Mental Illness and Psychotropic Drug Use Among Prescription Drug Overdose Deaths: A Medical Examiner Chart Review

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Objective: Between 1999 and 2006, there was a 120% increase in the rate of unintentional drug overdose deaths in the United States. This study identifies the prevalence of mental illness, a risk factor for substance abuse, and chronic pain among prescription drug overdose deaths in West Virginia and ascertains whether psychotropic drugs contributing to the deaths were used to treat mental illness or for nonmedical purposes.

Method: In 2007, we abstracted data on mental illness, pain, and drugs contributing to death from all unintentional prescription drug overdose deaths in 2006 recorded by the West Virginia Office of the Chief Medical Examiner. Decedent prescription records were obtained from the state prescription drug monitoring program.

Results: Histories of mental illness and pain were documented in 42.7% and 56.6% of 295 decedents, respectively. Psychotropic drugs contributed to 48.8% of the deaths, with benzodiazepines involved in 36.6%. Benzodiazepines contributing to death were not associated with mental illness (adjusted odds ratio [AOR] = 1.1; 95% CI, 0.6–1.8), while all other psychotropic drugs were (AOR = 3.9; 95% CI, 2.0–7.6). Of decedents with contributory benzodiazepines, 46.3% had no prescription for the drug.

Conclusions: Mental illness may have contributed to substance abuse associated with deaths. Clinicians should screen for mental illness when prescribing opioids and recommend psychotherapy as an adjunct or an alternate to pharmacotherapy. Benzodiazepines may have been used nonmedically rather than as a psychotropic drug, reflecting drug diversion. Restricting benzodiazepine prescriptions to a 30-day supply with no refills might be considered.

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Deaths resulting from unintentional drug overdoses have risen to epidemic proportions in the United States, increasing by 120% during the years 1999–2006.[1] This increase has largely been attributed to prescription drugs, rather than to illicit drugs. Most of the problem is due to deaths from opioid analgesics[2]; these deaths have increased in parallel with the number of prescriptions for such drugs.[3] While studies have focused on the role of chronic pain, drug diversion, and "doctor shopping" in prescription drug overdose deaths,[4,5] few studies of these deaths have focused on mental health problems and the medications used to treat such problems.

Previous research has found that those who have mental disorders are more likely to have drug use disorders (ie, drug abuse and drug dependence).[6] Approximately 15%–20% of persons with mental disorders have a drug use disorder at some point in their lifetimes.[6,7] People who report having a diagnosis of major depressive disorder within the past year are 3.7 times more likely to report drug dependence.[6] In addition, people with mental disorders are twice as likely as those without mental disorders to use prescribed opioids.[8]

Other epidemiologic studies have examined the mental disorders of those persons with drug use disorders. One study found that over half (53%) of persons with drug use disorders had non–substance abuse mental disorders, or 4.5 times the odds of persons without drug disorders.[7] Another epidemiologic survey found that 32% of drug abusers had mood disorders, while 25% had anxiety disorders[9]; the study also found that nonmedical use of opioids was strongly associated with mood disorders, anxiety disorders, and personality disorders.[10] Further, research regarding prescription drug overdose deaths suggests that a large proportion of decedents had histories of mental illness.[4]

In general, studies of deaths from drug overdoses have supported such self-reported associations.[11] In New Jersey, for example, 24.4% of persons who died of unintentional drug overdoses had histories of mental health risk factors.[5] However, the prevalence of mental illness may be higher for deaths involving prescription drugs, some of which are prescribed for mental disorders. Studies of deaths involving both illicit drugs and prescription opioids have reported a high likelihood of finding prescription psychotropic drugs (ie, drugs prescribed to treat mental disorders) on

postmortem toxicology reports,[12] even though such drugs are rarely responsible for overdose deaths by themselves.[4]

One aspect of the association between mental illness and psychotropic drugs that has not been examined is whether psychotropic drugs involved in prescription drug overdoses have been prescribed to treat mental illness or are being used nonmedically as part of a substance use disorder. Benzodiazepine sedatives, for example, are prescribed for anxiety disorders, but they are also often combined with drugs that produce a euphoric effect, such as heroin or prescription analgesics, and are addictive in their own right when misused.[13] Therefore, one aim of this study was to determine the prevalence of mental illness and psychotropic drug involvement in a population that had died of prescription drug–related overdoses and the overlap between the two.

