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Effect of Comorbid Alcohol and Drug Use Disorders on Premature Death Among Unipolar and Bipolar Disorder Decedents in the United States, 1999–2006

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Abstract

Objective—To quantify the effect of comorbid alcohol and drug use disorders on premature death, as reflected by the manner of death (suicide and other unnatural death versus natural death) and the age at death, among decedents with unipolar and bipolar disorders.

Methods—This study is based on the U.S. Multiple Cause of Death (MCD) public-use data files for 1999–2006. Secondary data analysis was conducted comparing decedents with unipolar/bipolar disorders and decedents with all other causes of death, based on the death records of 19,052,468 decedents in the MCD data files who died at age 15 and older. Poisson regression models were used to derive prevalence ratios (PRs) to assess the effect of comorbid substance use disorders on the risks for being an unnatural death among mood disorder deaths. Multiple-cause life table analysis and mean age at death were used to quantify the effect of comorbid substance use disorders on premature mortality among mood disorder deaths.

Results—Prevalence of comorbid substance use disorders was higher among unipolar and bipolar disorder deaths than that among all other deaths. Among unipolar and bipolar disorder deaths, comorbid substance use disorders were associated with elevated risks for suicide and other unnatural death in both males and females (prevalence ratios ranging 1.49–9.46, $p < .05$). They also were associated with reductions in mean ages at death (ranging 11.7–33.8 years, $p < .05$). In general, these effects were much stronger for drug use disorders than for alcohol use disorders. Both substance use disorders had stronger effects on suicide among females, whereas their effects on other unnatural deaths were stronger among males.

Conclusions—This study is among the first to provide population mortality-based evidence to further establish comorbid substance use disorder as one of the key risk factors for premature death among individuals with unipolar or bipolar disorders in the United States. Clinicians need to be aware of the potentially lethal risk associated with these comorbid conditions.

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1. Introduction

Mood disorders, including unipolar depression and bipolar affective disorder, are highly prevalent in the general population. Twelve-month prevalence estimates from two major U.S. population surveys—the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) [1] and the 2001–2003 National Comorbidity Survey Replication [2]—were 5.3% and 6.7%, respectively, for unipolar depressive disorder, and 2.8% and 2.6%, respectively, for bipolar disorder. Substance use disorders often co-occur within individuals who suffer from mood disorders [1–11]. According to the NESARC estimates, among individuals with 12-month unipolar depressive disorder, 14.1% had alcohol use disorders (AUD) and 4.6% had drug use disorders (DUD). These represented significantly elevated risks for the comorbid substance use disorders, with an odds ratio of 1.8 for AUD and 2.6 for DUD when compared with individuals without unipolar depressive disorder [1]. Among individuals with bipolar disorders, the comorbidity rates were even higher—23.4% for AUD and 11.2% for DUD—representing odds ratios of 3.5 and 7.6, respectively, when compared with individuals without bipolar disorder (the authors' estimates from NESARC).

Empirical evidence has shown that people with mood disorders and/or substance use disorders experience excess mortality [12–19]. The risk of completed suicide, as associated with either substance use disorders or mood disorders, has been documented extensively [20,21]. In addition to the suicide outcome, a number of studies have presented evidence of premature deaths from other unnatural causes for substance use disorders [16]. However, only a few studies have examined the association between mood disorders and other causes of unnatural death [13,17–18,22–24], despite the fact that individuals with mood disorders, especially those with bipolar disorder, are more likely to engage in fatal accidents due to impaired attention and concentration [25] or to be victims of homicide due to affective psychoses [17].

Treatment research findings also show that comorbid substance use disorders have an adverse impact on clinical outcomes and increase risks for impairment among individuals with mood disorders [9,26–32]. Nonetheless, most of the existing studies that examined the excess mortality for mood disorders did so without assessing the contribution of comorbid substance use disorders, with a few exceptions [33,34]. In these studies, the excess mortality often is measured by the standardized mortality ratio, which does not directly assess premature death as measured by age at death. Finally, many of them are based on clinical or small-area data that had fairly small sample sizes and/or limited generalizability. Prospective studies tended to be constrained by limited durations of followup and often focused on middle-aged or elderly populations.

To fill the gap in the literature, we use death records from recent U.S. mortality data to quantify the effect of comorbid substance use disorders on premature death from unipolar and bipolar disorders. The focus is on the extent to which comorbid substance use disorders affect the manner of death (suicide, other unnatural death, and natural death) and the age at death among decedents with unipolar and bipolar disorders. Death records present themselves as an advantageous data source for the current study because they (1) contain detailed diagnostic codes of the conditions that underlie or contribute to the final death; (2) cover a large number of cases from the total U.S. population; and (3) span the whole age spectrum. These features made it possible to overcome some of the aforementioned limitations in the existing studies. The large case numbers also allowed us to conduct all analyses for males and females separately, as gender differences in both mood disorders and substance use disorders have been well established in the literature [35,36].

