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Subtypes of Major Depression in Substance Dependence

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Abstract

Aims—This study evaluated features that differentiate subtypes of major depressive episode (MDE) in the context of substance dependence (SD).

Design—Secondary data analysis using pooled data from family-based and case-control genetic studies of SD.

Setting—Community recruitment through academic medical centers.

Participants—1,929 unrelated subjects with alcohol and/or drug dependence.

Measurements—Demographics, diagnostic criteria for psychiatric and substance use disorders, and related clinical features were obtained using the Semi-Structured Assessment for Drug Dependence and Alcoholism. We compared four groups: no lifetime MDE (no MDE), independent MDE only (I-MDE), substance-induced MDE only (SI-MDE), and both types of MDE.

Findings—Psychiatric measures were better predictors of MDE subtype than substance-related or sociodemographic ones. Subjects with both types of MDE reported more lifetime depressive symptoms and co-morbid anxiety disorders and were more likely to have attempted suicide than subjects with I-MDE or SI-MDE. Subjects with both types of MDE, like those with I-MDE, were also more likely than subjects with SI-MDE to be alcohol dependent only than either drug dependent only or both alcohol and drug dependent.

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Conclusions—SD individuals with both types of MDE have greater psychiatric severity than those with I-MDE only or SI-MDE only. These and other features that distinguish among the MDE subtypes have important diagnostic and potential therapeutic implications.

Keywords

Major Depressive Episode; Substance Dependence; Mood Disorder

Major depressive disorder (MDD) and substance dependence (SD) are highly prevalent in the general population and frequently co-occur, both in clinical samples [1–4] and the general population [5–10]. Explanations for the high rate of mood symptoms among individuals with SD include the presence of an independent mood disorder with concomitant substance use, secondary mood symptoms induced by protracted intoxication or withdrawal, or a combination of independent and substance-induced mood symptoms.

The DSM-IV [11] stipulates that a mood disorder can be considered independent if the signs and symptoms of the disorder predate the onset of substance use, exceed that attributable to substance use alone, or persist for more than four weeks beyond the period of acute substance intoxication or withdrawal. Although patients with mood symptoms and substance misuse should be carefully interviewed to establish the chronology of signs and symptoms of the two disorders [12,13], it is often difficult to obtain this information reliably, particularly at the earliest ages of onset, due to frequent periods of intoxication and possible cognitive impairment from protracted substance misuse. The use of temporal markers, *e.g.*, major life events, and the availability of knowledgeable collateral informants may help to establish a valid psychiatric history in substance-abusing patients with affective symptoms [14].

However, studies that have systematically analyzed the sociodemographic, psychiatric and substance-related features of independent or substance-induced depressive episodes have yielded conflicting results concerning the extent of psychopathology in patients with independent or substance-induced depression [12,15–19]. Some studies show that individuals with co-morbid depression and SD have a worse course of psychiatric illness [17–19], though in other studies independent depression among alcoholics was associated with more suicide attempts [15] or the psychiatric symptom burden during the worst episode of substance-induced depression was similar to the burden of independent depression [16].

Two studies from the Collaborative Study on the Genetics of Alcoholism (COGA) underscore the clinical utility of subtyping depression among individuals with SD [15,16]. In an initial study of 2,945 alcoholics, the lifetime prevalence of an independent major depressive episode (MDE) was 15.2%, similar to that in the general population, and 26.4% of participants endorsed a lifetime diagnosis of substance-induced MDE [15]. Alcoholics with independent MDE were more likely than those with substance-induced MDE to be female, European-American, and married. They were also more likely to have attempted suicide and to have a family history of independent mood disorders, but were less likely to have co-morbid drug abuse or to have received treatment for an alcohol use disorder [15]. Recently, Schuckit *et al.* [16] reported findings from a second COGA sample of 2,548 subjects that overlapped partly with the earlier study sample. Individuals with substance-induced depression were more likely to be male, probands, from alcohol dependence families, and to have an alcohol use disorder, antisocial personality disorder (ASPD), and more illicit drug use disorders. In contrast, subjects with independent depression were more likely to be older, female and white; to have co-morbid ASPD and a family history of primary depression; and to smoke at least 10 cigarettes per day.

