NIH Public Access
Author Manuscript
Am J Addict. Author manuscript; available in PMC 2009 October 5.

Published in final edited form as:
Am J Addict. 2009 ; 18(1): 5–14. doi:10.1080/10550490802544938.

Opioid Deaths in Rural Virginia: A Description of the High Prevalence of Accidental Fatalities Involving Prescribed Medications

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Abstract

In rural Virginia, drug overdose deaths increased 300% from 1997 to 2003. Polydrug deaths predominate (57.9%) in this review of 893 medical examiner cases. Prescription opioids (74.0%), antidepressants (49.0%), and benzodiazepines (39.3%) were more prevalent than illicit drugs. Two-thirds of decedents were 35–54 years old; 37% were female. When compared to western Virginia metropolitan cases, polydrug abuse was more common, specific medication combinations were found, the death rate per population was higher, and fewer illicit drugs were detected. These rural prescription overdose deaths differ from urban illicit drug deaths, suggesting the need for different strategies in prevention, treatment, and intervention by clinicians and policymakers.

Introduction

The National Institute on Drug Abuse has identified the nonmedical use of prescription medications as a serious and growing public health problem, and the National Survey on Drug Use and Health (NSDUH),[1–4] Drug Abuse Warning Network (DAWN),[5] and Treatment Episode Data Set[6] all report an increase in such use over the last decade. The 2006 NSDUH reported that 7 million (2.8%) persons aged 12 or older engaged in the nonmedical use of prescription-type psychotherapeutic drugs in the past month, and the nonmedical use of prescription pain relievers increased from 4.7 million in 2005 to 5.2 million in 2006. The nonmedical use of prescription pain relievers in 2006 surpassed that of marijuana among new initiates to illicit drug use.[4]

The last decade has also seen an alarming increase in the number of deaths from overdose where prescription medications are identified by toxicology. The Centers for Disease Control[7] identified 11 states in which undetermined and unintended poisoning deaths combined increased by an average of 145% between 1990 and 2001. While the number of fatal heroin poisonings increased by 12.4% from 1999 to 2002, the number of fatal opioid analgesic

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poisonings in the United States increased by 91.2%.[7] In 2003, DAWN (Medical Examiner) reported increased opioid-related drug deaths in Maine, New Hampshire, Vermont, Maryland, Utah, and New Mexico, involving predominantly the prescription medications oxycodone, hydrocodone, and methadone.[5]

Little is known about this newly emerging group of decedents other than their age at the time of death and the prescription medications identified by toxicology. More detailed description is needed to better understand the unique features of this problem. For example, it is curious that respondents reporting the nonmedical use of opioids to the NSDUH tend to be younger than victims in whom prescription opioid poisoning deaths are occurring.[1–3,7] Specifically, individuals aged 12–25 years old report the highest rates of nonmedical use of prescription drugs, while in five of the six states, the highest death rates were among adults aged 35–54 years old.

In order to examine the problem of prescription overdose fatalities in more detail, we studied drug overdose case records of the Office of the Chief Medical Examiner (OCME) in rural western Virginia, where the number of deaths involving prescription opioids increased rapidly between 1997 and 2003.[8,9] In this paper, we report the demographic characteristics of the decedents, the manner and assigned toxicological cause of death, and the medications and illicit drugs commonly present as identified by toxicology—notably, prescription opioids, benzodiazepines, and antidepressants. We then discuss the implications of these findings with respect to the rural populations, a group that displays an elevated risk for death from prescription opioids and combinations of opioids with other medications.

Materials and Methods

This retrospective, population-based review of medical examiner cases in the Office of the Medical Examiner (OCME), Western District of Virginia, began by identifying all cases classified as poisoning deaths occurring between the years 1997 and 2003. This time period coincides with a significant increase in drug overdose deaths, beginning with 67 drug deaths investigated by the OCME in 1997 and concluding with 223 drug deaths in 2003. The work is not intended to be an epidemiological study focused on population comparisons; rather, it is a comprehensive investigation into a set of clearly defined cases in which prescription medications were identified by toxicology. From an epidemiological perspective, our criterion for inclusion, any poisoning death in which a drug or drugs were a direct or contributing cause of death, may exclude some deaths involving indirect drug-related causes and thus underestimate the problem.

A medical examiner case is defined as including suspicious or violent deaths, unnatural deaths, or deaths related in the public interest such as incarcerated prisoners or patients in mental institutions. We selected all OCME Western District of Virginia cases categorized as poisoning deaths. We extracted the complete subset of drug deaths, which also included cases with prescription medications, classified as a direct or contributing cause of death. In the OCME, Western District of Virginia, when there is suspicion of drugs of abuse or poisoning in a death, a full autopsy is conducted, and specimens are obtained for toxicological analyses. After autopsy, the pathologists and toxicologists review cases to determine if and what additional toxicological examinations are required. If history and circumstances do not indicate that drugs are a cause of death, a limited toxicology is performed. In cases where there is a well-established cause of death, such as smoke inhalation, directed toxicological analysis for alcohol and other relevant substances (eg, carbon monoxide determinations) are conducted. All of the cases we reviewed included toxicological analyses, and all except one included an autopsy.

The region served by the OCME, Western District, includes 34 counties and 16 municipalities, largely west of the Blue Ridge Mountains, with a population of 1.6 million people. This geographic area is inclusive of seven metropolitan statistical areas (Roanoke, Lynchburg, Blacksburg, Christiansburg, Radford, Harrisonburg and Danville) and two micropolitan statistical areas (Staunton-Waynesboro and Martinsville). No metropolitan area in western Virginia exceeds 100,000 in population; thus, even the metropolitan areas in this region are relatively small. The remainder of the region (classified rural) consists of 19 counties where no municipality exceeds 10,000 in population and six independent municipalities with populations less than 10,000.