2. Methods

2.1. Data

Mortality data were drawn from the Multiple Cause of Death (MCD) public-use data files for 1999–2006 compiled by the National Center for Health Statistics (NCHS). In the MCD data, causes of death were classified according to the International Classification of Diseases, Tenth Revision (ICD-10) [37]. Each death record includes codes for one underlying cause and up to 20 contributing causes of death. The diseases of interest in this study and their ICD-10 codes are listed in Table 1. Following the World Health Organization's *Global Burden of Disease 2004* report [38] the ICD-10 codes used to identify unipolar depression are F32 and F33, and bipolar affective disorder F30 and F31. According to the National Center for Health Statistics' *Deaths: Final Data for 2006* report [39], the ICD-10 codes used to identify substance use disorders are F10 for alcohol use disorders, F11–F16 and F18–F19 for drug use disorders, and F17 (excluding F17.1 and F17.6) for tobacco use disorder. Additionally, following the NCHS report, the ICD-10 codes used to identify the manner of death are A00–R99 for natural deaths, *U03, X60–Y09, and Y87.1 for intentional self-harm (i.e., suicide by various means such as firearm, poisoning, hanging, etc.), and V01–Y89.9 (minus intentional self-harm) for other unnatural deaths (including deaths from unintentional injuries [i.e., accidents], assault [i.e., homicide], events of undetermined intent, war, legal intervention, and complications of medical and surgical care).

We checked the quality of mood disorder diagnoses recorded on death certificates in a separate study with data from the National Violent Death Reporting System (NVDRS), 2003–2006. Compiled by the Center for Disease Control and Prevention (CDC), the NVDRS includes data from 16 participating states based on several sources: death certificates, the offices of coroners and medical examiners (CME), police reports, toxicology laboratories, and interview with family and friends of the decedents. The CME records record mental illness diagnoses assessed by mental health practitioners based on diverse sources of information (e.g., hospital records and treatment history) [40], thereby providing an opportunity to cross-validate the mental illness diagnoses listed on the death certificates. Limited to the data available to us, our cross-validation was confined to suicide deaths in the NVDRS database. The results provided credible evidence to the accuracy of the mood disorder diagnoses recorded on the death certificates. In the NVDRS, a total of 1,556 suicide decedents had a diagnosis of unipolar depression/dysthymia ($N=1,426$) or bipolar disorder ($N=130$) on their death certificates. Among them, 1,050 (or 67.5%) also had mental health practitioners' assessments available on their CME records. In these 1,050 suicide decedents, death certificates showed a positive predictive value of 90.5 percent for unipolar depression/dysthymia, and 94.1 percent for bipolar disorder ($\chi^2=554.1678$, $df=2$, $P < .0001$, and Cramer's $V=.7265$). These high positive predictive values ensure that the mood disorder diagnoses on the death certificates are generally accurate as confirmed independently by the CME records.

Because deaths with unipolar or bipolar disorders as well as substance use disorders are rare below age 15, we selected deaths of age 15 and older. This resulted in a total of 19,052,468 decedents, 15 years of age and older, who resided in the United States at the time of their death during 1999–2006. Among them, 106,190 (0.6%) had unipolar depression and 11,859 (0.1%) had bipolar affective disorder coded as either the underlying cause or one of the contributing causes of death, which are the focus of our analysis; the remaining 18,934,419 (99.4%) had all other causes of death.

The 1999–2006 mid-year population data used to calculate mortality rates and life table parameters were taken from two sets of the United States population estimates developed by

the U.S. Census Bureau for NCHS: the bridged-race intercensal resident population estimates [41] for 1999 and the bridged-race vintage postcensal estimates of the resident population for 2000 through 2006 [42]

2.2. Measures

- Age at death: in years as reported on the death certificate.
- Manner of death: three categories, including natural death, suicide, and other unnatural death.
- Substance use disorder status: three categories, including no substance use disorders, alcohol use disorders only, and drug use disorders (with or without alcohol use disorders). There is a small proportion of decedents with mood disorders (0.3%) who had both alcohol and drug use disorders recorded on their death certificates. They are included in the drug use disorder category because preliminary analyses showed that their risk profile was very similar to those who had drug use disorders only.
- Other variables that served as control variables for adjusted estimates include: tobacco use disorder (yes/no), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and Other), and education (less than high school education, high school graduate, associate degree or some other college, and 4-year college graduate or more).

2.3. Statistical analyses

Cross-tabulations were used to compare the prevalence of comorbid substance use disorders between deaths with mood disorders (i.e., unipolar depression and bipolar disorder) and deaths with all other causes. The significance tests were based on chi-square statistics.

Poisson regression models were used to derive prevalence ratios (PRs) to assess the effect of comorbid substance use disorders on the risks for unnatural death among mood disorder deaths. Specifically, the PRs are estimated by the prevalence of unnatural deaths (suicide or other unnatural causes) in the substance use categories divided by that in the “no substance use” category, adjusting for tobacco use disorder, education, and race/ethnicity. Prevalence ratios and their 95 percent confidence intervals were generated by SAS software’s PROC GENMOD procedure.