To characterize more fully the subtypes of MDE, we conducted a secondary analysis of data obtained using a semi-structured instrument designed to assess SD and co-morbid psychiatric disorders in a large sample of subjects with SD [20–24]. Subjects were divided into four groups: those with no lifetime history of MDE ("no MDE"), those with only a lifetime diagnosis of one or more episodes of MDE not attributable to substance use ("independent MDE"), those with only a lifetime history of one or more episodes of MDE in the context of substance use ("substance-induced MDE"), and those endorsing a lifetime history of both independent and substance-induced MDEs ("both types of MDE"). Analyses compared these groups on a variety of sociodemographic and clinical measures, to identify risk factors for the development of MDE in the context of SD and the features that differentiate the MDE subtypes. The predictors were chosen based on their prior association with either depression or SD [7,10], or to ensure that they did not confound the analysis of the MDE subtypes.

METHODS

Subjects (N = 1,929 unrelated individuals) were recruited from among those seeking treatment in clinical facilities and through advertisements in the community. Evaluations were conducted at four academic sites in the Eastern United States: Yale University (New Haven, CT; N = 849), the University of Connecticut Health Center (Farmington, CT; N = 820), the Medical University of South Carolina (Charleston, SC; N = 153), and McLean Hospital (Belmont, MA; N = 107). The institutional review board at each of the participating institutions approved the study protocol and informed consent document.

Recruitment and Assessment Procedures

The study sample was recruited and paid to participate in genetic studies of SD [21–24]. Cocaine and/or opioid dependent probands from family-based genetic linkage studies were included in this analysis, as were alcohol, cocaine, or opioid dependent individuals recruited to participate in case-control studies of the genetics of SD.

All participants were evaluated using the Semi-structured Assessment for Drug Dependence and Alcoholism (SSADDA), which was used to elicit demographics and diagnostic information for substance use and a variety of co-morbid psychiatric disorders. A detailed description of the instrument, the methods used to administer it, and data showing its diagnostic reliability are provided elsewhere [20,25]. When administering the SSADDA, the interviewer inquires about substance use at the time of each depressive episode, making it possible to stratify subjects into groups based on the absence of a lifetime MDE or, among those with a lifetime MDE, on the temporal relationship of their substance abuse and depressive episode(s).

DSM-IV [11] defines an MDE as a period of two weeks or longer during which an individual experiences at least five symptoms (of which at least one must be depressed mood or anhedonia) that either impairs functioning or is incapacitating. In an independent MDE, the depressive symptoms are not associated with substance use, a general medical condition or bereavement. In contrast, in a secondary MDE, the depressive symptoms occur during substance intoxication or withdrawal or are judged to be due to a general medical condition or bereavement. In this study, we excluded individuals with MDE due either to an underlying medical condition or bereavement, focusing only on MDE that was independent or substance induced. For a substance-induced MDE, the SSADDA requires full temporal and symptom criteria, a more stringent approach than is used to diagnose a substance-induced mood disorder in DSM-IV [11]. Further, depressive symptoms must persist for at least two weeks, which exceeds the duration of symptoms typically occurring during substance intoxication or withdrawal. Because an individual depressive episode could not be

considered to be both independent and substance-induced, subjects with both types of MDE had a lifetime history of at least two MDEs. Additionally, subjects with bipolar disorder and those without a lifetime SD (alcohol, cocaine or opioid dependence) diagnosis were excluded from the analysis.

The SSADDA-derived diagnoses relevant to the present study showed moderate-to-good reliability. The inter-rater and test-retest reliability estimates for MDD were $\kappa = 0.53$ (95% CI = 0.33, 0.73) and $\kappa = 0.49$ (0.25, 0.73), respectively [20]. The inter-rater and test-retest reliabilities of independent MDE were $\kappa = 0.68$ (0.55, 0.81) and $\kappa = 0.76$ (0.62, 0.89), respectively, and for substance-induced MDE, the reliability coefficients were $\kappa = 0.46$ (0.30, 0.62) and $\kappa = 0.69$ (0.53, 0.84).

