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Associations between depression subtypes and substance use disorders

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Abstract

Evaluating whether certain subtypes of Major Depressive Disorder (MDD) are more strongly associated with Substance Use Disorders (SUDs) may help clarify reasons for MDD–SUD relations. Therefore, this study compared *DSM-IV*-defined non-atypical/non-melancholic depression (undifferentiated depression; $n=365$), atypical depression ($n=117$), melancholic depression ($n=245$), and atypical-melancholic depression ($n=68$) in the prevalence of current SUDs, while controlling for relevant demographic and clinical variables. Psychiatric outpatients with a current diagnosis of unipolar MDD were assessed using the Structured Clinical Interview for *DSM-IV*, supplemented by questions from the Schedule for Affective Disorders and Schizophrenia. Results showed that compared with patients with undifferentiated depression, melancholic patients had higher rates of current nicotine dependence (34% vs. 26%) and drug abuse/dependence (8% vs. 3%), $P_s < 0.05$. These differences were explained by the association between specific melancholic features (marked psychomotor agitation and weight loss/decreased appetite) and nicotine and drug use disorders. Atypical depression, atypical-melancholic depression, and other subtype symptoms were not significantly associated with any SUDs. Although this study is limited by low prevalence of alcohol and drug use disorders, the present findings suggest that different symptomatic expressions of MDD differentially associate with some SUDs.

Keywords

Major depressive disorder; Melancholic depression; Atypical depression; Substance use disorders; Nicotine dependence; Psychomotor agitation; Decreased appetite

1. Introduction

Different psychopathologic forms of major depressive disorder (MDD) are associated with distinct biological, psychological, and behavioral correlates and potentially distinct etiologies (Fountoulakis et al., 2004; Leventhal and Rehm, 2005). Therefore, evaluating whether certain

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subtypes of MDD are more strongly associated with substance use disorders (SUDs) may help clarify reasons for MDD–SUD relations and generate a more precise understanding of the clinical profiles of dual diagnosis patients.

Atypical and melancholic depression have been identified as two psychopathologic subtypes of MDD in the *DSM-IV* (American Psychiatric Association, 1994). The atypical features specifier requires: (a) mood reactivity and (b) two or more of the following: interpersonal rejection sensitivity, leaden paralysis, significant weight gain or overeating, and oversleeping. The melancholic features specifier requires: (a) pervasive anhedonia or lack of mood reactivity and (b) three or more of the following: distinct quality of depressed mood, early morning awakening, mood worse in the morning, marked psychomotor disturbance, reduced appetite or weight loss, and excessive guilt. Investigators have used these definitions and others to determine whether certain subtypes of MDD are differentially comorbid with SUDs.

Research on the association between atypical (vs. non-atypical) MDD and SUDs has been mixed. Data from both the Epidemiological Catchment Area Study and the National Comorbidity Survey suggest a link between atypical depression (as defined by the presence of hyperphagia and hypersomnia) and drug use disorders (Horwath et al., 1992; Matza et al., 2003). In contrast, analyses of Ontario Health Supplement data indicated that atypical depression, defined by reversed neurovegetative features, was not associated with greater incidence of SUDs (Levitan et al., 1997). Likewise, data from the Rhode Island Hospital Methods to Improve Diagnostic Assessment and Services (MIDAS) project and the Zurich Cohort Study both showed no increased incidence of SUDs in *DSM-IV*-defined atypical depression (Angst et al., 2006; Posternak and Zimmerman, 2002).

Studies examining the melancholic (vs. non-melancholic) MDD distinction suggest a potential link between this subtype and non-alcohol SUDs. Female twins in the Virginia Twin Registry with the *DSM-IV* melancholic features subtype of MDD had higher rates of nicotine dependence but not alcohol dependence (Kendler, 1997). Additionally, data from the Oregon Adolescent Depression Project indicated that *DSM-IV*-defined melancholic MDD was associated with stimulant use disorders but not alcohol abuse/dependence (Leventhal et al., 2008a). Similarly, melancholic depression (as defined by *DSM-IV*) was not associated with alcohol use disorders in the Vantaa Depression Study; the prevalence of other SUDs was not reported in that study (Melartin et al., 2004).