U.S. Government Office of Management and Budget definitions and identifications of metropolitan and micropolitan areas were used to classify locations in which deaths occurred. Metropolitan statistical areas have at least one urbanized area of 50,000 or more population, plus adjacent territory that has a high degree of social and economic integration with the core as measured by commuting ties. Micropolitan statistical areas have at least one urban cluster of at least 10,000 but less than 50,000 population, plus adjacent territory that has a high degree of social and economic integration with the core as measured by commuting ties. Metropolitan and micropolitan statistical areas are defined in terms of whole counties, or equivalent entities.[10]

Cases Reviewed

We reviewed 893 cases, excluding four cases in which decedents were children under the age of four years, resulting in a final case total of 889 deaths. We exclude the four cases because the manner and circumstances of poisoning in young children differs significantly from adults. The youngest case we included was 14 years of age. The information reviewed from the medical examiner files include autopsy reports, hospital records, physician notes, and records obtained by the OCME in death investigations, death scene reports, police reports of investigation including witness statements, and death certificates. Information was extracted from the decedent files by one research associate (RA). The first 100 files were entered simultaneously by both the RA and the PI (MW). Due to the objective nature of the data, interater reliability was nearly 100%. Only five discrepancies were noted in the 100 cases. The research team, including the forensic toxicologist (GB), forensic pathologist (WM), and statistician (KN), reviewed the dual entries to resolve discrepancies in data coding. In this manner, we assured accuracy and completeness in extraction and coding of the data. Throughout the remainder of the project, ten percent of the remaining files were chosen for review using a random number table; data were coded by both PI and RA, and reviewed by the research team for accuracy and completeness. The data were reviewed quarterly for completeness and accuracy by a multidisciplinary team, including a forensic toxicologist (GB), forensic pathologist (WM), and statistician (KN).

Decedent socio-demographic information, including date of birth, sex, race, and employment status, was extracted from death certificates. Toxicology data were available for all cases in our review and did not vary in level or source of testing, or by decedent year group. Quantitative analyses of drugs and drug metabolites in postmortem blood, body fluids, and tissues was performed by a number of validated analytical methods employing gas chromatography-mass spectrometry (GCMS), GCMS/selected ion monitoring (SIM), high-performance liquid chromatography (HPLC) with diode array or fluorescence detection, and gas chromatography (GC) with electron capture detection. The presence of drug(s) and drug metabolite(s) in body fluids (blood, urine, gastric fluid, bile, or liver), for each decedent, was coded as present or absent and, when concentrations were available, the information was included in the database. The presence of heroin was predicated on the identification of 6-acetyl morphine, the unique metabolite that distinguishes it from other opioids. Tests for the presence of this compound were conducted in both blood and urine; while the half-life of 6 acetyl- morphine is short in blood, it is more stable in urine. Although the focus of the paper is prescription medications, several other common substances of abuse were identified by toxicology (alcohol, cocaine, tetrahydrocannabinoids, methamphetamine, and amphetamine) and were included for completeness.

Statistical Analysis

The data in this study are almost all nominal (categorical) variables. As such, the predominant analyses were in the form of cross tabulations; the chi-square test was used to test for statistical significance at or above the $p < .05$ level between variables or differences in distribution (eg, occurrence) among groups. Age and crude death rates were recorded or calculated as continuous variables (and means and standard deviations are reported); however, age groupings were constructed for subsequent analyses.

Results

Between 1997 and 2003, in rural western Virginia, the medical examiner's office reported a 300% increase in the number of deaths in which drugs, including prescription medications, were determined to be related or contributory to cause. Deaths in which drugs, including prescription medications, were either a direct or contributing cause of death increased steadily over the time period. Specifically, there were 65 drug deaths in 1997, 69 drug deaths in 1998, 83 drug deaths in 1999, 104 drug deaths in 2000, 163 drug deaths in 2001, 185 drug deaths in 2002, and 220 drug deaths in 2003. As shown schematically in Figure 1, the number of non-opioid deaths (cases of a drug-related nature, but exclusive for the absence of an opioid) averaged 29.3 per year and remained steady for the seven-year period ($\chi^2 = 3.76$, ns). However, deaths in which opioids were present by toxicology increased six-fold from 33 in 1997 to 184 in 2003 ($\chi^2 = 231.85$, $p < .001$). The highest proportion of deaths (568 of 889) occurred during the time interval 2001–2003.

Medications and drugs identified by toxicology in these cases are shown in Table 1. In the remainder of this analysis, we focus on three classes of medications that are present with high frequency in these decedents: opioids, benzodiazepines, and antidepressants.

Overall, in 57.9% of the cases, the cause of death involved more than one drug or medication; these are classified as polydrug deaths.

Prescription opioids were identified in 658 of the cases (74.0%). The most common prescription opioids identified were methadone (28.0%), hydrocodone (20.4%), and oxycodone (19.6%). 6-Acetylmorphine, the metabolic marker for heroin, was present in only 2.4% of cases.

Antidepressants were identified in 436 cases (49.0%). The most commonly identified include sertraline (22.7%), venlafaxine (20.8%), amitryptiline (9.8%), nortriptyline (9%), and citalopram (6.1%) or fluoxetine (6.1%).

Benzodiazepines were identified in 349 cases (39.3%). The most commonly identified were diazepam (24.3%) and alprazolam (15.4%).