To assess the effect of comorbid substance use disorders on premature mortality among mood disorder deaths, two analyses were conducted. First, multiple-cause life table analysis [43] was used to reveal the age patterns of different comorbid substance use disorder categories. This procedure builds on the single-cause life table analysis and is aimed at isolating the effect of specific causes. Unlike a single-cause life table which contains survival probabilities and cumulative probabilities of death by age based on a set of age-specific death rates from all causes, a multiple-cause life table shows cause-specific survival probabilities and cumulative probabilities of death by age for subpopulation groups with the respective causes. The “lifetabl” command [44] implemented in the statistical software package Stata (Stata Corp., College Station, Texas) was used to construct the multiple-cause life table. Second, mean age at death was compared across different comorbid substance use disorder categories and by the manner of death. In addition to unadjusted means, multiple linear regression procedures were used to calculate adjusted means and standard errors based on predictive margins [45], which are directly standardized to the distribution of each covariate in the model. This analysis included the same control variables (tobacco use disorder, education, and race/ethnicity) and was conducted by the statistical software package SUDAAN, Version 10 [46].

All analyses were carried out separately for males and females, and the significance of gender differences was evaluated by the non-overlapping confidence intervals. The significance level for all tests was set at least $p < .05$.

3. Results

3.1. Numbers and rates of unipolar and bipolar disorder deaths

Over the 8 years from 1999 to 2006, the total number of unipolar depression deaths was 41,395 (5,174 annually) in males and 64,795 (8,099 annually) in females (see Table 2). These numbers can be translated to annual age-adjusted rates of 56.3 and 57.3 deaths per million of population in males and females, respectively. For the same period, the total number of bipolar affective disorder deaths was 4,925 (616 annually) in males and 6,934 (867 annually) in females. These numbers can be translated to annual rates of 6.1 and 6.7 deaths per million of population in males and females, respectively.

3.2. Prevalence of comorbid substance use disorders among unipolar and bipolar disorder deaths

Table 2 shows prevalence estimates of alcohol and drug use disorders among mood disorder deaths in comparison with those among all other deaths.

Regardless of gender, the prevalence of alcohol use disorders among decedents with unipolar depression or with bipolar disorder was higher than that among decedents with all other causes of death. The prevalence of alcohol use disorders for males and females was 5.4% and 1.4%, respectively, among decedents with unipolar depression, and 5.8% and 1.8%, respectively, among decedents with bipolar disorder. In contrast, the respective estimates were 1.7% and 0.5% for male and female decedents with all other causes of death.

Similarly, regardless of gender, the prevalence of drug use disorders among decedents with unipolar depression or with bipolar disorder was higher than that among decedents with all other causes of death. In general, the prevalence of drug use disorders (ranging 0.2%–4.2%) was lower than the prevalence of alcohol use disorders (ranging 0.5%–5.8%) within each of the “cause of death by gender” categories except for female bipolar disorder deaths (1.9% vs. 1.8%).

3.3. Effect of comorbid substance use disorders on manner of death among unipolar and bipolar disorder deaths

The prevalence ratios (i.e., the ratio of the prevalence of suicide to the prevalence of natural death, and the ratio of the prevalence of other unnatural deaths to the prevalence of natural death) are shown in Table 3.

The PRs were greater than 1 and statistically significant for all categories (e.g., for both males and females, and among both unipolar and bipolar disorders), suggesting a strong effect of comorbid substance use disorders on unnatural deaths. Among decedents with unipolar depression, the risk of dying from suicide and other unnatural causes as opposed to natural causes was significantly greater for individuals with substance use disorders than those without substance use disorders. Moreover, the relative risk of dying from unnatural death was greater for drug use disorders (PR ranging 2.98–9.46) than for alcohol use disorders (PR ranging 2.01–4.91). Similarly, bipolar affective disorder exhibited a pattern that was remarkably consistent for each of the manner of death categories by gender. The prevalence ratios for drug use disorders (ranging 2.56–4.92) were greater than the corresponding prevalence ratios for alcohol use disorders (ranging 1.46–3.11). The strongest effect was observed with drug use disorders on risks for suicide death (PR=9.46, 95% CI:

7.89–11.35) and for other unnatural death (PR=7.19, 95% CI: 5.99–8.61) among female decedents with unipolar depression, and on risks for other unnatural death among male decedents with unipolar depression (PR=6.78, 95% CI: 5.81–7.92).

Although the effect of comorbid substance use disorders on the manner of death were all significant and in the same direction for both males and females, there were some gender differences in the magnitude of the effect. The prevalence ratio of suicide for comorbid alcohol use disorders as well as comorbid drug use disorders among females (PR=4.91, 95% CI: 4.27–5.65, and PR=9.46, 95% CI: 7.89–11.35, respectively) was more than double that among males (PR=2.01, 95% CI: 1.88–2.15, and PR=2.98, 95% CI: 2.67–3.32, respectively). Generally speaking, male decedents who had a mood disorder comorbid with an alcohol or drug use disorder were most likely to die from other unnatural causes, whereas their female counterparts were most likely to die from suicide.

3.4. Effect of comorbid substance use disorders on premature mortality among unipolar and bipolar disorder deaths: Life table results

Figure 1 presents the cumulative probability of death (CPD) from the life table analysis for the three substance use disorder status categories for unipolar and bipolar disorder deaths.

