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A description of Medical Examiner prescription-related deaths and prescription drug monitoring program data

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ABSTRACT

Background: The Centers of Disease Control and Prevention have declared prescription drug abuse an epidemic in the United States. However, demographic data correlating prescription-related deaths with actual prescriptions written is not well described. The purpose of this study is to compare toxicology reports on autopsy for prescription-related deaths with Prescription Drug Monitor Program (PDMP) data.

Methods: This is a retrospective analysis comparing 2013 San Diego Medical Examiner data on 254 unintentional prescription-related deaths obtained for 12 months before death with data from the California PDMP. Data were analyzed on age, sex, whether there was information on the PDMP, types and quantities of prescribed medications, number of pharmacies and providers involved, and whether there was a match between the Medical Examiner toxicology report and data from the PDMP.

Results: In 2013, there were 254 unintentional prescription-related deaths; 186 patients (73%) had PDMP data 12 months before death. Ingesting prescription medications with illicit drugs, alcohol, and/or over-the-counter medications accounted for 40% of the unintentional deaths. Opioids were responsible for the majority of single medication deaths (36; 70.6%). The average number of prescriptions was 23.5 per patient, and the average patient used 3 pharmacies and had 4.5 providers. Chronic prescription use was found in 68.8% of patients with PDMP data.

Conclusions: The PDMP data highlight important patterns that can provide valuable insight to clinicians making decisions regarding types and amounts of medications they prescribe. Although there is no guaranteed solution to prevent prescription-related deaths, PDMP data can be useful to prevent coprescribing and medication interaction and by following best clinical practices.

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1. Introduction

The Centers of Disease Control and Prevention (CDC) have declared prescription drug abuse an epidemic with 114 unintentional deaths per day in the United States [1]. In 2011, there were 16,651 opioid overdose deaths [2] compared with 2749 in 1999 [3]. From 1999 to 2011, drug poisoning death rates were highest in middle-aged men, but profoundly affects all ages and sexes [3].

Demographic data correlating prescription-related deaths with actual prescriptions written is not well described in the medical literature. There are several studies that review prescription-related deaths and prescribing patterns, but few that make direct comparisons [3–5]. However, some literature has focused on opioids, and awareness is increasing regarding the correlation of increased opioid-related deaths with increased opioid prescribing [6]. Kenan and colleagues [7] found that the number of opioid prescriptions per 100 persons increased by 35.2% between 2000 and 2009, and the average size of an oxycodone and hydrocodone prescription increased by 69.7% and 69.4%, respectively, during the same period. For 146 million opioids dispensed, 0.7% of purchasers accounted for 1.9% of all opioid prescriptions, 69.4%, respectively, during the same period. For 146 million opioids dispensed, 0.7% of purchasers accounted for 1.9% of all opioid prescriptions [8].

“Doctor shopping” has been an ongoing issue with controlled substances. Doctor shopping is a strategy used by individuals to obtain multiple prescriptions. In a study done in Los Angeles in 2012 and in Massachusetts in 2006, doctor shoppers were defined as 4–12, or having 4 or more providers and 4 or more pharmacies in a 12-month period [4,9]. Doctor shoppers were found to have an increased number of prescriptions, higher number of pills, and higher number of morphine equivalents [4]. The work of McDonald and Carlson [8] in
2008 found that patients who were diverting opioids had an average of 32 prescriptions from 10 providers.

Taking opioids with other substances, such as benzodiazepines, can also be dangerous because it has an additive central nervous system depression effect. In a study of 9940 managed care patients between 1997 and 2005 who received 3 or more opioid prescriptions within 90 days, there were 51 individual patients with opioid-related overdoses including 6 deaths [10]. Benzodiazepines were involved in 31% of opioid-analgesic poisonings deaths in 2011, up from 13% in 1999 [3]. The Drug Abuse Warning Network reported that in 58,000 emergency department visits between 2005 and 2011, hospitalizations involving benzodiazepine and opioids were higher than hospitalizations for benzodiazepines alone [11]. New York City mortality of opioids data showed that benzodiazepines were found in 37% of opioid deaths and 24.5% of methadone deaths [12]. The American Society of Interventional Pain Physicians has recommended evaluating relative and absolute contraindications of prescribing benzodiazepines in combination with opioids [13].