Integrating these findings has been difficult for several reasons. First, investigators typically have not accounted for the influence of relevant demographic and clinical characteristics that could explain MDD subtype-SUD associations. Second, disparate subtype definitions have been used (e.g., reversed neurovegetative features definition vs. *DSM-IV* definition of atypical depression, which places priority on mood reactivity). Third, studies have not compared atypical and melancholic MDD to each other. On a similar note, little is known about the substance use characteristics of individuals who simultaneously meet criteria for both the melancholic and atypical subtypes. Although such individuals are relatively rare, they have been present in clinical samples (Farabaugh et al., 2004).

Accordingly, the current study evaluated whether there are differences between *DSM-IV*-defined non-atypical/non-melancholic depression (undifferentiated depression), atypical depression (MDD with atypical features only), melancholic depression (MDD with melancholic features only), and atypical-melancholic depression (individuals that simultaneously meet criteria for both atypical and melancholic features specifiers) in the prevalence of nicotine, alcohol, and drug use disorders. We also examined the relationship between specific atypical and melancholic symptoms and SUDs to identify which psychopathologic features underlie subtype-SUD relationships. Our analyses were based on

data collected from the MIDAS project. This dataset and study design addresses the limitations of previous studies because it: (1) compares undifferentiated, atypical, melancholic, and atypical-melancholic depression in the same investigation; (2) calculates associations after adjusting for the effects of relevant demographic variables (i.e., age, sex, race, education, marital status), psychiatric characteristics (i.e., comorbid non-SUD disorders), and MDD features (i.e., severity, age of onset, recurrence, illness duration); and (3) utilizes *DSM-IV* definitions of atypical and melancholic MDD as well as examines the influence of specific atypical and melancholic symptoms on SUDs.

We hypothesized that patients with atypical depression would not have higher rates of SUDs than patients with undifferentiated depression based on previous investigations of the *DSM-IV* atypical subtype (Angst et al., 2006; Posternak and Zimmerman, 2002). Because studies utilizing the reversed neurovegetative features definition of atypical MDD have shown higher rates of drug use disorders more often (Horwath et al., 1992; Matza et al., 2003) than not (Levitin et al., 1997), we expected that hypersomnia and hyperphagia would be associated with drug use disorders. Given that previous reports have shown that melancholia is associated with a greater incidence of cocaine and nicotine use disorders but not alcohol abuse/dependence (Kendler, 1997; Leventhal et al., 2008a), we hypothesized that patients with melancholic depression would have higher rates of nicotine dependence and drug abuse/dependence than undifferentiated depression patients. We had no specific hypotheses regarding differences between atypical and melancholic depression and how atypical-melancholic depression would compare with the other groups because of the paucity of previous research in this area.

Group and symptom-level comparisons were conducted both with and without adjustment for demographic, psychiatric, and MDD characteristics. The decision to adjust for MDD characteristics was based on Kendler (1997), who pointed out that associations between different forms of MDD and relevant clinical variables could either be due to a general effect of clinical severity (because individuals with particular forms of MDD may be more severely ill) or a specific effect of the MDD feature(s) of interest.

2. Methods

2.1. Subjects

Subjects were recruited from the Rhode Island Hospital Department of Psychiatry's outpatient practice. During their initial telephone screen, patients were invited to participate in an in-depth diagnostic evaluation prior to meeting with their treating clinician (psychiatrist, psychologist, or social worker). To date, 2300 patients have been evaluated. Among those evaluated, 795 were diagnosed as having a current unipolar MDD and were evaluated for all melancholic and atypical symptoms, forming the cohort of interest for the current report. We decided not to include subjects with a history of (hypo) mania ($n=60$) because bipolar disorder has been shown to associate with atypical (Benazzi, 2002, 2005) and melancholic depression (Mitchell and Malhi, 2004) as well as SUDs (Winokur et al., 1998) and may therefore confound associations between depression subtypes and SUDs. The Rhode Island Hospital institutional review board approved the research protocol, and all participants provided informed written consent.

