whether persons prescribed methadone or buprenorphine were using these drugs for their psychoactive effect, for pain control, or for self-treatment of drug abuse. The risk levels calculated in this study were in relation to other persons also using controlled substances. Therefore, the true risk when compared with a person not using any controlled substances is likely to be higher. The New Mexico population is largely white and Hispanic, so results found here may differ in states with varied demographic profiles.

Conclusions

In this study, we used prescription drug monitoring program data to estimate overdose risk associated with selected prescription drugs, multiple prescriptions, providers, and pharmacies, and high daily doses of opioid analgesics. Health care providers can best identify patients with these risk factors by routinely obtaining prescription histories from state prescription drug monitoring programs [46]. Providers can then make future prescribing decisions with a better appreciation of a patient’s risk for serious adverse events. Similarly, prescription drug monitoring programs, insurance carriers, and regulatory agencies can use such information to determine the most appropriate thresholds in terms of numbers of prescriptions or providers for triggering interventions designed to reduce risk of drug overdose.

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