The purpose of this study is to describe the toxicology reports from autopsy records for prescription-related deaths and from a Prescription Drug Monitor Program (PDMP).

2. Methods

2.1. Study design

This is a retrospective study comparing all unintentional prescription-related deaths from January 1, 2013, to December 31, 2013, as determined by a San Diego Medical Examiner (ME) investigation, with prescription data obtained for 12 months before date of death. Prescription data were obtained from the California PDMP also known as the Controlled Substance Utilization Review and Evaluation System database [14,15]. The San Diego population includes about 3.2 million people, with about 20,000 deaths per year, of which about 10,000 a year are investigated by the ME.

2.2. Study population

The San Diego County ME’s office follows Government Code Section 27491 which states that an investigation be conducted for all unnatural deaths that include homicides, suicides, accidents, deaths in custody, and certain infectious diseases. All unintentional deaths caused by prescription drugs, as determined by the San Diego ME, were evaluated. This included prescription drugs mixed with over-the-counter (OTC) medications, alcohol, or illicit drugs. The toxicology reports for these deaths were reviewed.

A PDMP inquiry was run for a 12-month period before date of death on all patients that included dates of prescription, names of medication, dosage, strength, number of pills, names of pharmacies, and names of providers. The medications entered into the California PDMP database include all Schedule II-IV medications. In 2013, this did not include tramadol (Ultram), as inclusion of this drug started in 2014. The data are obtained from pharmacy information that is uploaded into the state system on a regular basis. All major pharmacies have the software necessary to comply with the regulation (SB 809) that requires data be uploaded within 1 week [16]. Prescriptions obtained from inpatient hospital pharmacies, the Veterans Administration, military hospitals, methadone clinics, and out-of-state pharmacies are not included.

2.3. Data analysis

Deaths identified in the ME database were matched to records found within the PDMP database, which identified 3 cohorts (overall ME deaths, deaths with PDMP records within 12 months of the death, and those with no PDMP information). Those with a prescription within 2 months of a death were identified as a “PDMP match.” Doctor shopping was defined as a minimum of 4 prescriptions plus 4 pharmacies in a 12-month period.

The frequency of various medications is reported for deaths found on ME toxicology report (N = 254), those who had a PDMP report that did not match the ME report, deaths with an ME report matching PDMP prescriptions 2 months before death, and patients with no PDMP data.

Patient demographics (age and sex), whether the patient had any information on PDMP, the types and quantities of medications prescribed, the number of pharmacies involved, the number of providers involved, whether patients had a match between ME toxicology reports and PDMP prescriptions, data on doctor shoppers, and specific medication combinations are reported across study cohorts.

3. Results

3.1. Demographics and deaths

The San Diego ME Office reported 254 unintentional prescription-related deaths in 2013. Table 1 reports the demographics of the study population and cohorts. Of those, 186 (73%) had PDMP data in the 12 months before death. The total cohort of 254 included 64% males, with an average age of 46.6. The cohort of 186 patients that had a PDMP report included 60% males, with an average of 46.4. The cohort of 68 patients who had no information on PDMP included 76.1% males, with an average age of 46.6. Combinations of illicit drugs, alcohol, and OTC prescriptions were included in the 254 deaths. Table 2 reports prescription drug deaths and combination of other substances.

3.2. PDMP

3.2.1. Prescriptions

There were 33 medications with 42 types of formulations on the PDMP reports that included opioids, benzodiazepines, sleep aids, stimulants, and others. Prescription formulations that included combinations of several medications were included in a single category. For example, hydrocodone with acetaminophen, or ibuprofen, or chlorpheniramine, or homatropine were grouped as hydrocodone. Oxycodone HCI andoxycodone with acetaminophen were grouped as oxycodone. Specific medications are listed in Table 3.

PDMP data (n = 186) were reported in terms of the total number of prescriptions written for that medication and the number of patients who were prescribed that medication. Table 4 reports the type of prescriptions found in the different cohorts. A similar analysis is provided on selected medications and reported in Table 5. Hydrocodone was the most common medication on the ME report in 48 of the 254 (18.9%) patients. Of those 48 patients, 24 received their prescription with a PDMP match, meaning the medication was prescribed less than 2 months before death. The remaining patients included 16 (6.3%) who had a PDMP report that did not include hydrocodone and 8 (3.1%) patients that had no PDMP data. Hydrocodone was also the most common prescription found on PDMP with 990 prescriptions written for 120 patients.