In addition, little is known about how persons with mental illness and a history of chronic pain come to use prescription painkillers. Therefore, a second aim of the present study was to describe the association between mental illness and chronic pain among drug overdose deaths. Our hope was to identify associations among mental illness, psychotropic drugs, and pain to help guide prevention efforts in reducing prescription drug overdose deaths.

METHOD

Case Identification and Data Sources

All decedents were West Virginia residents who died within the state in 2006. West Virginia was selected because it experienced the largest increase (675%) in the unintentional drug overdose mortality rate among all US states between 1999 and 2004.[1] Decedent records were reviewed if the death certificates listed the underlying cause of death as unintentional drug poisoning (*International Classification of Diseases, 10th Revision* [*ICD-10*] codes X40–X44). All cases were identified via an electronic database of vital records at the Health Statistics Center of the West Virginia Department of Health and Human Resources using the appropriate *ICD-10* codes. Identifying information was cross-referenced with the case logbook and electronic database of the investigations of the Office of the Chief Medical Examiner (OCME) to identify decedent records. We excluded all decedents certified without benefit of autopsy as well as those decedents in whom the only drugs contributing to death were illicit or over-the-counter drugs. In West Virginia, the chief toxicologist routinely screens all potential victims of drug overdose for illicit and prescription drugs. Trained and certified death investigators conduct scene-of-death investigations and write reports on all drug-related cases. Subsequently, OCME staff forensic pathologists review these reports, medical records, decedents' prescription records, autopsy and toxicology findings, and other evidence to determine which factors, including drugs, are contributory to death.

In late 2007, we abstracted information from autopsy reports, toxicology reports, death-scene investigation reports, death certificates, and copies of medical records in the OCME files. The West Virginia Board of Pharmacy also provided decedent prescription histories available through the state's Controlled Substances Monitoring Program (CSMP), which, since its inception in 2003, has maintained electronic records of all Schedule II, III, and IV, and prescribed Schedule V controlled substances* dispensed by all pharmacies licensed by the State of West Virginia.

Variables

We characterized the decedents in terms of sociodemographic factors, history of chronic pain, and history of mental illness. Demographic information on the decedents, including sex, age, marital status, and highest level of education, was collected from death certificates. The OCME death scene investigation reports, medical records, and autopsy reports were also used to determine past medical histories and comorbidities.

A history of mental illness (hereafter referred to as mental illness) was derived from diagnoses recorded in medical records and information reported to death scene investigators. Specific diagnoses could not be independently verified with criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (*DSM-IV*) due to the study population of decedents. Thus, diagnoses were recorded as they appeared, even when mutually exclusive disorders were listed. Disorders were grouped into major diagnostic categories. However, 2 individual disorders, major depressive disorder and bipolar disorder, were recorded separately because they are strongly associated with substance abuse and chronic pain and have different pharmacotherapies.

A history of pain was identified from medical records and death scene investigation records. Pain was classified by anatomic system as decided before our investigation. The nature and location of the pain was used to classify the pain as *subjective*—the source of the pain was likely to be taken from the patient's own statement; *objective*—the pain was likely to be apparent from physical findings; and *unclassifiable*. Subjective pain included that of fibromyalgia, headaches, neck/back, and neuralgia. Objective pain included that of cancer, infection, recent dental work, and trauma. Unclassifiable pain included arthritis, gastrointestinal, genitourinary, heart/chest, and orofacial pain.

We also assessed the proportion of cases that had at least 1 psychotropic drug contributing to death, as determined by the OCME. Psychotropic drugs were prescription drugs usually used to treat mental disorders. We categorized

*As defined by the Controlled Substances Act, the term *controlled substance* means a drug or other substance, or immediate precursor, included in Schedule I, II, III, IV, or V, available at http://www.usdoj.gov/dea/pubs/csa.html. Narcotic painkillers are primarily Schedule II, and benzodiazepines are Schedule IV.