Measures

Predictor variables were examined in relation to the subjects' four-level MDE classification, with adjustment for other characteristics that were significantly related to the classification schema to avoid confounding and without adjustment to study their marginal effects. The predictor variables included six sociodemographic characteristics: sex, race/ethnicity (European-American, African-American, or Hispanic), age, marital status (married, widowed, separated, divorced, or never married), current employment status, and annual household income (divided roughly into quintiles bounded at $10,000, $20,000, $30,000, and $50,000). Race/ethnicity was self-identified and, although there is known overlap among these racial/ethnic groups due to genetic admixture, we did not genotype all subjects to refine that determination.

Four substance-related characteristics were also considered. The first of these yielded three groups based on the subject's alcohol and drug (cocaine or opioid) dependence diagnoses: alcohol dependent only, drug dependent only and both alcohol and drug dependent. There were 316 subjects (16.4% of the total) with alcohol dependence but no drug dependence. Of the 1613 subjects with drug dependence, 1,005 (52.1%) also had alcohol dependence. Of the drug-dependent subjects, 884 (54.8%) had cocaine but not opioid dependence, 114 (7.1%) had opioid but not cocaine dependence and 615 (38.1%) had both cocaine and opioid dependence. The second substance-related variable was the total number of lifetime SD disorders (0–7, based on the presence of nicotine, alcohol, cocaine, opioid, cannabis, stimulant, and sedative-hypnotic dependence). Substance-related variables also included the age of onset of substance use and of the first SD diagnosis. Finally, six psychiatric measures were included in the analysis: the number of lifetime anxiety disorders (posttraumatic stress disorder, generalized anxiety disorder, obsessive-compulsive disorder, social phobia, panic disorder, and agoraphobia); antisocial personality disorder (ASPD); the number of lifetime depressive symptoms (maximum= 9); suicidal ideation; attempted suicide; and the age of onset of the first MDE.

Statistical Analysis

First, 13 single-predictor models using generalized logistic regression (also known as multinomial logit regression [26], a generalization of binary logistic regression) were run to examine the unadjusted relationship of each of the potential predictors to the four MDE categories. To yield an overall significance level of 0.05, the significance level was Bonferroni adjusted (i.e., 0.05/13 = 0.0038). Next, stratified Kaplan-Meier (also known as product-limit) non-parametric survival curves were fitted to the three age-of-onset predictors based on the subjects' MDE classification, and log-rank tests were used to test for homogeneity across strata.

In addition, a generalized logistic regression model with all 13 predictors was fitted to evaluate the fully adjusted relationship and to determine whether this model could be simplified by omitting non-significant predictors. A significance level of 0.05 was used to evaluate the type 3 Wald χ^2 p-values.

Finally, to determine the most parsimonious model, a series of generalized logistic regression models was considered following stepwise selection and backward elimination at a 0.05 level of significance. The probability of being in each of the four outcome categories was estimated for given values of the set of predictors in the model. This yielded six pair wise comparisons: independent MDE vs. no MDE, substance-induced MDE vs. no MDE, both types of MDE vs. no MDE, independent MDE vs. substance-induced MDE, both types of MDE vs. independent MDE and both types of MDE vs. substance-induced MDE. Because they were the focus of the analysis, we present only the comparisons among the three groups with at least one MDE. Comparisons involving the group with no MDE are presented in a supplementary table.

All analyses were conducted using SAS. Because some subjects had missing information on some variables, the sample size varied slightly in the generalized logistic regression models.

RESULTS

Sample Characteristics

The characteristics of the study sample are listed in Table 1. In the simple four-level generalized logistic regression analysis, all characteristics except age, current employment, annual household income, ASPD and marital status were significant at an overall 5% level after Bonferroni multiple comparison correction. Based on non-parametric survival analyses, the age of onset of substance use, of SD and of MDE did not differentiate among the three subtypes of MDE (data not shown).

Analysis of the temporal sequence of depressive episodes in subjects with both types of MDE showed that, of the 163 for whom data were available (97%), 74 (45.4%) endorsed experiencing a substance-induced MDE first, and 83 (50.9%) described their first depressive episode as independent of substance use. Six subjects (3.7%) reported the onset of both types of depressive episode within the same year.