2.2. Assessment

Patients were interviewed using the Structured Clinical Interview for *DSM-IV* (SCID; First et al., 1997). The SCID was supplemented with questions from the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer, 1978) to assess the severity of symptoms during the week prior to the evaluation. Baseline Clinical Global Impression—Severity (CGI-S; Guy, 1976) ratings were also made for each patient by the diagnostic rater.

Diagnostic interviewers were PhD psychologists or college graduate research assistants who had undergone extensive training, as described elsewhere (Zimmerman and Mattia, 1999).

Individual atypical and melancholic symptoms were evaluated as part of the SCID and were rated according to *DSM-IV* definitions. Marked psychomotor retardation and agitation were evaluated using the SADS and were considered present if patients scored a 4 (marked) or 5 (extreme) on the psychomotor disturbance items. The prevalence of each symptom in the current sample was as follows: mood reactivity ($n=587$, 73.8%); hyperphagia ($n=191$, 24.0%); hypersomnia ($n=159$, 20.0%); leaden paralysis ($n=211$, 26.5%); rejection sensitivity ($n=319$, 40.1%), lack of mood reactivity ($n=172$, 21.6%); anhedonia ($n=640$, 80.5%); distinct quality of mood ($n=502$, 63.1%); mood worse in the morning ($n=181$, 22.8%); weight loss/decreased appetite ($n=371$, 46.7%); early morning awakening ($n=365$, 45.9%); excessive/inappropriate guilt ($n=434$, 54.6%); marked retardation ($n=29$, 3.6%); marked agitation ($n=40$, 5.0%). It should be noted that a small portion of patients were rated as having subthreshold levels of poor mood reactivity ($n=36$, 4.5%) and therefore were neither coded as mood reactive nor non-reactive. Interrater reliability estimates for each of the atypical and melancholic symptoms were obtained from 45 joint interviews. The reliability estimates [Kappa (K) values] for each symptom were as follows: mood reactivity ($K=0.81$); hyperphagia ($K=0.76$); hypersomnia ($K=0.54$); leaden paralysis ($K=0.70$); rejection sensitivity ($K=0.77$); lack of mood reactivity ($K=0.81$); anhedonia ($K=0.89$); distinct quality of mood ($K=0.94$); mood worse in the morning ($K=0.90$); weight loss/decreased appetite ($K=0.83$); early morning awakening ($K=0.60$); excessive/inappropriate guilt ($K=0.74$). All symptoms demonstrated adequate reliability. The reliability of marked retardation and agitation could not be examined because of low base rates in the joint interview subsample (i.e., only one person was rated with marked psychomotor agitation by both the raters; two patients were rated with marked psychomotor retardation by one rater and one patient was rated with marked retardation by the other rater).

All diagnoses were made according to *DSM-IV* criteria. Our analyses comparing the depression subtypes are based on current rather than lifetime diagnoses of disorders. Previous studies have shown that atypical and melancholic features are not highly stable across depressive episodes (Angst et al., 2006; Levitan et al., 1997; Melartin et al., 2004). Therefore, we also used current as opposed to lifetime diagnoses of SUDs. Consistent with previous investigations of comorbidity across depressive subtypes (Angst et al., 2006; Horwath et al., 1992; Leventhal et al., 2007; Matza et al., 2003; Posternak and Zimmerman, 2002), abuse and dependence were combined into a single category to enhance prevalence of these diagnoses (except for nicotine dependence, which was highly prevalent in this sample). Patients who met criteria for drug abuse/dependence had one or more of the following SUDs: cannabis ($n=22$), cocaine ($n=10$), sedative ($n=3$), opioid ($n=8$), hallucinogen ($n=2$), and other ($n=1$).