Table 1. Prevalence of Key Variables Among Persons Dying of Prescription Drug Overdoses in West Virginia in 2006 (N = 295)

Characteristic	n	%
Mental illness (excludes substance abuse)[a]	126	42.7
Mood disorders		
Major depressive disorder	77	26.1
Bipolar disorder	24	8.1
Anxiety disorders	52	17.6
Sleep disorders	10	3.4
Psychotic disorders	7	2.4
All other disorders	7	2.4
Substance abuse disorders[b]	232	78.6
Alcohol use disorder	97	32.9
Pain	167	56.6
Any psychotropic drug	144	48.8
Any benzodiazepine	108	36.6
Only benzodiazepine	84	28.5
Antidepressant or other psychotropic drug[c]	61	20.7
Antidepressant	49	16.6
Other psychotropic drug	16	5.4

[a]Mental illness classification is based on a history of mental illness as found in medical records or reported in death investigations; categories are not mutually exclusive, so that totals exceed 100%.
[b]Although substance abuse disorders are considered mental disorders, in this study, mental illness refers to non–substance abuse mental disorders.
[c]Other psychotropic drugs include carbamazepine, hydroxyzine, phenobarbital, quetiapine, topiramate, and zolpidem.

Table 2. Association of History of Mental Illness and Contributory Drug Classes in West Virginia in 2006

	Mental Illness		
Contributory Drug Class	N (%)[a]	Adjusted Odds Ratio[b,c]	95% CI[c]
Any psychotropic drug	75 (52.1)	**2.1**	**1.3–3.5**
Any benzodiazepine	46 (42.6)	1.1	0.6–1.8
Only benzodiazepine	33 (39.3)	0.9	0.5–1.6
Antidepressant or other psychotropic drug[d]	42 (68.9)	**3.9**	**2.0–7.6**
Antidepressant	33 (67.4)	**2.7**	**1.3–5.3**
Other psychotropic drug[e]	14 (87.5)	**9.8**	**2.1–45.7**

[a]Number and percent of decedents with a history of mental illness among all deaths involving this class of drugs.
[b]Referent is all others not included in each row.
[c]Boldface type indicates statistical significance.
[d]Decedents with these contributory drugs may also have had a contributory benzodiazepine.
[e]Other psychotropic drugs include carbamazepine, hydroxyzine, phenobarbital, quetiapine, topiramate, and zolpidem.

psychotropic drugs into drug class on the basis of the drug reference vocabulary established by the Drug Alert and Warning Network.[12] Drug classes included benzodiazepines, antidepressants, and "other psychotropics," which included anticonvulsants and antipsychotics, among others. We used information from both the CSMP and the OCME to determine whether decedents using benzodiazepines had prescriptions for those drugs.

Statistical Analysis

First, we calculated the prevalence of mental illness and specific disorders as well as classes of contributory psychotropic drugs. We then used multiple logistic regression to examine the association between mental illness and psychotropic drugs, controlling for age and sex, which were found to be significantly associated with mental illness in univariate models. We ran multiple logistic regressions to determine if each drug class was associated with mental illness.

Next, we compared decedents with and without mental illness, using multiple logistic regression to examine associations with demographic factors. Except for cases in which age was the variable of interest, age was used as a continuous variable. Consistent with census methodology,[14] we limited the analysis of highest level of education attained to decedents aged ≥ 25 years. For analyses that involved cell sizes less than 5, the Fisher exact test was used.

We also calculated the associations between demographic variables and having at least 1 psychotropic drug contributory to death, having a benzodiazepine as the only psychotropic drug, and having at least 1 psychotropic drug that was not a benzodiazepine. We examined benzodiazepines independently due to their propensity for abuse.

We used available information on prescription history to further characterize how benzodiazepines were being used. We conducted a Cochrane-Armitage test for trend in the association between mental illness and the number of benzodiazepines prescribed. We also identified the proportion of decedents who had been prescribed benzodiazepines that contributed to death.