For unipolar depression deaths, the curves of CPD showed little difference before age 20 among these categories. After age 20 there was an increasing divergence in the CPD, with the fastest increase of deaths in the drug use disorders category (“DUD”). The curves presented a clear ordering regardless of gender, with the drug use disorders category being the highest, followed by “alcohol use disorders (“AUD only”), and “no comorbid substance use disorders” (“No SUD”), indicating that the combination of unipolar depression and any substance use disorders resulted in dying at younger ages than from unipolar depression alone. Specifically, the cumulative probability of “unipolar depression plus DUD” (data not shown) increased rapidly from 0.04 at age 20 to 0.95 at age 65 among males and from 0.02 at age 20 to 0.87 at age 65 among females. The cumulative probability of “unipolar depression plus AUD” increased slightly less rapidly from 0.01 at age 20 to 0.66 at age 65 among males and from 0.00 at age 20 to 0.68 at age 65 among females. In contrast, the increase was slowest for the “unipolar depression without SUD” category, from 0.01 at age 20 to 0.26 at age 65 among males and from 0.00 at age 20 to 0.16 at age 65 among females.

For bipolar affective disorder deaths, the ordering of the CPD curves showed a remarkably similar pattern to that of unipolar depression deaths. However, decedents with bipolar disorder showed a faster increase of probability of deaths than those with unipolar depression after age 30 for all categories by gender, except for males with drug use disorders. This suggests that bipolar disorder generally resulted in dying at younger ages compared with unipolar depression. The contrast was largest for the “no SUD” category. Specifically, the CPD of “bipolar disorder plus DUD” (data not shown) increased rapidly from 0.02 at age 20 to 0.96 at age 65 among males and from 0.00 at age 20 to 0.94 at age 65 among females. The CPD of “bipolar disorder plus AUD” increased slightly less rapidly—from 0.00 at age 20 to 0.74 at age 65 among males and from 0.00 at age 20 to 0.71 at age 65 among females. In contrast, the increase was slowest for the “bipolar disorder without SUD” category, from 0.01 at age 20 to 0.39 at age 65 among males and from 0.00 at age 20 to 0.30 at age 65 among females.

3.5. Effect of comorbid substance use disorders on premature mortality among unipolar and bipolar disorder deaths: Comparisons of mean age at death

The effect of comorbid substance use disorders on premature death also was evidenced by the mean age at death (see Table 4 and Figure 2).

The mean age at death for “unipolar depression plus AUD” was 53.1 and 56.7 in males and females, respectively, about 18.0 and 23.0 years younger than that for “unipolar depression without SUD” (71.1 and 79.7 years), respectively. Comorbid drug use disorders shortened one’s life even further; the mean age at death for “unipolar depression plus DUD” was 40.3 and 45.9 in males and females, respectively, about 30.8 and 33.8 years younger than that for “unipolar depression without SUD,” respectively.

Among bipolar disorder deaths, the mean age at death for “bipolar disorder plus AUD” was 51.2 and 53.2 in males and females, respectively, about 11.7 and 16.7 years younger than that for “bipolar disorder without SUD” (62.9 and 69.9 years), respectively. The mean age at death for “bipolar disorder plus DUD” was 40.2 and 44.2 in males and females respectively, about 22.7 and 25.4 years younger than that for “bipolar disorder without SUD,” respectively. Overall, male decedents with bipolar disorder died almost 8.3 years younger than those with unipolar depression (61.3 vs. 69.6 years), and the gap in their female counterparts was 10.1 years (69.1 vs. 79.2 years).

Figure 2 illustrates the mean age at death stratified by the manner of death for both males and females. The figure shows that the reduction in age at death by substance use disorders occurred across all manners of death for both unipolar and bipolar disorders and for both sexes. Consistent with the patterns shown by the life table results, the effect of drug use disorders on mean age at death was stronger than that of alcohol use disorders. However, there appeared to be a floor effect with suicide such that the reduction in mean age was smaller among suicide deaths than that among natural causes and other unnatural causes of death. This was especially noticeable among bipolar disorder deaths. The age reduction by alcohol use disorders was not significant among suicide victims with bipolar disorder for either sex. Moreover, the effect of drug use disorders was not significant among female suicide victims with bipolar disorder.

The adjusted means of age at death estimated by predictive margins from Poisson regression models showed quite similar patterns to the unadjusted means reported above. These data are presented in the table in Appendix A.

4. Discussion

As far as we are aware, this study is among the first to provide population-based mortality evidence to further establish comorbid substance use disorder as one of the key risk factors for premature death among individuals in the United States with unipolar or bipolar affective disorders. Notably, we found that the prevalence of comorbid substance use disorders was higher in unipolar and bipolar disorder deaths than that in all other deaths. Among unipolar and bipolar disorder deaths, comorbid AUD and DUD were associated with very elevated risks for suicide and other unnatural death in both males and females. They also were associated with reductions in the mean ages at death. This relationship holds true for suicide and other unnatural causes of death as well as for natural causes of death. The data also suggest that there is a differential mortality risk for individuals with comorbid DUD relative to those with comorbid AUD. Additionally, there appears to be gender differences beyond those attributable to differential prevalence among males and females. Both substance use disorders had stronger effects on suicide among females, whereas their effects on other unnatural deaths were stronger among males.