Generalized Logistic Regression Analysis of the Four-Level MDE Classification

Using multiple generalized logistic regression analysis, both stepwise selection and backward elimination procedures yielded the same set of eight significant predictors: the number of lifetime depressive symptoms, the number of lifetime anxiety disorders, the three-level SD classification, age, sex, race/ethnicity, attempted suicide, and ASPD.

It should be noted that the unadjusted analyses yielded results that, in nearly all cases, were similar to the adjusted analyses. There were only two predictors for which differences were evident after adjustment: substance dependence classification and race/ethnicity. Because these effects were comparatively modest, we present only the adjusted results in Table 3.

The best predictor of MDE subtype was the number of lifetime depressive symptoms. With each additional depressive symptom endorsed, there was approximately a two-fold greater risk of having both types of MDE than either independent or substance-induced MDE only. Further, with each additional depressive symptom, the likelihood of having only independent MDE was 13% less than having only substance-induced MDE.

After controlling for the number of lifetime depressive symptoms, the next most significant predictor was the number of lifetime anxiety disorders. With each additional anxiety disorder diagnosis, the risk of endorsing both types of MDE increased by 35% and 41% relative to independent MDE and substance-induced MDE, respectively. The number of anxiety disorders was not a significant factor in differentiating between independent MDE and substance-induced MDE.

The next most significant predictor was the three-level SD classification. Subjects with only alcohol dependence were more than twice as likely as those with either drug dependence only or both alcohol and drug dependence to have both types of MDE compared to substance-induced MDE. Subjects with alcohol dependence only were also nearly three times as likely as those with only drug dependence or both alcohol and drug dependence to have independent compared with substance-induced MDE. The three-level SD classification was not a significant factor in differentiating between both types of MDE and independent MDE.

Age was the next most significant predictor of MDE subtype. With each additional year, the risk of having both types of MDE increased by 3% relative to substance-induced MDE. Age did not significantly differentiate between independent MDE only and substance-induce MDE only, and between independent MDE only and both types of MDE.

The next two significant predictors were sex and race/ethnicity. Women were almost twice as likely as men to endorse either only independent or both types of MDE than substance-induced MDE only. European-Americans were nearly twice as likely as African-Americans to report both types of MDE. Further, African-Americans were less than half as likely as Hispanics to report both types of MDE relative to substance-induced MDE. There was no significant difference in the distribution of MDE subtypes between European-American and Hispanic subjects.

Subjects with a history of a suicide attempt were nearly twice as likely to endorse both types of MDE as independent MDE only. Risk of attempted suicide did not differentiate the substance-induced MDE subjects from either the group with both types of MDE or the group with independent MDE only.

The final significant predictor was ASPD. Although ASPD did not significantly differentiate between MDE classifications in the three pair wise comparisons shown in Table 3, subjects with ASPD were more likely to report independent MDE (OR=2.17; 95% CI 1.13, 4.17) or both types of MDE (OR=2.25; 95% CI 1.14, 4.47) than no lifetime MDE diagnosis (see supplementary table for this comparison).

DISCUSSION

This study adds to a growing literature examining the epidemiology and clinical features of substance-induced mood disorders. Use of the SSADDA, an instrument with demonstrated reliability in the diagnosis of DSM-IV substance use and psychiatric disorders [20,25] made it possible to stratify subjects into four groups based on the presence of independent and substance-induced MDE. In contrast to the more loosely defined and less stringent approach used in DSM-IV, which does not require that full MDE criteria be met in the diagnosis of substance-induced depression, this study required subjects to met full DSM-IV criteria for a major depressive episode. This enabled us to compare more directly the MDE subtypes and has underscored the group with both types of MDE. Given its greater specificity, a diagnosis of substance-induced MDE may have greater clinical utility and predictive validity than a substance-induced mood disorder diagnosis. Hence, this study, and other studies that have

used rigorous criteria to diagnose substance-induced depression [15,27], is of potential utility in redefining the diagnosis of substance-induced mood disorders in DSM-V.