2.3. Statistical analyses

The primary analytic approach involved comparing the four patient groups: undifferentiated, atypical, melancholic, and atypical-melancholic. For each dependent variable (i.e., demographic, clinical, and substance use characteristics), omnibus tests were first conducted to compare differences across groups. ANOVA, Chi-square, and Kruskal–Wallis tests were used for omnibus tests of continuous, categorical, and count variables, respectively. Outcomes with significant omnibus tests were followed by two-group logistic/multiple regression contrasts that compared each pair of groups (i.e., undifferentiated *vs.* atypical; undifferentiated *vs.* melancholic; undifferentiated *vs.* atypical-melancholic; atypical *vs.* melancholic; atypical *vs.* atypical-melancholic; melancholic *vs.* atypical-melancholic). For SUD analyses, a priori two-group contrasts were performed using logistic regression regardless of results of omnibus significance tests in order to test specific hypotheses regarding the prevalence of SUDs across subtypes. For symptom-level analyses, presence *vs.* absence of each atypical and melancholic

feature was used to predict SUDs in logistic regression models. Separate models were used to evaluate the effect of each symptom on each type of SUD. For two-group comparisons and symptom-level analyses predicting SUDs, each logistic regression model was first conducted while adjusting for the set of demographic variables (age, sex, race, level of education, and marital status). The model was run again when adjusting for the sets of demographic and psychiatric variables (lifetime history of dysthymia and any anxiety disorder). A final model was run that adjusted for the sets of demographic, psychiatric, and MDD characteristics (CGI-S, duration of current episode, age of MDD onset, number of episodes). Results from logistic regression analyses are reported as odds ratios (ORs). For all comparisons, statistical significance was set at $P < 0.05$, and all tests were 2-tailed.

3. Results

3.1. Demographic and clinical characteristics across subtypes

The demographic and clinical features of patients with undifferentiated, atypical, melancholic, and atypical-melancholic depression are presented in Table 1. There was a significantly higher prevalence of females in the atypical group than the melancholic and undifferentiated groups. Education levels were significantly different across groups and were lower in the atypical and atypical-melancholic groups.

Analyses of MDD characteristics demonstrated that atypical-melancholic and melancholic patients had higher CGI-S scores than undifferentiated and atypical patients when controlling for demographics. The duration of the current depressive episode was shorter in participants with melancholic than atypical or atypical-melancholic depression when controlling for demographics. Age of onset was earlier for patients with atypical-melancholic than melancholic depression when controlling for demographics.

3.2. Prevalence of current SUDs across depression subtypes

Rates of current nicotine dependence, alcohol abuse/dependence, and drug abuse/dependence in the entire sample were 29.1%, 7.7%, and 5.0%, respectively. Rates of SUDs by depression subtype are reported in Table 2. There were no significant overall differences across subtypes for any SUD category (P s ranging from .08 to .15). Planned two-group comparisons of melancholic patients to undifferentiated and atypical patients showed that melancholic depression was associated with nicotine dependence when controlling for demographic characteristics in both cases (melancholic vs. undifferentiated: OR = 1.43, $P = 0.05$; melancholic vs. atypical: OR = 1.89, $P = 0.02$). Effects were not markedly changed when prevalence of comorbid anxiety disorders and dysthymia were added to the models (melancholic vs. undifferentiated: OR = 1.41, $P = 0.06$; melancholic vs. atypical: OR = 1.81, $P = 0.03$). However, these effects were reduced when the entire set of demographic, psychiatric, and MDD characteristics were added to the models (melancholic vs. undifferentiated: OR = 1.30, $P = 0.17$; melancholic vs. atypical: OR = 1.63, $P = 0.09$), suggesting that the increased severity of melancholic patients explain part of the effect on nicotine dependence. Comparisons between melancholic and undifferentiated patients showed that melancholic depression was associated with increased prevalence of drug abuse/dependence when controlling for demographic characteristics (OR = 2.64, $P = 0.01$). This effect remained significant when psychiatric and MDD characteristics were added to the model (OR = 2.49, $P = 0.02$). There were no other significant two-group comparisons between any subtypes for any SUD.