Recent studies of alcohol and the global burden of disease suggest that in the Americas, alcohol-attributable deaths account for a total of 5.6% of all deaths, and for 9% of all deaths among men and 1.8% among women [47]. In related research, alcohol consumption *per se* is cited as the 10th leading preventable cause of death in the United States, with approximately

90,000 deaths arising from alcohol-related cardiovascular disease, cancers, liver cirrhosis, pancreatitis, AUD, and road traffic accidents and other injuries and violence [48]. Research from the CDC cites alcohol consumption as the third leading cause of death in the United States and illicit drug use as the ninth cause of death, accounting for about 17,000 deaths annually [49]. In this line of research, alcohol-attributable mortality is estimated based on aggregation of effect sizes established in numerous clinical and epidemiological studies. Some of these studies have included neuropsychiatric disorders as a category in the aggregate, but they were not able to break down alcohol's impact on mortality for specific neuropsychiatric disorders such as unipolar and bipolar affective disorders, likely because of the lack of original research findings. Our study presents itself as one step toward closing this research gap, although we were not able to assess the effect of alcohol consumption unless it led to a diagnosis of alcohol use disorders.

Because of the nature of the mortality data, this study has several limitations. First, as in other observational studies, our estimates are subject to measurement error. Although we selected all cases with a unipolar or bipolar disorder recorded as either the underlying or a contributing cause on the death certificate, the mood disorder deaths might have been underidentified. The underreporting of psychiatric conditions in death registration is common in many countries [50–52]. A study showed that, compared with Australia, the U.S. death certification is less likely to report psychopathology for the suicide victims, partly because U.S. death investigations are less standardized than those in Australia, and U.S. coders have less access to medicolegal records than their Australian counterparts [51]. While there have been estimates of the prevalence of mood disorders in the general population [1,2], it is difficult to evaluate the extent of underreporting in mortality data based on morbidity data from population surveys. Second, death records do not provide information on age of onset, treatment history, or other life style information, which may be confounders in the associations between comorbidities and premature deaths. Although we tried to produce adjusted estimates (i.e., prevalence ratios and mean age at death) utilizing several important health covariates—such as tobacco use disorder, race/ethnicity, and education—the results still may be subject to other confounding biases. Third, the data lack specificity on the mood disorder conditions. In ICD-10 codes, some codes are reserved for identifying severity and recurrence of depression, and others for the presence and absence of psychotic symptoms and remission status for bipolar disorders. These subcategories of the disorders would be useful in assessing the effect of comorbidity with substance use disorders among subtypes of mood disorders, but such detailed codes are rarely used in death certificates. In examining the distribution of these codes in our data, we found that about 95% of unipolar depression diagnoses were coded as F32.9 (depressive episode, unspecified), and 95% of bipolar affective disorder diagnoses were coded as F31.9 (bipolar affective disorder, unspecified).

Despite the limitations we face in using the MCD data, our cross-validation analysis of the NVDRS data indicated a high consistency between death certificates and mental health practitioner's assessments recorded on the CME records for mood disorders among suicide decedents. This evidence is compelling enough to justify studying unipolar and bipolar disorder deaths using information from death certificates in national mortality data for the general population. While the NVDRS data also confirm the known underreporting of mental disorders on the death certificates (data not presented), the underreporting problem should not significantly affect the validity of our findings as our focus is on comparisons among identified cases and not on prevalence estimates.

To our knowledge, there are no better alternative data available at present to examine the association between substance use disorder and unipolar and bipolar disorder deaths at the national level. Any meaningful generalizations from existing survey data are likely to be

hindered by very small numbers of co-morbid cases who would die in relatively short time periods of follow-up. Although the extent to which MCD data are attenuated by the limitations is hard to quantify, it is likely to be modest, as our results are validated by their confirming with the existing literature. For instance, our study showed that the rate of comorbid substance use disorders was higher for bipolar disorder than for unipolar depression, and this conforms with a previous prospective study [8] that found that bipolar disorder, compared with unipolar depression, was more associated with the development of alcohol, cannabis, and benzodiazepine use, abuse, and dependence. Further, the higher relative risk of DUD compared with AUD for suicide and other unnatural death found in our study is in agreement with the standardized mortality ratio (SMR) results from previous meta-analyses on the association of alcohol and drug use disorders and completed suicides [20–21].

In conclusion, this study provides an important addition to the extant literature on comorbid psychiatric and substance use disorders. Not only are such patients clinically complex and relatively severe in their psychopathology, but as we see in this study, they also are patients who have a significantly elevated risk of premature death due to medical illness (i.e., natural causes), suicide, and injury. Early recognition and effective treatment of both the affective disorder and the substance use disorder may attenuate this mortal risk for such patients. And it is incumbent upon the treating clinicians to have a high index of suspicion concerning the presence of such comorbidities, and an awareness of their potentially lethal consequences.

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Note: SUD: substance use disorders; AUD: alcohol use disorders; DUD: drug use disorders.

Figure 1. Cumulative probability of death from unipolar depression and bipolar disorders based on complete multiple-cause life tables for “No SUD,” “AUD only,” and “DUD,” by gender: United States, 1999–2006.

Note: SUD: substance use disorders; AUD: alcohol use disorders; DUD: drug use disorders.