The comparatively large number of subjects endorsing both types of MDE (N=168) in this sample made it possible to examine their features in detail, which is the first phenomenological analysis of this group in the psychiatric literature. These subjects fared much worse on a variety of psychopathological measures, suggesting that the dichotomous distinction between independent and substance-induced depression is inadequate to characterize depressive episodes among substance-dependent individuals, and that subjects with both types of MDE may require more sustained and intensive psychiatric interventions.

Psychiatric parameters were the most robust predictors of MDE subtype, with the two best clinical predictors (i.e., the number of depressive symptoms and the number of co-morbid anxiety disorders) being elevated in the group with both types of MDE compared with those with independent MDE only or substance-induced MDE only. Age of onset of MDE, which was evaluated using survival analysis, was not a significant predictor of MDE subtype. However, among the psychiatric predictors, only the number of lifetime depressive symptoms differentiated the independent MDE group from the substance-induced MDE group. This contrasts with a recent report from the multi-site Sequential Treatment Alternatives to Relieve Depression (STAR*D) study of 4,010 non-psychotic depressed outpatients with or without concurrent substance use disorder (SUD) [28]. In that study, subjects with co-occurring MDD and SUD reported an earlier age of onset of depression, more depressive symptoms and a greater number of comorbid anxiety disorders than those without SUD [28]. The comparison between studies is limited by both sociodemographic differences, *e.g.*, the sample from STAR*D was predominantly Caucasian (~75%) and female (~61%), while the present sample is predominantly African-American (~53%) and male (~54%), and the fact that subjects with co-occurring MDD and SUD in STAR*D included those with substance-induced MDE and both types of MDE.

There was a greater likelihood that subjects with both types of MDE had attempted suicide than subjects with independent depression. This greater risk of suicide raises the question of whether screening patients with alcohol, cocaine or opioid dependence for the presence of combined independent and substance-induced MDE could set the stage for interventions aimed at preventing additional suicide attempts in this high-risk group.

Although it did not distinguish among the MDE subtypes, ASPD was more common among individuals with either independent MDE or both types of MDE compared with substance-dependent subjects with no history of depression. In contrast, Schuckit *et al*. [16] found that ASPD was a significant predictor of independent, but not substance-induced, depression. Similarly, in the VA-based Vietnam Twin Era Registry study, shared genetic risk estimates of lifetime ASPD and major depression were 69% and 40%, and the genetic risk between major depression and alcohol and marijuana dependence was largely explained by genetic effects of ASPD [29]. Also, in a study of 132 substance-dependent Turkish inpatients, ASPD was significantly associated with lifetime major depressive disorder, attempted suicide, and other self-injurious behaviors [30]. Together, these findings demonstrate that the relations among SD, ASPD, and MDE are complex, but of considerable clinical importance.

In the present study, the nature of the SD diagnosis also differentiated among the subtypes of MDE. Interestingly, subjects with alcohol dependence were more likely to endorse independent depression or both types of MDE than substance-induced MDE only. These results are consistent with the hypothesis that subjects with primary depression often “self-medicate” their symptoms with alcohol. Our results are also similar to those reported from

the National Epidemiologic Survey on Alcohol and Related Disorders, where high rates of depression were identified in alcohol-dependent subjects but few depressive episodes were substance-induced [7]. Similar results were observed in the first COGA study, in which alcoholics were more likely to endorse traits associated with an independent MDE, *i.e.*, female sex, white race, and a family history of an independent mood episode [15]. However, the present findings differ from those of the first COGA study, where drug-dependent subjects were also more likely to endorse substance-induced MDE.

Race/ethnicity is also an important feature distinguishing MDE subtype in substance-dependent subjects. In the present study, African-Americans were significantly less likely to experience both types of MDE than either European-Americans or Hispanics. These findings are consistent with a prior study of a national probability sample of pre-retirement adults in which there was a significantly lower risk of MDE in African-Americans compared to whites, who had a rate of MDE that was similar to that of Hispanics [31]. A greater prevalence of MDD was also observed in a nationally representative sample of whites aged 15–40, compared with African-Americans and Mexican-Americans [32]. However, these findings contrast with those of Smith *et al*. [33], who found similar rates of co-morbid SUD and MDD across white, black, and Hispanic groups in a U.S. population study. The association of depression with racial/ethnic groups in these studies could be confounded by reluctance on the part of minority groups to report depressive symptoms [34] or by inadequate differentiation of independent and substance-induced depressive symptoms.