The majority of patients died with combinations of medications, but there were 51 patients who died with only a single medication on toxicology report. The majority of the single medications on toxicology report were opioids (36; 70.6%). The opioids most often found as a single

<table>
<thead>
<tr>
<th>Demographic</th>
<th>ME total</th>
<th>PDMP data</th>
<th>No PDMP information</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>254</td>
<td>186</td>
<td>68</td>
</tr>
<tr>
<td>Percentage male</td>
<td>64.0</td>
<td>60.0</td>
<td>76.1</td>
</tr>
<tr>
<td>Average age</td>
<td>46.6</td>
<td>46.4</td>
<td>46.6</td>
</tr>
<tr>
<td>Age range</td>
<td>15-73</td>
<td>19-73</td>
<td>15-72</td>
</tr>
</tbody>
</table>

medication on the toxicology report were methadone (12 patients) and morphine (7 patients). Figure reports all single medications found on toxicology reports.

3.2.2. Pharmacies
The PDMP data showed that 275 pharmacies dispensed 4366 prescriptions with 42 medications to the 186 patients who died in 2013. The majority of the pharmacies (149; 54.2%) gave prescriptions to only 1 patient. However, there were outliers, and 1 pharmacy had 12 patient deaths in 1 year, 2 pharmacies had 10 deaths, and 3 pharmacies had 9 deaths. The average number of prescriptions per patient was 23.5, with 1 patient receiving 123 prescriptions in 1 year. The average number of pharmacies used per patient was 3.1, with 1 patient using 21 pharmacies in 1 year. Both the patient with 123 prescriptions and the 21 pharmacies were a PDMP match with no alcohol or illicit drug use but were doctor shoppers.

3.2.3. Providers
The PDMP data showed that 713 providers wrote prescriptions for 12 months before death to the 186 patients who had PDMP data. Unique Drug Enforcement Agency (DEA) license numbers identified the number of providers. The average number of providers per patient was 4.5, and the maximum number of providers for 1 patient was 36. According to the DEA, there are 16,000 providers with DEA licenses in the San Diego and Imperial County region [17]. The Imperial County numbers could not be separated from the San Diego numbers. Active vs nonactive DEA licenses could not be separated. Therefore, more than 4.5% of providers were listed in the PDMP reports 12 months before patient death. Most providers had only 1 patient death (604; 84.7%). However, 3 providers had 4 patient deaths.

3.2.4. Doctor shoppers
Doctor shoppers were found in 52 of the 186 (20.5%) with PDMP report and accounted for 95.81% of all prescriptions written. (68.8%) of the 186 with PDMP report and accounted for 95.81% of all prescriptions written. A PDMP match was found in 100 (39.4%) patients. Further review found that 68 (26.8%) patients had a PDMP match and did not have illicit drugs or alcohol on autopsy. In addition, 42 (16.5%) patients did not have a PDMP match, did not have illicit drugs or alcohol, and were not doctor shopping. The 42 patients who had PDMP match, did not have illicit drugs or alcohol, and were not doctor shopping had different demographics than the study population as a whole. This subset of patients, by definition, was more compliant than the total population. They were also different by being predominately female and older with a higher number of prescriptions, less providers, and less pharmacies. This group’s medications included a higher rate for opioids, sleep aids, other medications, single-medication deaths, higher morphine equivalents, higher long-acting opioids, higher chronic users, and more benzodiazepine-opioid combination. Table 6 reports the demographics of the 42 patients with PDMP match, no illicit or alcohol use, and no doctor shopping and the total study group.

### Table 2
Prescription drug deaths and combination of other substances

<table>
<thead>
<tr>
<th>Substance</th>
<th>Number (%) (n = 254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription</td>
<td>154 (60.6)</td>
</tr>
<tr>
<td>Prescription + illicit</td>
<td>44 (17.3)</td>
</tr>
<tr>
<td>Prescription + alcohol</td>
<td>39 (15.4)</td>
</tr>
<tr>
<td>Prescription + illicit + alcohol</td>
<td>10 (3.9)</td>
</tr>
<tr>
<td>Prescription + OTC</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Prescription + alcohol + OTC</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Prescription + illicit + OTC</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Prescription + illicit + alcohol + OTC</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