As with heroin, other illicit drugs of abuse occurred with much lower frequency: cocaine 12.0%, THC 0.3%, methamphetamine or amphetamine 1.4 %. Alcohol was identified in 29% of the cases.

Demographics

Table 2 summarizes decedent demographics. The population of this region of rural western Virginia is predominantly Caucasian, with 50.8% of the population male, and 75% of the population ages 18–65 years old.[9] Among our cases, the majority of deaths occurred among males (63%) and Caucasians (96.8%). Female decedents were slightly older (female mean = 42.8 years, SD = 11.80; male mean = 38.5 years, SD = 10.40; t = 5.60, $p < .001$) and the greatest number of deaths (40.7% of women and 38.6% of men) occurred among individuals aged 36–45 years old. Most of the decedents had at least a high school education, with women more likely to have a trade, associate's degree, or a bachelor's or graduate degree ($p < .005$). A majority of the decedents were employed either part or full time (56.8%); men were more often unemployed or disabled ($p < .001$). The predominant manner of death was accident (78.9%); suicide accounted for 18.1% of cases. More female deaths were classified as suicide (female 38.3% vs. male 18.1%), while a higher proportion of male deaths were classified as accident (female 57.8% vs. male 78.9%; $p < .001$).

Location of Death by Population Density

Using census classifications of population, cases were stratified by location of death (Table 3). We defined a rural death as one in which the decedent's home address, as noted on the death certificate, was not in a micropolitan or metropolitan MSA. While less than half of the cases occurred among decedents whose home address was in a rural area (42%), the death rate, when adjusted for population density, was higher among decedents who resided in rural areas ($p < .05$). In addition, rural decedents differed from the metropolitan and micropolitan decedents in terms of drugs identified by toxicology. Polydrug toxicity as a cause of death was significantly more likely among rural decedents (61.6% vs. 55.2%; $p < .005$).

Location of Death and Drugs Detected by Toxicology

As noted above, overall in this group of decedent cases illicit drugs of abuse were found less often than prescription medications. Specifically, heroin was identified in only 2.4% and cocaine in 12% of the cases. When heroin was identified by toxicology, more often it was among decedents in micropolitan or metropolitan locations (3.3%) than rural areas (1.1%, $p < .05$). Likewise, cocaine was found among metropolitan/micropolitan decedents more often than among rural decedents (16.7% vs. 6.1%, $p < .001$).

In contrast, prescription opioids were more likely to be identified in rural areas than metropolitan/micropolitan (80.3% vs. 69.5%; $p < .001$). Of the six most frequently occurring opioids, three were more common in rural than in micropolitan or metropolitan areas—hydrocodone (29.1% vs. 14.0%, $p < .001$), oxycodone (24.8% vs. 15.8%; $p < .001$), and fentanyl (7.2% vs. 3.5%; $p < .05$). The occurrence of methadone (27.5% vs. 28.4%, NS) did not differ between rural and micropolitan or metropolitan areas. Benzodiazepines were more likely to be identified among rural decedents (45.1% vs. 35.0%, $p < .005$). However, there was no significant difference between rural and micropolitan or metropolitan areas in numbers of cases where antidepressants were identified (50.1% vs. 48.2%, NS).

Combinations of Substances

Polydrug toxicity was more likely than single drug toxicity to be the cause of death (57.9% vs. 36.2%; $\chi^2 = 44.5$, $p < .001$). In the remaining 5.9% of the cases, the deaths were classified by the medical examiner as drug deaths because of supporting toxicological identifications. For example, COD in a decedent could be hypothermia; however, prescription medications were identified by toxicology and also listed as contributory.

Single Drug Toxicity—In the 22.7% of cases of single drug opioid toxicity, methadone was most commonly identified by toxicology and assigned as cause of death. In the 3% of cases of single drug class benzodiazepine toxicity, diazepam was most commonly identified and assigned as cause of death. Although venlafaxine was the most commonly found antidepressant overall, in the 10.6% of cases of single drug antidepressant toxicity the cases were distributed across citalopram (six cases), fluoxetine (five cases), and doxepin (seven cases).

Figure 2 is a schematic illustrating the distribution of COD across medication classes. Because the majority of deaths were due to multiple medications, we examined differing combinations of drugs present in these cases.

Opioids and Other Drug Classes—Drugs from other pharmaceutical classes were also detected in combination with opioids. In particular, benzodiazepines and anti-depressants were frequently co-occurring. Figure 2 depicts the concomitant presence of opioids, benzodiazepines, and anti-depressants in these decedent cases.

Most notably, all three classes of pharmaceuticals were present in 151 decedent cases (19.0% of the deaths), and an opioid and one of the other classes were present in an additional 327 cases. Overall, 478 of the 658 cases positive for opioids (including heroin) had an anti-depressant, benzodiazepine, or both present.

Multiple Opioids—Table 4 illustrates the distribution of the number of opioids detected when one of the most commonly occurring opioids was also present. Of the 658 decedents in which opioids were identified by toxicology, one opioid was detected in 62.9% of cases, two opioids were detected in 26.6% of the cases, and three or more opioids were detected in 10.6% of cases. Methadone, when found by toxicology, was significantly more likely than other opioids to be the sole opioid identified ($p < .05$). Hydrocodone was most frequently found with one other opioid. Oxycodone was equally likely to be found alone or with one other opioid.

In contrast, in the 21 cases when 6-AM (heroin) was identified, decedents were more likely to combine it with prescription opioids. Specifically, in more than 60% of the cases where heroin was found, more than two prescription opioids were also detected, a pattern different than noted for other opioids ($p < .001$).