Finally, controlling for sex and age, we conducted a series of multiple logistic regressions to look at the association between mental illness and varied types of pain by comparing decedents with each pain type to decedents with no pain: a history of any pain; subjective, unclassifiable, or objective pain; and specific subtypes of pain. All analyses were conducted by use of SAS software, Version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

The study included 295 decedents who met inclusion criteria. Men composed 67.1% of the study population. More than half of the decedents (53.2%) were 35–54 years of age, while 38.6% were aged 18–34 and the remainder (8.1%) were aged 55 or older. Roughly half of the decedents (51.6%) had a high school education, a third (31.0%) had not graduated from high school, and the remainder (17.3%) had some college. Marital status was about evenly split between never married (34.9%), married (32.9%), and divorced or widowed (32.2%).

Of these 295 decedents, 126 (42.7%) had a history of mental illness other than substance abuse (Table 1). Mood disorders and anxiety disorders were most prevalent. A history of pain was found in 56.6% of decedents. Opioid analgesics contributed to 93% of the deaths. Psychotropic drugs contributed to 48.8% of all deaths (Table 1).

Table 3. Characteristics of Decedents With History of Mental Illness and Decedents With Contributory Psychotropic Drug Use in West Virginia in 2006 (N = 295)

Characteristic	All Deaths, n	Mental Illness (n = 126)		Any Psychotropic Drug (n = 144)	
		Percent With Mental Illness	Adjusted Odds Ratio[a,b] (95% CI)	Percent With Psychotropic Drug at Death	Adjusted Odds Ratio[a] (95% CI)
Sex					
Male	198	32.3	Reference	48.0	Reference
Female	97	63.9	**3.7 (2.2–6.4)**	50.5	1.1 (0.7–1.8)
Age group, y					
18–34	114	27.2	Reference	43.0	Reference
35–54	157	51.6	**2.9 (1.7–5.3)**	51.0	1.4 (0.8–2.2)
≥ 55	24	58.3	**3.8 (1.3–11.1)**	62.5	2.2 (0.9–5.4)
Marital status					
Married	97	50.5	Reference	50.5	Reference
Never married	103	27.8	0.6 (0.3–1.2)	41.2	0.8 (0.4–1.5)
Divorced/widowed	95	49.5	0.8 (0.4–1.5)	54.7	1.1 (0.6–2.0)
Highest education[c]					
Less than high school	77	44.1	Reference	48.0	Reference
High school diploma	128	43.8	1.1 (0.6–2.0)	53.1	1.3 (0.7–2.3)
Some college	43	58.1	1.8 (0.8–4.0)	44.2	0.9 (0.4–1.8)

[a]Adjusted for age and sex.
[b]Boldface type indicates statistical significance.
[c]Education calculated only for those aged ≥ 25 years (n = 248).

Table 4. Association of Pain Subtypes and Mental Illness as Compared to Decedents With No Pain in West Virginia in 2006

Pain Subtype	All Deaths, N	Mental Illness		
		n (%)[a]	Adjusted Odds Ratio[b,c]	95% CI[c]
Any pain	167	94 (56.3)	**3.5**	**2.0–6.1**
Subjective pain	107	67 (62.6)	**4.7**	**2.5–8.6**
Neck/back	88	54 (61.4)	**4.6**	**2.4–8.9**
Headache	28	18 (64.3)	**4.5**	**1.8–11.4**
Fibromyalgia	5	5 (100.0)	NA[d]	NA[d]
Neuralgia	6	4 (66.7)	NA[d]	NA[d]
Unclassified pain	50	22 (44.0)	**2.3**	**1.1–4.8**
Arthritis	41	24 (58.5)	**3.6**	**1.6–8.0**
Heart/chest	16	8 (50.0)	2.9	0.9–8.9
Gastrointestinal	15	10 (66.7)	NA[d]	NA[d]
Genitourinary	3	1 (33.3)	NA[d]	NA[d]
Orofacial	6	3 (50.0)	NA[d]	NA[d]
Objective pain	17	7 (41.2)	1.6	0.5–4.7
Cancer	5	2 (40.0)	NA[d]	NA[d]
Dental work	3	1 (33.3)	NA[d]	NA[d]
Infection	3	1 (33.3)	NA[d]	NA[d]
Trauma	6	3 (50.0)	NA[d]	NA[d]
Referent (decedents with no pain)	128	32 (25.0)	Referent	

[a]Number and percent of decedents in each row who had a history of mental illness.
[b]Adjusted for age and sex.
[c]Boldface type indicates statistical significance.
[d]Indicates an association with cell sizes too small to conduct multiple logistic regression.