Figure 2. Mean age at death by comorbid substance use disorder status stratified by manner of death among decedents with unipolar depression and bipolar disorder, United States, 1999–2006.

Table 1

ICD-10 codes for cause and manner of death used in this study.

Unipolar depression	
F32	Depressive episode
F33	Recurrent depressive disorder
Bipolar affective disorder	
F30	Manic episode
F31	Bipolar affective disorder
Alcohol use disorders	
F10	Mental and behavioral disorders due to alcohol use
Drug use disorders	
F11.0–F16.9, F18.0–F19.9	Mental and behavioral disorders due to use of opioids, cannabinoids, sedatives or hypnotics, cocaine, other stimulants, including caffeine, hallucinogens, volatile solvents, multiple drug use, and use of other psychoactive substances
Tobacco use disorders	
F17.0, F17.2–F17.5, F17.7–F17.9	Mental and behavioral disorder due to use of tobacco
Manners of Death	
Natural causes	
A00–R99	Naturally occurring disease process (i.e., all causes excluding “intentional self-harm” and “other unnatural causes” below)
Intentional self-harm	
*U03, X60–X84, Y87.0	Suicide by various means (firearm, poisoning, hanging, etc.)
Other unnatural causes	
V01–Y89.9 (minus intentional self-harm), *U01–*U02	Accidents (unintentional injuries), assault (homicide), events of undetermined intent, war, legal intervention, and complications of medical and surgical care

Table 2

Eight-year total number of deaths and percent distribution^a of comorbid substance use disorders among deaths with unipolar depression and bipolar disorder and among deaths with all other causes, United States, 1999–2006.

Causes of death category	Male				Female			
	Total	Natural cause	Suicide	Other unnatural cause	Total	Natural cause	Suicide	Other unnatural cause
Unipolar depression								
Total	41,395 (100.0) (100.0)	29,055 (100.0) (70.2)	9,542 (100.0) (23.1)	2,798 (100.0) (6.8)	64,795 (100.0) (100.0)	57,224 (100.0) (88.3)	3,237 (100.0) (5.0)	4,334 (100.0) (6.7)
No SUD	38,482 (93.0) (100.0)	27,815 (95.7) (72.3)	8,266 (86.6) (21.5)	2,401 (85.8) (6.2)	63,513 (98.0) (100.0)	56,538 (98.8) (89.0)	2,900 (89.6) (4.6)	4,075 (94.0) (6.4)
w/ AUD only	2,251 (5.4) (100.0)	1,081 (3.7) (48.0)	947 (9.9) (42.1)	223 (8.0) (9.9)	905 (1.4) (100.0)	552 (1.0) (61.0)	215 (6.6) (23.8)	138 (3.2) (15.2)
w/ DUD	662 (1.6) (100.0)	159 (0.5) (24.0)	329 (3.4) (49.7)	174 (6.2) (26.3)	377 (0.6) (100.0)	134 (0.2) (35.5)	122 (3.8) (32.4)	121 (2.8) (32.1)
Bipolar affective disorder								
Total	4,925 (100.0) (100.0)	3,612 (100.0) (73.3)	633 (100.0) (12.9)	680 (100.0) (13.8)	6,934 (100.0) (100.0)	5,761 (100.0) (83.1)	403 (100.0) (5.8)	770 (100.0) (11.1)
No SUD	4,436 (90.1) (100.0)	3,352 (92.8) (75.6)	547 (86.4) (12.3)	537 (79.0) (12.1)	6,674 (96.3) (100.0)	5,620 (97.6) (84.2)	365 (90.6) (5.5)	689 (89.5) (10.3)
w/ AUD only	284 (5.8) (100.0)	183 (5.1) (64.4)	47 (7.4) (16.5)	54 (7.9) (19.0)	125 (1.8) (100.0)	81 (1.4) (64.8)	18 (4.5) (14.4)	26 (3.4) (20.8)
w/ DUD	205 (4.2) (100.0)	77 (2.1) (37.6)	39 (6.2) (19.0)	89 (13.1) (43.4)	135 (1.9) (100.0)	60 (1.0) (44.4)	20 (5.0) (14.8)	55 (7.1) (40.7)
All other causes								
Total	9,299,211 (100.0) (100.0)	8,189,745 (100.0) (88.1)	189,184 (100.0) (2.0)	920,282 (100.0) (9.9)	9,635,208 (100.0) (100.0)	9,000,677 (100.0) (93.4)	46,837 (100.0) (0.5)	587,694 (100.0) (6.1)
No SUD	9,074,412 (97.6) (100.0)	8,039,369 (98.2) (88.6)	184,089 (97.3) (2.0)	850,954 (92.5) (9.4)	9,567,403 (99.3) (100.0)	8,955,788 (99.5) (93.6)	44,939 (95.9) (0.5)	566,676 (96.4) (5.9)
w/ AUD only	162,539 (1.7) (100.0)	124,928 (1.5) (76.9)	3,847 (2.0) (2.4)	33,764 (3.7) (20.8)	43,764 (0.5) (100.0)	34,158 (0.4) (78.1)	1,259 (2.7) (2.9)	8,347 (1.4) (19.1)
w/ DUD	62,260 (0.7) (100.0)	25,448 (0.3) (40.9)	1,248 (0.7) (2.0)	35,564 (3.9) (57.1)	24,041 (0.2) (100.0)	10,731 (0.1) (44.6)	639 (1.4) (2.7)	12,661 (2.2) (52.7)
Chi-square test of independence								
	Chi-sq. = 5,156, DF=4, p < .0001	Chi-sq. = 1,665 DF=4, p < .0001	Chi-sq. = 3,604 DF=4, p < .0001	Chi-sq. = 389 DF=4, p < .0001	Chi-sq. = 2,595 DF=4, p < .0001	Chi-sq. = 1,137 DF=4, p < .0001	Chi-sq. = 321 DF=4, p < .0001	Chi-sq. = 216 DF=4, p < .0001