Combinations of Prescription Medications with a Prescription Opioid—Other medications identified by toxicology, given the identification of methadone, hydrocodone, or oxycodone, are listed in Table 5. As noted in the table, in many cases, decedents ingested other prescription medications and alcohol and cocaine. Of note, 21–29.7% of the time alcohol was present, while cocaine was identified 8–10.9% of the time. Additionally, sertraline and venlafaxine were present about 22.5–31.6% of the time regardless of the opioid found. A benzodiazepine was present in at least 19% of the cases; alprazolam was present in at least 19% of the cases, and diazepam present in nearly one-third of cases.

Discussion

Between 1997 and 2003, there was a 300% increase in drug deaths in western Virginia—an increase strongly associated with the presence of prescription medications by toxicology, with prescription opioids the most commonly identified drug class (74.0%). The findings of this review of decedent cases are consistent with national findings reporting an increase in poisoning deaths over the last decade.[7] They are also consistent with reports in which opioid analgesic deaths outnumber deaths when heroin is involved.[7,11,12] Thus, these decedent cases reflect what is currently known about prescription overdose deaths, and this review expands our understanding of such drug overdose deaths by providing a level of detail not previously reported. Specifically, in this rural region:

- Older individuals, aged 35–45 years, represent the majority of the overdose cases, and women represent 37.1% of decedents. This is a group of decedents not previously identified at risk other than at an epidemiological level.
- Death rates are highest in rural areas, and prescription medications are much more likely to be found than illicit drugs of abuse.
- Polydrug deaths predominate, and we have identified the specific opioids, benzodiazepines, and antidepressants and combinations found on toxicology.

Older Individuals and Women

We might expect fatalities to be greatest among individuals using non-medically prescribed opioids, but this is not what we, or others, have reported. This group of decedents includes a disproportionate number of older individuals and women, a finding consistent with demographics reported nationally in prescription medication fatalities[5,7] and in New Mexico.[13,14] Consistently, epidemiological studies[2,3] state that adolescents and young adults (12–24 years old) are most likely to report drug abuse, and males who are 18–25-years-old report the highest rates of nonmedical prescription pain reliever use. Perhaps these epidemiological studies do not capture rates of nonmedical use of prescription medications among older people. Alternatively, it may be that the behavior that increases the risk of overdose and death is not what has been identified as nonmedical use. Although some use may have been for euphoria with diverted medications, some of the decedents may have had prescriptions for these medications, and inappropriate use, rather than behavior focused upon achieving euphoria (ie, abuse or addiction), led to overdose death. Therefore, use other than as prescribed by older individuals, which some authors have described as misuse,[15] may be a key factor in the increase in overdose deaths instead of abuse and addiction.

Rural Overdose Deaths

Although there are reports of increased numbers of prescription opioid deaths elsewhere in the nation,[5] our analysis allowed us to specifically focus upon rural prescription overdose deaths and highlight how they are different from urban deaths from the same cultural and political region of Virginia. Overall, this group of cases differs systematically from reports of illicit urban drug overdose deaths,[16,17] although in western Virginia, micropolitan and metropolitan decedents were more likely to die from abuse of heroin and cocaine. We have no explanation for the significantly higher death rate among rural cases; the prevalence of prescription opioids oxycodone, hydrocodone, and fentanyl; and the finding that benzodiazepines were more often identified among rural decedents. The similar prevalence of methadone equally among rural and urban decedents may be secondary to the lethality of this drug as a long-acting pharmaceutical. In this rural area, these decedents appear to have had access to prescription medications rather than heroin and cocaine, more available even in the smaller urban areas of western Virginia. Setting aside the issue of whether or not a decedent had a prescription for the medication listed as cause of death or whether the use is licit or illicit, interventions to prevent overdose deaths where a prescription medication is causal differ from those to prevent fatal overdoses where illegal drugs (ie, heroin and cocaine) predominate. In at least some of the cases, these medications were diverted from patients for whom they were prescribed, and in others, the fatal agent may have been prescribed to the decedent. In any case, the potential toxicity of these agents must be balanced with appropriate access for use as effective medications along with a clear message about safe use of medications with potential for overdose.

Our findings align with descriptions of the treatment needs of rural residents abusing and addicted to prescription medications. Perhaps adequate access to prescription medication addiction treatment, often a problem in rural areas, might have prevented some of these deaths. For example, among patients in rural New Hampshire, patients are less likely to abuse illicit substances, prescription opioids predominate as drugs of abuse, and patients may have been prescribed the drug they are abusing in addition to other prescription medications with abuse potential such as benzodiazepines.[18] The medications abused by these patients are similar to those that were fatal among rural decedents. Among 5,663 prescription opioid-dependent individuals admitted to methadone maintenance programs, Rosenblum reported that patients from low-density populated counties were more likely to abuse prescription opioids and were predominantly younger, employed women.[19] Similarly, among our decedents, women were more likely to be employed than men and have more education, as evidenced by a bachelor's degree, trade, or graduate degree.

Rosenblum proposes that the lack of availability of heroin in rural populations explains the predominance of prescription opioids abuse and addiction. There is also a dearth of heroin in rural Virginia; however, this would not explain the presence of multiple classes of prescription medications in the same decedent as well as deaths where antidepressant medications and benzodiazepines were identified. This would seem to have little to do with a lack of availability of heroin but might again indicate foci of effective treatment and targets for intervention to prevent diversion.