As might be predicted given a greater period at risk, older subjects were more likely to have both types of MDE than substance-induced depression, though age did not differentiate both types of MDE from independent MDE only. Independent depression was also more likely later in life than substance-induced depression only, consistent with a decline in substance use with age. The effect of sex (i.e., both independent MDE and both types of MDE were more common among women than men) was consistent with the greater risk in the general population of independent depression among women [35–37].

As in the COGA sample, we found that subjects endorsing independent MDE only were more likely to be female and to have ASPD [16]. However, that study also showed the group with substance-induced MDE to have a greater number of drug dependence diagnoses, which we did not observe [16]. Schuckit *et al*. [16] also found an increased likelihood of a family history of independent depression in the independent MDE group. Comparable data on family history obtained via direct interview with family members were not available for our sample, so we did not evaluate this measure as a predictor of MDE subtype.

Our study differed from COGA both in the ascertainment and composition of the study sample and in the assessments that were used. We excluded subjects who had no lifetime substance dependence diagnosis. In contrast, nearly half of the subjects with a lifetime independent MDE in the COGA sample failed to meet criteria for an alcohol use disorder (which was the focus of that study). We recruited subjects from family-based studies of cocaine or opioid dependence and case-control studies of alcohol, cocaine or opioid dependence. Schuckit *et al*. [16] recruited alcohol-dependent probands entering treatment for an alcohol use disorder and their family members, as well as a group of comparison families. In the COGA sample, there was an equal proportion of individuals with independent and substance-induced MDE, while in our sample the number of subjects with substance-induced MDE was more than three times the number with an independent MDE only. This difference in the relative proportions of independent and substance-induced MDE is likely due to multiple factors. First, although the SSADDA was adapted from the SSAGA (which was developed by COGA), we were able to diagnosis subjects with both independent and substance-induced MDEs. In contrast, the independent MDE group in Schuckit *et al*.

[16] likely included both subjects with independent MDE only and both types of MDE. Finally, greater than 40% of the subjects in our sample had a lifetime diagnosis of MDE compared to only 23% of the subjects in the COGA sample, a difference that probably stemmed from the fact that 70% of subjects in the COGA study were family members of ascertained probands, among whom the diagnosis of SD (and the risk for substance-induced MDE) was substantially lower than it was among probands.

The importance of this diagnostic approach is supported by our findings of greater psychiatric and substance-related pathology among the group with both types of MDE. These findings are also consistent with those obtained by Nunes *et al*. [27], who divided 110 psychiatric inpatients with current MDD and alcohol, cocaine, or opiate dependence into those with independent (N=54) or substance-induced (N=56) major depression. During a 12-month follow-up period, 57% of these patients experienced recurrent major depression, with recurrence being equally likely among patients with independent or substance-induced depression. However, among the substance-induced group, a past diagnosis of independent MDD increased the likelihood of major depression during the follow-up. This is consistent with the increased psychiatric burden observed in our study in the group with both types of MDE. It should be noted that, because greater depressive symptom severity in the group with both types of MDE could have resulted from their having more lifetime episodes of depression, we controlled for the number of lifetime depressive episodes. In this analysis, subjects with both types of MDE had an earlier age of onset of a first depressive episode, more lifetime depressive symptoms and a greater likelihood of suicide attempts.

There are a number of limitations to the present study. First, we focused on lifetime co-morbidity, and, as such, the validity of the findings may be limited by recall bias. Recall bias may be more pronounced in subjects with a history of SD due to the direct toxic effects of drugs or traumatic head injury associated with increased risk-taking behavior leading to persistent cognitive impairment. Second, “pseudocomorbidity” bias, or the incorrect designation of disorders as co-occurring when they are, in fact, randomly associated, is a potential limitation in all studies of co-occurring disorders such as MDD and SD, which are highly prevalent in the general population [38]. Third, because of the high rate of co-occurring SD diagnoses, it was not possible to analyze the data separately by SD subgroup, which may have obscured different susceptibilities for the MDE subtypes in relation to specific substances. Finally, because the present study recruited subjects from case-control and family-based genetic studies, the study sample is not representative of all alcohol- and drug-dependent subjects. Rather, based on the high proportion of cocaine- and opioid-dependent subjects in our sample, our findings are most applicable to a severely affected SD population.