^dColumn percentages are in parentheses following the number of deaths; row percentages are in parentheses below the column percentages.

Note: SUD: substance use disorders; AUD: alcohol use disorders; DUD: drug use disorders.

Table 3

Adjusted prevalence ratios for manner of death by comorbid substance use disorder status among decedents with unipolar depression and bipolar disorder, United States, 1999–2006.

Cause of death category	Male			Female		
	Suicide vs. Natural		Other Unnatural vs. Natural	Suicide vs. Natural		Other Unnatural vs. Natural
	Prevalence ratio	95% CI	Prevalence ratio	95% CI	Prevalence ratio	95% CI
Unipolar depression						
Alcohol use disorders only	2.01***	1.88 – 2.15	2.21***	1.92 – 2.53	2.98***	2.51 – 3.53
Drug use disorders	2.98***	2.67 – 3.32	6.78***	5.81 – 7.92	7.19***	5.99 – 8.61
Bipolar affective disorder						
Alcohol use disorders only	1.46*	1.08 – 1.96	1.72***	1.30 – 2.28	2.24***	1.51 – 3.31
Drug use disorders	2.56***	1.85 – 3.55	3.80***	3.03 – 4.78	4.41***	3.34 – 5.81

Notes:

Prevalence ratios are adjusted for tobacco use disorder, education, and race/ethnicity.

* $p < .05$;

*** $p < .001$

Table 4

Mean age at death by substance use disorder status and manner of death among decedents with unipolar depression and bipolar disorder, United States, 1999–2006.

	Male				Female			
	Natural causes of deaths	Unnatural causes of deaths		Total	Natural causes of deaths	Unnatural causes of deaths		Total
		Suicide	Other unnatural causes			Suicide	Other unnatural causes	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Unipolar depression deaths								
Total	76.8 (76.6 – 77.0)	48.7 (48.3 – 49.1)	66.0 (65.2 – 66.8)	69.6 (69.4 – 69.8)	81.3 (81.2 – 81.4)	47.7 (47.2 – 48.2)	74.2 (73.6 – 74.8)	79.2 (79.1 – 79.3)
No SUD	77.6 (77.4 – 77.8)	49.6 (49.2 – 50.0)	69.3 (68.5 – 70.1)	71.1 (70.9 – 71.3)	81.6 (81.5 – 81.7)	48.1 (47.5 – 48.7)	75.9 (75.4 – 76.4)	79.7 (79.6 – 79.8)
w/ AUD only	60.8 (60.0 – 61.6)	44.7 (43.9 – 45.5)	51.1 (49.1 – 53.1)	53.1 (52.5 – 53.7)	62.5 (61.3 – 63.7)	45.5 (43.9 – 47.1)	51.1 (48.9 – 53.3)	56.7 (55.7 – 57.7)
w/ DUD	49.1 (47.5 – 50.7)	36.6 (35.4 – 37.8)	39.3 (37.6 – 41.0)	40.3 (39.4 – 41.2)	52.3 (49.7 – 54.9)	41.4 (39.2 – 43.6)	43.3 (41.3 – 45.3)	45.9 (44.5 – 47.3)
Bipolar affective disorder deaths								
Total	66.4 (65.9 – 66.9)	40.8 (39.7 – 41.9)	53.3 (51.9 – 54.7)	61.3 (60.8 – 61.8)	72.2 (71.8 – 72.6)	42.8 (41.5 – 44.1)	60.1 (58.8 – 61.4)	69.1 (68.7 – 69.5)
No SUD	67.5 (67.0 – 68.0)	41.1 (39.9 – 42.3)	56.6 (55.0 – 58.2)	62.9 (62.4 – 63.4)	72.6 (72.2 – 73.0)	43.1 (41.7 – 44.5)	61.9 (60.5 – 63.3)	69.9 (69.5 – 70.3)
w/ AUD only	55.0 (53.1 – 56.9)	42.5 (39.7 – 45.3)	46.0 (42.5 – 49.5)	51.2 (49.6 – 52.8)	57.6 (54.7 – 60.5)	40.4 (34.7 – 46.1) ^a	48.4 (43.0 – 53.8) ^a	53.2 (50.6 – 55.8)
w/ DUD	45.9 (43.5 – 48.3)	34.3 (30.8 – 37.8)	37.8 (35.4 – 40.2)	40.2 (38.6 – 41.8)	46.7 (43.9 – 49.5)	39.8 (34.6 – 45.0) ^a	43.0 (40.4 – 45.6)	44.2 (42.4 – 46.0)
Difference (in years)								
AUD – No SUD	–16.8	–4.9	–18.2	–18.0	–19.1	–2.6	–24.8	–23.0
DUD – No SUD	–28.5	–13.0	–30.0	–30.8	–29.3	–6.7	–32.6	–33.8
DUD – AUD	–11.7	–8.1	–11.8	–12.8	–10.2	–4.1	–7.8	–10.8