Prevalence of Polydrug Deaths

Rarely was the cause of death one drug, and in 151 cases, all three focal drug classes (opioids, benzodiazepines, and antidepressants) were detected. These patterns are consistent with those of other descriptions of polydrug overdose deaths[20–25] and indicate that this is a rather complex area in which to intervene, as there are multiple medications implicated in these deaths.

In our review, when hydrocodone or oxycodone was present, more than one opioid was found, indicating that, from whatever source, decedents have access to multiple opioids. When methadone was present, it was the sole opioid present in nearly 70% of the cases. Additionally, methadone was found more commonly among younger people age 14–25 years old. Because of the pharmacology of methadone and the potential for lethal overdose, we were not surprised that methadone was found often, and alone, in these drug deaths. Nonetheless, we suggest that the frequent presence of methadone as the sole opioids in young decedents should inform the interventions to prevent opioid overdose deaths. Particularly among older decedents, methadone was often combined with benzodiazepines and antidepressants. Again, some of these medications may not have been prescribed (eg, they were obtained by diversion), but these results emphasize the importance of educating patients to take medications only as directed, and not to share medications or combine medications.

Given the known potential for overdose secondary to respiratory suppression, we were not surprised to find significant numbers of cases where benzodiazepines and opioids were identified and that at least 20% of the cases alcohol was present with an opioid.[26,27] However, identification of substantial numbers of antidepressants on toxicology, and their association with opioids in 22% of overdoses, was of particular interest from a clinical and toxicological perspective. As has already been discussed, we do not know if antidepressants found were prescribed for the decedent; however, given the co-occurrence of depression and substance abuse, some of these decedents may have had prescriptions for antidepressants. Recent DAWN results emphasize the co-occurrence of depression and substance abuse as well as potential for overdose using prescribed medications. According to 2006 DAWN ED reports of drug-related visits, in 68% of mentions, the co-occurring disorder was depression, and over a third of the time, patients were diagnosed with an overdose.[28] Therefore, the identification of antidepressants in these decedents suggests an area for intervention in prescribing patterns and patient education. There may be an overdose risk in the patient prescribed antidepressants, like the opioids and benzodiazepines, if they are not taken as prescribed, combined with other medications, or “shared” with others.

Investigation of the metabolic and toxicological implications of antidepressants, with particular emphasis on the drug-drug interactions and combinations present most often in overdose deaths, is a significant area of interest to forensic toxicologists and forensic pathologists. For example, several antidepressants in the SSRI and SNRI class (eg, fluoxetine, fluvoxamine, paroxetine, and sertraline) are capable of inhibiting, to varying degrees, CYP2D6 (primarily), CYP3A4, and CYP1A2 enzymes. The result is perturbation in the biotransformation of opioids resulting in increased blood concentrations of the drug and increased pharmacological effect and toxic side effects.[29]

These cases illustrate that it is not only younger people who are using prescription medications other than as prescribed. One of the factors increasing deaths where prescription medications are found, particularly opioids, may be use by individuals who are not the younger age group typically identified as abusing drugs and alcohol. For clinicians, the education of patients over age 35 years about appropriate use of prescribed medications may prevent overdose deaths in this population. When prescribing any psychoactive drug for any patient, clinicians must remind all patients that medications should be taken only as directed, should not be combined with other medications unless prescribed, and should be taken only by the patient for whom they are prescribed. In the case of opioid prescriptions, nonmedical use may be prevented by the use of Gourlay and Heit's Universal Precautions.[30] For patients with chronic non-malignant pain and a diagnosis of addiction, careful prescribing of opioids to prevent diversion is well outlined in guidelines proposed by Weaver and Schnoll.[31]

Limitations

There are inherent limitations in the study and characterization of a population where the cause of death is drug overdose. First, it is difficult to define the exact cause of death in cases with multiple or mixed drug intoxications. Postmortem toxicology is confronted by challenges such as anatomical sampling sites (eg, central or heart blood versus peripheral blood, such as femoral or iliac vessel blood), putrefactive and decompositional effects, postmortem redistribution of drugs, and the effects of drug tolerance and abstinence.[32] There are inherent difficulties in assigning causation.[20] Nonetheless, important findings emerged from our analysis. Second, classification for cause of death is determined by more than the presence or absence of a drug by toxicological analyses. Assignment of significance of each drug or drug metabolite may differ among toxicologists and forensic pathologists. We did not include concentrations of drugs or metabolites in this report because contribution to establishing causation without benefit of complete autopsy reports and the totality of each case's investigative information is limiting.

Comprehensive toxicological studies are directed by the nature and circumstances of the death. We are aware that some deaths in this region were not included in this analysis, as described in the methods section, and some decedent's cases were not included because of limited toxicology. Additionally, some of the medical examiner calls in the Western District of Virginia are initially investigated by local or field medical examiners and not referred for autopsy. Blood specimens collected undergo limited toxicological examinations, usually only for ethyl alcohol. Decedents in this group would not be included in the 889 cohort of cases we reviewed. We propose that exclusion of this data probably results in an underestimation of the problem, but in reality we have little information about the characteristics of those cases not included in our analysis.