Decedents with mental illness had over twice the odds of having a psychotropic drug contribute to death and were nearly 4 times as likely to have had an antidepressant or "other" psychotropic drug contribute to death, compared to decedents without mental illness. However, benzodiazepines contributing to death were not associated with mental illness (Table 2).

Mental illness was associated with female sex and greater age, while no associations were identified between contributory psychotropic drugs and any of the demographic variables examined (Table 3). There was no association between demographics and benzodiazepines as the only contributory psychotropic drug or between demographics and having at least 1 contributory antidepressant or "other" psychotropic (not shown).

Of decedents with contributory benzodiazepines, 53.7% had prescriptions for all benzodiazepines; the remaining 46.3% had at least 1 benzodiazepine for which they did *not* have a valid prescription. Regardless of whether benzodiazepines were involved in the decedent's fatal overdose, the number of different benzodiazepines prescribed in the year prior to death (eg, diazepam versus alprazolam) was significantly associated with mental illness in a dose-response fashion (test for trend: $Z = -5.3$, $P < .001$). The odds ratios were 2.5, 3.5, and 5.2 for 1, 2, and 3 or more unique benzodiazepines prescribed in the year prior to death, respectively.

Most decedents (56.6%) had a history of pain. Decedents with both subjective and unclassifiable pain were more likely to have mental illness (Table 4). The association with mental illness varied by pain subtype. Neck and back pain, headaches, and arthritis were all associated with mental illness, with odds ratios of 4.6, 4.5, and 3.6, respectively.

DISCUSSION

We found that nearly one-half of the people dying from a prescription drug overdose in West Virginia in 2006 had a history of mental illness during their lifetime and that over one-half had a history of chronic pain. Psychotropic drugs contributed to nearly one-half of the overdoses in this study population, usually in combination with an opioid; of these, about three-fourths of those deaths involved a benzodiazepine. We found that psychotropic drugs were associated with mental illness, but, for benzodiazepines, specifically, there was no association with mental illness. Mental illness

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was associated with sex, age, and both subjective and unclassifiable pain; therefore, we were surprised that psychotropic drugs, commonly used to treat mental health problems, were not associated with these same demographic or pain variables. These findings suggest that benzodiazepines are being diverted and used nonmedically.

Although mental illness was common in our study, its prevalence is comparable to the lifetime prevalence in the United States as a whole.[15] The prevalence of mood disorders, including major depressive disorder and bipolar disorder, was higher than national figures. Anxiety disorders and sleep disorders were lower in study decedents than in national data, and psychotic disorders were equivalent. The increased rate of mood disorders in this study is not surprising in light of the fact that substance use disorders and mood disorders are highly correlated.[15]

There was a significant association between contributory psychotropic drug use and mental illness. This association was strong for antidepressant and other psychotropic drug classes, but it did not hold for benzodiazepines, which constituted the largest proportion of psychotropic drugs. However, the significant dose-response relationship between the number of prescriptions for different benzodiazepines and mental illness suggests that some benzodiazepines were being used medically. Perhaps those with multiple prescriptions had a specific mental illness requiring more complex treatment, whereas those with complaints of nonspecific anxiety received a prescription without a diagnosable illness. Nonetheless, the widespread use of benzodiazepines by people without mental illness and the finding that 46.3% of people did not have prescriptions for at least 1 benzodiazepine that contributed to death suggest that abuse of benzodiazepines was involved. This finding is consistent with the known use of benzodiazepines by drug abusers to moderate the effects of cocaine, heroin, or opioids and the Drug Enforcement Administration's opinion that benzodiazepines are among the most commonly abused drugs in West Virginia.[16]