### Table 4
Type of prescriptions found in different cohorts

<table>
<thead>
<tr>
<th>Prescription</th>
<th>ME data, N = 254</th>
<th>PDMP data, n = 186</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opoids</td>
<td>% Patients</td>
<td># PDMP match</td>
</tr>
<tr>
<td>Opioids</td>
<td>190 (74.8)</td>
<td>75</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>93 (36.6)</td>
<td>32</td>
</tr>
<tr>
<td>Sleep aid</td>
<td>17 (6.7)</td>
<td>6</td>
</tr>
<tr>
<td>Stimulants</td>
<td>31 (12.2)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>112 (43.7)</td>
<td>56</td>
</tr>
<tr>
<td>OTC</td>
<td>33 (13)</td>
<td>23</td>
</tr>
<tr>
<td>Alcohol</td>
<td>52 (20.5)</td>
<td>41</td>
</tr>
<tr>
<td>Illicit</td>
<td>56 (22.0)</td>
<td>36</td>
</tr>
</tbody>
</table>

3.2.5. Chronic use
Chronic use was defined as obtaining prescriptions for 3 or more consecutive months. The definition is an important indication for placing patients on a Medication Agreement, which allows for the documentation of understanding between a doctor and patient regarding their medication use. Chronic use was found in 128 patients (68.8%) of the 186 with PDMP report and accounted for 95.81% of all prescriptions written.

Additional comparison data provided by the California PDMP office showed that the number of unique patients who receive controlled prescriptions for 3 consecutive months in San Diego for 2013 was 13,567 or 1.6% of the 816,372 total patients who received PDMP medications that year. For California, there were 200,080 with chronic use criteria or 2.8% of the 7,057,000 total patients.

### Table 3
Number of patients with specific medications on PDMP

<table>
<thead>
<tr>
<th>Opioids</th>
<th>Benzodiazepines</th>
<th>Sleep aid</th>
<th>Stimulants</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>(123)</td>
<td>Clonazepam</td>
<td>(44)</td>
<td>Zolpidem (43)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>(84)</td>
<td>Alprazolam</td>
<td>(39)</td>
<td>Lunesta (4)</td>
</tr>
<tr>
<td>Morphine</td>
<td>(32)</td>
<td>Lorazepam</td>
<td>(37)</td>
<td>Chloral Hydrate (2)</td>
</tr>
<tr>
<td>Codeine</td>
<td>(27)</td>
<td>Diazepam</td>
<td>(26)</td>
<td>Zaleplon (2)</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>(3)</td>
<td>Chloridiazepoxide</td>
<td>(17)</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>(20)</td>
<td>Temazepam</td>
<td>(17)</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>(14)</td>
<td>Triazolam</td>
<td>(6)</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>(13)</td>
<td>Oxazepam</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>(11)</td>
<td>Clonazepate</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td>(9)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.3.1. Opioid and benzodiazepine combinations

Opioid and benzodiazepine combinations were studied as a specific group. Of the 186 PDMP reports, 100 (54%) included the benzodiazepine-opioid combination. This combination was found in 55 (21%) of all deaths. Of those 55 deaths, a PDMP report with the same combination was found in 39 (71%) of patients. The Holy Trinity is a colloquial description for the combination of opioids, benzodiazepines, and carisoprodol. Of the 254 deaths, 5 (2%) involved the combination of opioid, benzodiazepines, and carisoprodol. Of the 5 patients who died with the benzodiazepines, opioid, and carisoprodol (Soma), Of the 254 deaths, 5 (2%) involved the combination of opioid, benzodiazepines, and carisoprodol. Of the 5 patients who died with the benzodiazepines, opioid, and carisoprodol combination, 4 (80%) received prescriptions from a PDMP source. The 186 PDMP reports found 24 (13%) with the triad combination.

4. Discussion

In 2013, 186 of the 254 unintentional prescription-related deaths had PDMP data 12 months before death. Deaths occurred most frequently in males, and although males were the majority of deaths, many of those had no data on PDMP. The age range for this group was 15–73, with an average age of 46-47. The greatest deaths occurred in the 45-54 age range. Hydrocodone was responsible for the highest number of deaths and the largest quantity of prescriptions. Alprazolam had the highest number of benzodiazepine deaths, and clonazepam had the highest number of prescriptions. Doctor shoppers accounted for less than a third (28%) of the patient with PDMP reports and more than half (51%) of all the prescriptions. The majority of patients (68.8%) met the definition of chronic prescribing. A small proportion of patients had a toxicology match with PDMP data, did not have illicit drugs or alcohol, and were not doctor shopping. Benzodiazepine and opioid combination accounted for many deaths and accounted for more than half of the PDMP reports.