Finally, the decedents we studied were from a specific geographic region, and so results may not generalize to other rural areas. However, our results are similar to those found in other primarily rural states across the nation and therefore should be of some utility in defining and addressing this emerging problem.[5]

Summary

Our in-depth study of overdose fatalities presents findings aligned with national epidemiological studies that describe increasing numbers nationwide of prescription medication overdose deaths, particularly among older individuals. In 889 drug overdose deaths from 1997–2003 among rural western Virginians, a predominance of prescription opioids, in combination with antidepressants and benzodiazepines on toxicology, is reported as a contributing cause of death rather than illicit drugs. Motivation for possession and use of these medications, treatment of a medical condition, or euphoria is unknown; however, these deaths have occurred disproportionately among an older population (age 35–45 years old), not the population described as engaging in nonmedical use in national surveys. Particularly among those rural decedents, illicit drugs were not often found in these deaths, suggesting that these decedents were not abusing or addicted to heroin or cocaine at the time of overdose. Interventions to prevent these deaths will involve, of course, identifying the rural individuals who are abusing or addicted to prescription medications and providing treatment that is focused upon those medications instead of upon primarily illicit drugs. In addition to the awareness about potential diversion and the nonmedical use of medications by youths, physicians should also be aware that an older population of patients (ie, patients 35-45-years-old) may be at risk. Given the identification of older decedents in our study and nationally, this population may not be taking these medications as directed or may be abusing or addicted to prescription medications, instead of illicit drugs. As policy makers and researchers formulate a response to the increase in non-medical use of prescription medications, an older population should be targeted for education as well as youths. We should educate all patients, and their families, about taking medication only as prescribed, only by the individual for whom is it intended, and the dangers of combining medications without prescriber knowledge.

Acknowledgments

Work on this project was supported by research grant #R03 DA019047-01A1 from the National Institute of Drug Abuse, Institutes of Health, Bethesda, Md. (Dr. Wunsch).

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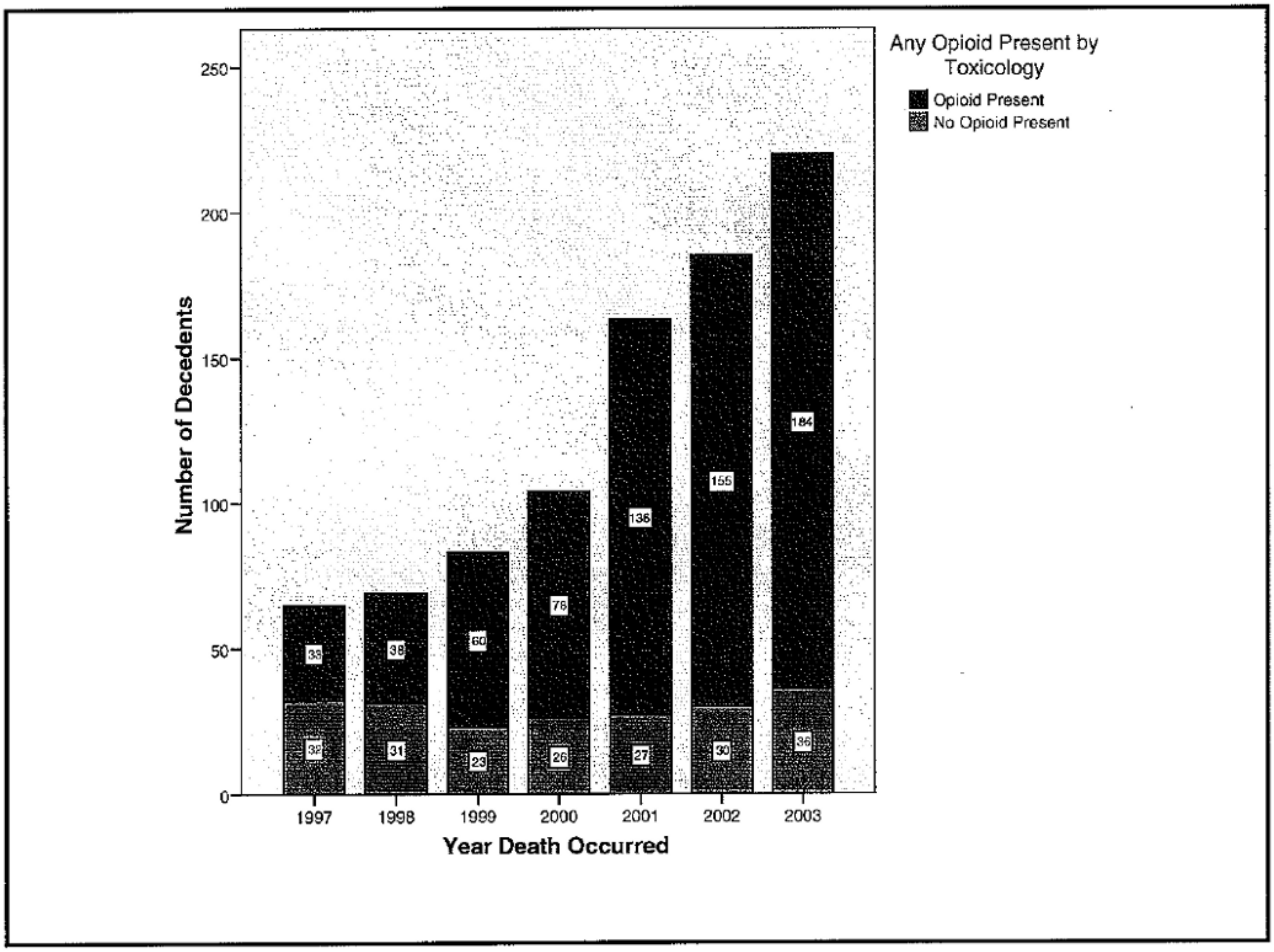

FIGURE 1.

Medical examiner drug-related deaths in Western Virginia. Figure 1 illustrates that the increase in overall drug-related deaths in western Virginia from 1997 to 2003 was primarily due to cases where an opioid was present on toxiology.