	Male					Female				
	Natural causes of deaths		Unnatural causes of deaths			Natural causes of deaths		Unnatural causes of deaths		
			Suicide		Other unnatural causes			Suicide		Other unnatural causes
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Difference (in years)										
AUD – No SUD	-12.5	1.4 ^b	-10.6	-11.7	-15.0	-2.7 ^b	-13.5	-16.7		
DUD – No SUD	-21.6	-6.8	-18.8	-22.7	-25.9	-3.3 ^b	-18.9	-25.4		
DUD – AUD	-9.1	-8.1	-8.2	-11.0	-10.9	-0.6 ^b	-5.4 ^b	-9.0		

^aNumber of deaths < 30.

^bNot statistically significant at 0.05 level.

Note: SUD: substance use disorders; AUD: alcohol use disorders; DUD: drug use disorders.

Appendix A

Adjusted mean age at death by substance use disorder status and manner of death among decedents with unipolar depression and bipolar disorder, United States, 1999–2006.

	Male				Female			
	Natural causes of deaths	Unnatural causes of deaths		Total	Natural causes of deaths	Unnatural causes of deaths		Total
		Suicide	Other unnatural causes			Suicide	Other unnatural causes	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Unipolar depression deaths								
Total	77.6 (77.4 – 77.8)	49.5 (49.1 – 49.9)	69.2 (68.4 – 70.0)	71.0 (70.8 – 71.2)	81.6 (81.5 – 81.7)	48.1 (47.5 – 48.7)	75.7 (75.2 – 76.2)	79.7 (79.6 – 79.8)
No SUD								
w/ AUD only	61.6 (60.8 – 62.4)	45.0 (44.2 – 45.8)	51.8 (49.9 – 53.7)	53.7 (53.1 – 54.3)	64.0 (62.8 – 65.2)	45.2 (43.6 – 46.8)	52.5 (50.2 – 54.8)	58.2 (57.2 – 59.2)
w/ DUD	51.5 (49.7 – 53.3)	36.8 (35.5 – 38.1)	39.7 (37.9 – 41.5)	40.9 (39.9 – 41.9)	54.4 (51.7 – 57.1)	41.5 (39.3 – 43.7)	44.4 (42.3 – 46.5)	47.0 (45.5 – 48.5)
Difference (in years)								
AUD – No SUD	–16.0	–4.5	–17.4	–17.3	–17.6	–2.9	–23.2	–21.5
DUD – No SUD	–26.1	–12.7	–29.5	–30.1	–27.2	–6.6	–31.3	–32.7
DUD – AUD	–9.6	–8.2	–12.1	–12.8	–9.6	–3.7	–8.1	–11.2
Bipolar affective disorder deaths								
Total	67.5 (67.0 – 68.0)	41.1 (39.9 – 42.3)	56.4 (54.8 – 58.0)	62.9 (62.4 – 63.4)	72.6 (72.2 – 73.0)	43.0 (41.6 – 44.4)	61.8 (60.4 – 63.2)	69.9 (69.5 – 70.3)
No SUD								
w/ AUD only	55.6 (53.7 – 57.5)	42.0 (39.3 – 44.7)	45.4 (42.0 – 48.8)	51.5 (50.0 – 53.0)	58.3 (55.4 – 61.2)	40.9 (35.3 – 46.5) ^a	48.3 (43.1 – 53.5) ^a	53.6 (51.0 – 56.2)
w/ DUD	47.4 (44.8 – 50.0)	35.1 (31.7 – 38.5)	39.5 (37.0 – 42.0)	41.4 (39.7 – 43.1)	48.4 (45.5 – 51.3)	40.9 (36.1 – 45.7) ^a	44.0 (41.2 – 46.8)	45.2 (43.3 – 47.1)
Difference (in years)								

	Male				Female			
	Natural causes of deaths		Unnatural causes of deaths		Natural causes of deaths		Unnatural causes of deaths	
			Suicide				Suicide	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
AUD – No SUD	–11.9	0.9 ^b	–11.0	–11.4	–14.3	–2.1 ^b	–13.5	–16.3
DUD – No SUD	–20.1	–6.0	–16.9	–21.5	–24.2	–2.1 ^b	–17.8	–24.4
DUD – AUD	–8.2	–6.9	–5.9	–10.1	–9.9	–0.0 ^b	–4.3 ^b	–8.4

^a Cell with number of deaths < 30.

^b Not statistically significant at 0.05 level.

Notes:

¹ Means are adjusted for tobacco use disorder, education, and race/ethnicity.

² SUD: substance use disorders; AUD: alcohol use disorders; DUD: drug use disorders.