While we found that female decedents in this study were nearly twice as likely as male decedents to have mood and anxiety disorders, consistent with national findings in the general population,[15] we found no association between sex and psychotropic drug involvement in the overdoses, a finding not consistent with data demonstrating that women are more likely to be prescribed psychotropic drugs than men in the United States.[17–19] Because men composed two-thirds of the study population, this lack of association is very likely due to the high prevalence of nonmedical use and diversion of psychotropic drugs in this population and the known association between male sex and drug abuse.[4,20] Although the literature does not suggest that increasing age is a risk factor for mental illness, we found that, in our population, increasing age was associated with mental illness but not with psychotropic drug involvement. However, there may be differences between a decedent population and the general population.

The association we found between mental illness and pain is consistent with the literature. The World Health Organization suggests that people with chronic pain have a 4-fold increase in anxiety and depressive disorders.[21] Among decedents dying of drug overdoses, however, we found that mental illness was associated with only certain types of pain. There are several potential explanations for this finding. People without a physically verifiable cause of pain may have been more likely to have been labeled as mentally ill. Alternatively, people with mental illness may have been more likely to seek care and complain of some types of pain. Underlying symptoms of mental illness tend to exacerbate the intensity of and focus upon one's pain.[22] Finally, given the established association between substance abuse disorders and other mental illnesses, individuals with such disorders might use subjective pain complaints as a mechanism to obtain prescription drugs for nonmedical purposes. The comorbidity of substance abuse and other mental disorders generates such complaints when patients realize they have a high likelihood of obtaining narcotic painkillers.

Limitations

The limitations of this study are the result of substantial uncertainties inherent in the nature of death investigation systems and CSMP prescription data collection. First, the diagnosis of mental disorders and reporting of pain were based upon the OCME records, which were not always consistent among data sources. For instance, medical records were available for only 43% of decedents, and not all death-scene investigation reports addressed mental illness. Further, some diagnoses were based on reports by friends and family and, therefore, may not have met true criteria for diagnosis. In addition, listing of death-scene medications and statewide CSMP data collection were incomplete, and CSMP data were limited to scheduled drugs; thus, no reliable analyses of the prescription history for antidepressants and other psychotropic drugs could be conducted.

Recommendations

Clinicians should assess pain patients for a history of both drug abuse and mental illness. Currently, clinicians are told to use caution in their prescribing of opioids to people with a history of substance abuse.[23] This guidance should also apply for prescribing to patients with a history of mental illness, particularly if patient reports of pain have no physical findings. Chronic pain has high comorbidity with anxiety and mood disorders. Clinicians should consider referring patients for psychotherapy because it has been shown to be an important adjunct in the treatment of chronic pain[24] and may reduce the need for opioid analgesics. Further, cognitive-behavioral therapy has been shown to be highly effective in treating adult anxiety disorders,[25] and such therapy may reduce the need for benzodiazepines. Clinicians should be cautious when prescribing opioids

and benzodiazepines concurrently for chronic pain, even in patients without mental illness, unless there is a specific medical indication.[23] Judicious prescribing of opioid analgesics and benzodiazepines not only might help prevent abuse in patients but also might reduce the ambient level of drugs subject to abuse in the community.

States can also employ administrative tools to address the problem of abuse of psychotropic drugs. West Virginia and other states with benzodiazepine abuse problems should consider treating benzodiazepines, currently Schedule IV drugs, like Schedule II drugs by specifically restricting them to a 30-day supply with no refills. States with prescription drug abuse problems should also consider expanding their use of prescription drug monitoring program data for case management and surveillance. With these data, clinicians and pharmacists could monitor their patients' prescriptions, medical examiners could review the drug use history of decedents, and public health agencies could better identify provider characteristics and high-risk populations for prescription drug abuse as well as the impact of prevention measures.

Drug names: alprazolam (Xanax, Niravam, and others), carbamazepine (Carbatrol, Equetro, and others), diazepam (Diastat, Valium, and others), hydroxyzine (Vistaril and others) quetiapine (Seroquel), topiramate (Topamax), zolpidem (Ambien, Edluar, and others).

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