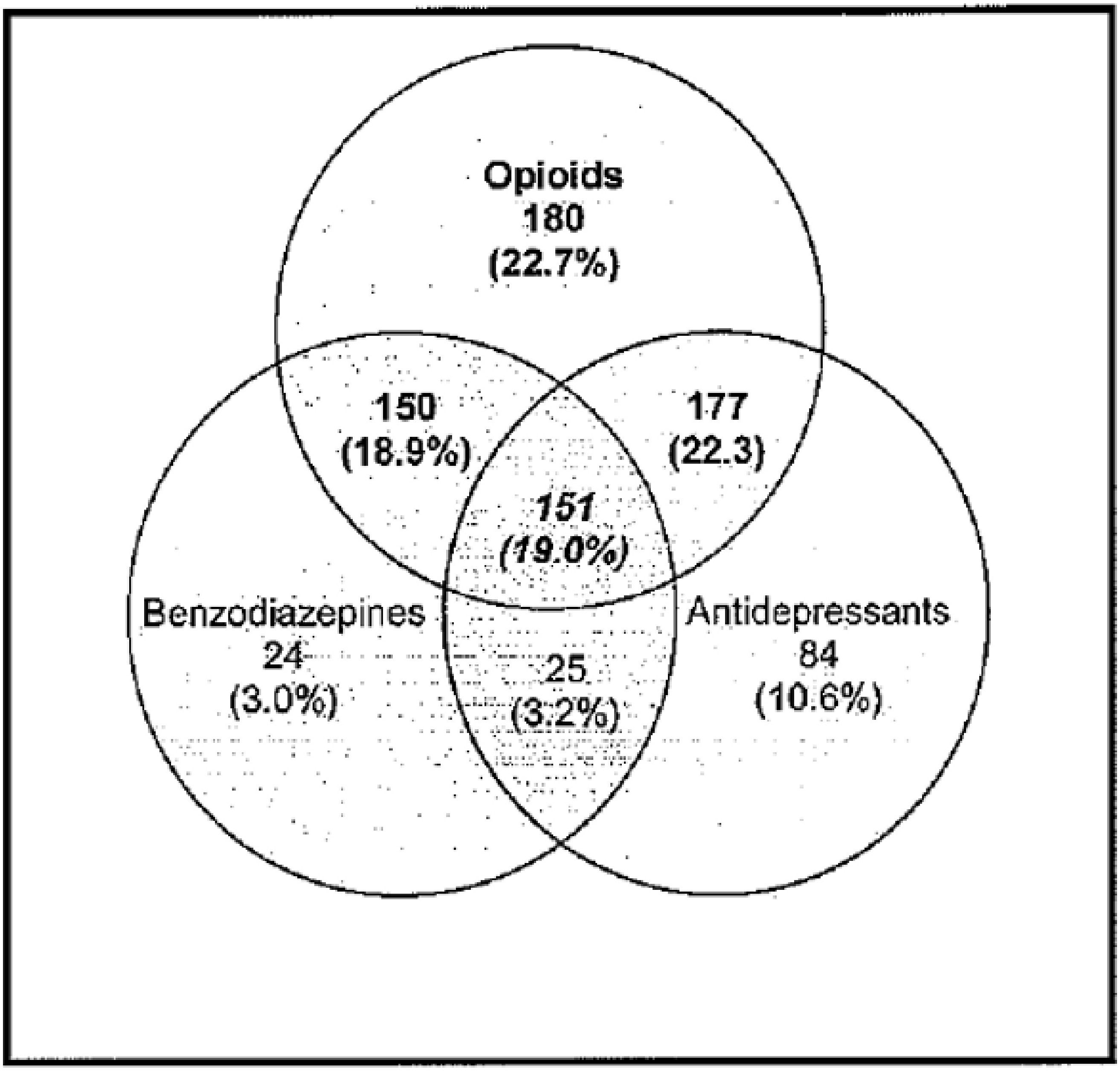

FIGURE 2.
Pharmaceutical classes found by toxicology (N = 793 cases; 96 cases with none of these three drug classes)

TABLE 1

Percentage of prescription medications and 6 AM (acetylmorphine) identified by toxicology

Opioids, benzodiazepines, and anti-depressants identified on toxicology (% of cases, N = 893)			
	Overall	**Male**	**Female**
Opioids			
Methadone	28.0	33.5	18.7
Hydrocodone†	20.4	19.8	21.5
Oxycodone†	19.6	21.7	15.7
Morphine	11.4	12.1	10.0
Propoxyphene	9.8	9.6	10.3
Fentanyl†	5.1	4.6	5.7
Oxymorphone	3.7	4.6	2.1
Codeine	3.1	3.4	2.7
Tramadol	3.1	2.0	5.1
Hydromorphone	2.8	3.4	1.8
6-acetylmorphine*	2.4	3.2	0.9
Meperidine	1.0	0.2	2.4
Dihydrocodeine	0.3	0.4	0.3
Pentazocine	0.2	0.0	0.6
Dihydrocodone	0.1	0.2	0.0
Hydrocodeine	0.1	0.2	0.0
Benzodiazepines†			
Diazepam	24.3	25.6	21.8
Alprazolam	15.4	15.5	15.4
Clonazepam	1.5	1.6	1.2
Chlordiazepoxide	0.7	0.9	0.3
Temazepam	0.7	0.9	0.3
Lorazepam	0.4	0.4	0.6
Flurazepam	0.2	0.0	0.6
Oxazepam	0.2	0.2	0.3
Triazolam	0.1	0.0	0.3
Anti-depressants			
SSRI			
Sertraline	22.7	22.8	22.7
Citalopram	6.1	5.0	7.9
Fluoxetine	6.1	3.2	10.9
Paroxetine	2.7	2.1	3.6
Fluvoxamine	0.4	0.4	0.6
Tricyclics			
Amitriptyline	9.8	6.8	14.8
Nortriptyline	9.0	5.7	14.5
Doxepin	2.2	1.4	3.6