The findings reported here are consistent with the findings from a number of other studies that sought to differentiate independent from substance-induced depression. Our study also underscores the clinical relevance of subtyping depression among individuals with SD and the potential importance of identifying individuals who have experienced both types of depression, since we would anticipate that this group would be less treatment responsive and would, therefore, require more intensive services [27]. Further characterization of this patient group will require prospective, longitudinal studies that examine these individuals’ response to specific treatments for depression and how that impacts the course of their substance use disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of the study sample according to the four-level Major Depressive Episode classification[1]

Characteristic	Overall (n = 1,929)	No MDE (n = 1,066)	Independent Only (n = 156)	Substance-Induced Only (n = 539)	Both Types (n = 168)
Sex					
Male	58.11%	65.01%	41.03%	54.92%	40.48%
Race/Ethnicity[2]					
EA	36.44%	31.14%	43.59%	40.26%	51.19%
AA	54.17%	60.13%	48.08%	49.91%	35.71%
Hispanic	9.38%	8.72%	8.33%	9.83%	13.10%
Annual Household Income					
<$10,000	51.68%	49.16%	48.72%	56.96%	53.57%
$10,000–$20,000	19.70%	20.45%	19.87%	16.70%	24.40%
$20,000–$30,000	11.04%	10.88%	10.26%	11.69%	10.71%
$30,000–$50,000	10.47%	11.16%	11.54%	9.83%	7.14%
>$50,000	7.10%	8.35%	9.62%	4.82%	4.17%
Currently Employed					
Yes	32.87%	35.46%	29.49%	30.61%	26.79%
Marital Status					
Married or Widowed	15.29%	14.54%	21.80%	14.28%	17.26%
Separated or Divorced	25.35%	22.98%	29.49%	25.97%	34.53%
Never Married	59.36%	62.48%	48.72%	59.74%	48.21%
Age					
Mean (s.d.)	39.44 (9.21)	39.38 (9.43)	39.84 (9.83)	39.12 (8.59)	40.48 (9.17)
Substance Dependence Classification					
Alcohol only	16.38%	19.70%	23.08%	8.53%	14.29%
Drug only	31.52%	35.65%	26.92%	27.46%	22.62%
Both	52.10%	44.65%	50.00%	64.01%	63.10%
Number of Lifetime Substance Dependence Disorders					

Characteristic	Overall (n = 1,929)	No MDE (n = 1,066)	Independent Only (n = 156)	Substance-Induced Only (n = 539)	Both Types (n = 168)
Mean (s.d.)	2.94 (1.30)	2.66 (1.22)	2.95 (1.33)	3.33 (1.28)	3.38 (1.37)
Nicotine	66.79%	60.79%	69.87%	75.65%	73.65%
Alcohol	68.48%	64.35%	73.08%	72.54%	77.38%
Cocaine	77.71%	73.45%	72.44%	88.31%	75.60%
Opioids	37.79%	35.08%	33.97%	39.89%	51.79%
Cannabis	31.05%	25.14%	29.49%	40.86%	38.69%
Stimulant	5.97%	3.56%	8.97%	8.38%	10.71%
Sedatives	5.92%	3.85%	7.10%	8.19%	10.71%
Other	14.77%	11.46%	18.59%	17.60%	23.21%
Number of LifetimeAnxiety Disorders					
Mean (s.d.)	0.33 (0.69)	0.15 (0.43)	0.47 (0.72)	0.47 (0.80)	0.89 (1.06)
Antisocial Personality Disorder					
Positive	14.88%	13.13%	17.31%	15.77%	20.83%
Number of Lifetime Depressive Symptoms					
Mean (s.d.)	4.48 (3.89)	1.59 (2.78)	7.71 (1.16)	7.99 (1.11)	8.56 (0.75)
Suicidal Ideation					
Yes	41.42%	25.70%	53.21%	59.37%	72.62%
Suicide Attempt					
Yes	16.28%	7.13%	19.87%	25.60%	41.07%