The number of deaths in this study was lower than that in the CDC data. In San Diego County in 2013, there were 8.1 prescription related deaths per 100,000 persons. The CDC Wonder data reported a rate of 12.4 for San Diego in 2010 and 11.4 for California [18]. The age range of 45-54 showed the highest number of deaths and followed the national data for 2011. The sex statistics follow the national reported data of predominately male deaths but also show higher male percentage for those without PDMP data and possibly using illegal means of obtaining prescriptions. Hydrocodone is known as the number one prescribed medication in the United States and is shown to have a correlation with the highest number of deaths and prescriptions written (source hydrocodone). The combination of opioid and benzodiazepine deaths in this study was less than that in the national data (21% vs 31%) [3].

A gold standard was established in 2013 by the San Diego County Prescription Drug Abuse Medical Task Force that patients with chronic prescription medication requirements, as defined as 3 or more consecutive
months, should have all their controlled prescriptions coordinated by a single provider and a single pharmacy [19]. This study showed that the majority of deaths occurred with chronic users and yet the total population used an average of 4.5 providers and 3 pharmacies.

A small proportion of the 186 deaths included an ME report with matching PDMP data, no illicit drugs, no alcohol, and no doctor shopping and may warrant special attention. The demographic of this group was different from the total group, with majority being female and older. The medications for this group involved a greater percentage of opioids with more morphine equivalents and long-acting opioids, more benzodiazepine and opioid combinations, and more chronic use.

4.1. Limitations

The study had several limitations. The PDMP system does not include prescriptions filled by the Veterans Affairs, military hospitals, methadone clinics, and out-of-state clinics, and online and illegal prescriptions. The ME toxicology reports did not always include all OTC medications, not all illicit drugs are detectable, and some may not have been tested for by the ME. On 2 ME reports, the toxicology report stated “positive opioid” without a specific name, and on 6 ME reports, the toxicology report stated “positive benzodiazepine” without a specific drug name. A PDMP match was considered positive when the exact drug formulation was found on the ME report and PDMP. However, in the cases when the ME did not specify the exact drug and only class of medication, the PDMP match was considered positive for the class of medication. The analysis of PDMP match was an attempt to analyze medication compliance. Using the prescription date of 2 months before death was an arbitrary time frame for using a prescription written typically for 30 days. It is also an assumption that the medications found on toxicology autopsy report are the same medications found on the PDMP report. In evaluating the percentage of providers that are shown on the PDMP reports, a total of DEA licenses for San Diego and Imperial Counties were used. The DEAs from Imperial County and the nonactive DEAs could not be separated.

5. Conclusions

There were 186 patients of the 254 prescription-related deaths in 2013 that had PDMP data. Some of those PDMP reports were "death diaries" that told a prescription story 1 year before death. The data provided had some red flags on many patients that included multiple prescriptions, multiple pharmacies, multiple providers, and drug interactions. Retrospectively, one can identify areas for potential intervention and prevention by providers, pharmacies, law enforcement, and health plans. The medical community would like to think that if patients take medications strictly as prescribed and not mix them with alcohol or illicit drugs, they should be safe. Although this is true the majority of the time, this study showed a potential of deaths with matching toxicology reports, PDMP data, no alcohol or illicit use, and no doctor shopping. There is no guaranteed solution to prevent prescription-related deaths. However, improvements can occur by using PDMP data, communication between providers, using special care with methadone prescribing, establishing a standard such as 1 provider and 1 pharmacy for chronic prescriptions, and minimizing opioid and benzodiazepine combinations. Health plans are currently paying for prescriptions that end up in death, and therefore have an important role in prevention.

Acknowledgments

Mike Small, Program Manager, Department of Justice, California Prescription Drug Monitoring Program (Controlled Substance Utilization Review and Evaluation System). For more information on the San Diego Prescription Drug Abuse Medical Task Force and safe prescribing recommendations/resources, please visit SanDiegoSafePrescribing.org.

References