Opioids, benzodiazepines, and anti-depressants identified on toxicology (% of cases, N = 893)			
	Overall	**Male**	**Female**
Imipramine	0.8	0.2	1.8
Desipramine	0.7	0.2	1.5
Clomipramine	0.4	0.4	0.6
Amoxapine	0.1	0.0	0.3
Trimipramine	0.1	0.2	0.0
Tetracyclics			
Mirtazapine	4.6	4.8	4.2
Other			
Venlafaxine	20.8	21.2	19.9
Trazodone	3.7	1.8	6.9
Bupropion	2.1	1.6	3.0

This table describes the percentage of cases in which prescription medications were identified on toxicology in these medical examiner cases.

*Toxicological and chemical marker for heroin

†Identified more often in rural rather than micropolitan and metropolitan areas

TABLE 2

Demographic profile of decedents

	Number of cases (column %)			
	All	**Female (37.1%)**	**Male (62.9%)**	***p* value**
Metropolitan	416 (46.8)	166 (50.3)	250 (44.7)	
Micropolitan	98 (11.0)	39 (11.8)	59 (10.6)	
Rural	375 (42.2)	125 (37.9)	250 (42.2)	
Race/ethnicity				NS
Non-Hispanic white	830 (96.8)	313 (94.8)	517 (93.5)	
African American	51 (2.5)	15 (4.5)	36 (6.5)	
Hispanic	2 (0.4)	0 (0.0)	2 (0.4)	
Native American	2 (0.4)	1 (0.4)	2 (0.4)	
Asian	1 (0.2)	0 (0.0)	1 (0.2)	
Age group (years)				<.001
10–25	98 (11.0)	27 (8.2)	71 (12.7)	
26–35	196 (22.0)	51 (15.5)	145 (25.9)	
36–45	361 (40.6)	145 (43.9)	216 (38.6)	
46–54	177 (19.9)	71 (21.5)	106 (19.0)	
55 or older	57 (6.4)	36 (10.9)	21 (3.8)	
Education				<.005
<High school	301 (34.8)	104 (32.9)	197 (35.9)	
High school diploma	386 (44.7)	124 (39.2)	262 (47.8)	
Trade/AS	118 (13.7)	58 (18.4)	60 (10.9)	
Bachelor's degree	42 (4.9)	21 (6.6)	21 (3.8)	
Graduate study	17 (2.0)	9 (2.8)	8 (1.5)	
Employment status				<.001
Employed	441 (56.8)	193 (65.4)	248 (51.5)	
Retired	23 (3.0)	10 (3.4)	13 (2.7)	
Disabled	206 (26.5)	59 (20.0)	147 (30.5)	
Unemployed	107 (13.8)	33 (11.2)	74 (15.4)	
Manner of death				<.001
Accident	631 (71.1)	190 (57.8)	441 (78.9)	
Suicide	227 (25.6)	126 (38.3)	101 (18.1)	
Undetermined	24 (2.7)	11 (3.3)	13 (2.3)	
Natural	6 (0.7)	2 (0.6)	4 (0.7)	

This table lists the location of death, demographics, education, employment status, and manner of death among medical examiner cases with stratification by gender.

TABLE 3

Location of decedent cases by population density

Population density	Decedent cases (%)	Population (2000 census)	Annual deaths per 100,000 (crude) (α = .95)	
Metropolitan (MSA)	420 (46.8%)	886,546	6.77	(6.12,7.42)
Micropolitan	98 (11.0%)	182,334	7.68	(6.16,9.20)
Rural	375 (42.2%)	497,725	10.76	(9.67,11.85)

TABLE 4

Number of opioids found in presence of specific opioids

Opioid present by toxicology	No other opioids identified by toxicology	Only one other opioid identified toxicology	Two or more other opioids identified by toxicology
Methadone	69.9%	22.1%	8.0%
Oxycodone	37.9%	37.9%	24.1%
Hydrocodone	27.6%	44.8%	27.6%
Heroin (6-AM)	None*	38.1%	61.9%

TABLE 5

Other drugs present on toxicology when methadone, hydrocodone, or oxycodone were detected (% of positive cases)

	Reference opioid present on toxicology		
	Methadone	**Hydrocodone**	**Oxycodone**
Number of cases	250	182	174
Other substance present			
Opioids			
Fentanyl	1.6	7.1	5.2
Hydrocodone	13.2		31.6
Hydromorphone	1.2	8.8	2.9
Methadone		18.1	14.4
Morphine	3.6	6.6	7.5
Oxycodone	10.0	30.2	
Oxymorphone	0.8	7.1	19.0
Propoxyphene	6.4	15.4	8.0
Tramadol	0.4	5.5	1.7
Benzodiazepines			
Alprazolam	19.2	23.1	18.4
Diazepam	32.8	26.9	32.2
Anti-depressants			
Sertraline	25.6	23.1	32.2
Amitriptyline	8.0	12.6	8.6
Nortriptyline	6.8	11.5	6.3
Venlafaxine	23.6	22.5	31.6
Other substances			
Cocaine	10.4	8.2	10.9
Ethanol	21.6	29.7	26.4