[1] No lifetime MDE, lifetime independent MDE only, lifetime substance-induced MDE only and lifetime independent and substance-induced MDE

[2] EA, European-American; AA, African-American

All comparisons (except those involving age, current employment, annual household income, ASPD and marital status) were significant at $p < 0.0038$ (the Bonferroni-corrected significance level)

Table 2

Generalized logistic regression analysis of the four-level MDE classification[1]

Predictor[2]	**Full Model Type 3 Wald χ^2 p-value**	**Order of selection (+) or elimination (−)**[3]	**Final Model Type 3 Wald χ^2 p-value**
Sex	0.0006	+5	0.0007
Race/Ethnicity	0.0204	+6	0.0073
Household Income	0.5385	−2	
Currently Employed	0.4295	-3	
Marital Status	0.3320	-4	
Age	0.0003	+4	< 0.0001
Substance Dependence Classification	0.0100	+3	0.0004
Number of SD Disorders	0.0562	−5	
Number of Lifetime Anxiety Disorders	0.0055	+2	0.0023
Antisocial Personality Disorder	0.0487	+8	0.0411
Number of Lifetime Depressive Symptoms	< 0.0001	+1	< 0.0001
Suicidal Ideation	0.7521	−1	
Suicide Attempt	0.0208	+7	0.0243

[1] No lifetime MDE, lifetime independent MDE only, lifetime substance-induced MDE only and lifetime independent and substance-induced MDE

[2] Statistically significant predictor variables are in **bold**

[3] The order of predictor selection in the stepwise selection procedure and the order of predictor elimination in the backward elimination procedure are based on type 3 Wald χ^2 p-values from models considered in each procedure (data not shown).

Table 3

Estimated odds ratio and 95% confidence interval of phenotype correlates of Major Depressive Episode (in order of entry in the generalized logistic regression analysis)

Predictor Variable[1]	Independent vs. Substance-Induced	Both Types vs. Independent	Both Types vs. Substance-Induced
Number of Lifetime Depressive Symptoms (0 – 9)			
+1[2]	**0.87 (0.75, 1.00)**	**2.05 (1.59, 2.63)**	**1.78 (1.41, 2.24)**
Number of Lifetime Anxiety Disorders (0 – 6)			
+1[2]	1.04 (0.82, 1.32)	**1.35 (1.04, 1.75)**	**1.41 (1.16, 1.71)**
Substance Dependence Classification			
Alcohol vs. Drug	**2.83 (1.60, 4.98)**	0.81 (0.39, 1.66)	**2.29 (1.19, 4.38)**
Alcohol vs. Both	**3.21 (1.91, 5.38)**	0.71 (0.37, 1.35)	**2.28 (1.27, 4.10)**
Drug vs. Both	1.14 (0.74. 1.75)	0.88 (0.50, 1.53)	1.00 (0.64, 1.56)
Age			
+1[2]	1.01 (0.99, 1.03)	1.02 (0.99, 1.04)	**1.03 (1.01, 1.05)**
Sex			
Female vs. Male	**1.96 (1.33, 2.88)**	0.89 (0.55, 1.45)	**1.74 (1.18, 2.57)**
Race/Ethnicity[3]			
EA vs. AA	1.14 (0.77, 1.67)	**1.63 (1.00, 2.66)**	**1.86 (1.25, 2.76)**
EA vs. Hispanic	1.02 (0.52, 2.01)	0.92 (0.42, 2.04)	0.94 (0.52, 1.70)
AA vs.Hispanic	0.90 (0.46, 1.76)	0.57 (0.25, 1.26)	**0.51 (0.28, 0.93)**
Ever Attempted Suicide			
Yes	0.71 (0.45, 1.13)	**1.97 (1.16, 3.35)**	1.41 (0.95, 2.09)
Antisocial Personality Disorder			
Positive	1.51 (0.91, 2.49)	1.04 (0.56, 1.90)	1.56 (0.96, 2.53)

[1] Statistically significant effects are in **bold**.

[2] Reflects a one-unit increment in the continuous dependent variable

[3] EA, European-American; AA, African-American