It should be noted, however, that the low prevalence of alcohol and drug use disorders in atypical and atypical-melancholic patients likely limited the multivariate comparisons involving these groups. Therefore, we conducted additional analyses that compared non-atypical vs. atypical depression and non-melancholic vs. melancholic depression in order to

increase the frequency of SUDs in each group. Results were generally consistent with the findings above. Univariate chi-squared tests showed no significant effect of atypical features on each SUD class (non-atypical vs. atypical patients: 29.2% vs. 28.7% nicotine dependence; 8.7% vs. 4.3% alcohol abuse/dependence; 5.1% vs. 4.9% drug abuse/dependence). Univariate tests showed significant effects of melancholic features on nicotine and drug use disorders (non-melancholic vs. melancholic patients: 25.7% vs. 34.2% nicotine dependence, $\chi^2 = 6.59$, $P = .01$; 3.7% vs. 7.0% drug abuse/dependence, $\chi^2 = 4.31$, $P = .04$) but non-significant effects on alcohol use disorders (non-melancholic vs. melancholic patients: 8.5% vs. 6.4%). Multivariate analyses showed that melancholic features were associated with nicotine use disorders when adjusting for demographic and psychiatric characteristics (OR=1.49, $P = 0.02$), but fell below significance when the entire set of demographic, psychiatric, and MDD characteristics were included in the model (OR=1.36, $P = 0.08$). Melancholic features were also significantly associated with drug use disorders when adjusting for demographic and psychiatric characteristics (OR=2.11, $P = 0.03$); however, effects fell below significance when the entire set of demographic, psychiatric, and MDD characteristics were included in the model (OR=1.87, $P = 0.07$).

3.3. Associations between subtype symptoms and SUDs

When controlling for demographics, weight loss/decreased appetite predicted whether or not patients had comorbid nicotine dependence (36.1% of patients with weight loss had nicotine dependence vs. 22.9% of patients without weight loss, OR=1.91, $P < 0.0001$) and drug use disorders (6.7% of patients with weight loss had drug abuse/dependence vs. 3.5% of patients without weight loss, OR=1.91, $P = 0.04$). These relations remained significant when also controlling for psychiatric and MDD characteristics (nicotine dependence: OR=1.94, $P < 0.0001$; drug abuse/dependence: OR=2.06, $P = 0.04$). When controlling for demographics, marked psychomotor agitation also predicted whether or not patients had comorbid nicotine dependence (50.0% of patients with agitation had nicotine dependence vs. 27.4% of patients without agitation, OR=2.46, $P < 0.01$) and drug use disorders (6.7% of patients with agitation had drug abuse/dependence vs. 3.5% of patients without agitation, OR=3.54, $P = 0.01$). These relations remained significant when also controlling for psychiatric and MDD characteristics (nicotine dependence: OR=2.26, $P = 0.02$; drug abuse/dependence: OR=3.13, $P = 0.03$). Marked psychomotor retardation was not present in any patient with a comorbid alcohol or drug use disorder (all 61 patients with alcohol abuse/dependence and all 40 patients with drug abuse/dependence did not meet criteria for marked psychomotor retardation). These data precluded logistic regression analysis and suggested that this symptom was strongly associated with reduced odds of having a current non-nicotine substance use disorder. No other atypical or melancholic symptoms associated with any SUDs.

Given that melancholic (vs. undifferentiated) depression was associated with nicotine and drug use disorders in subtype-level analyses, we conducted additional analyses to examine whether these effects were carried by specific melancholic symptoms (weight loss/decreased appetite and marked psychomotor agitation). Unadjusted logistic regressions showed that melancholic (vs. undifferentiated) depression was associated with increased incidence of nicotine dependence (OR=1.46, $P = 0.04$) and drug abuse/dependence (OR = 2.47, $P = 0.02$). When weight loss/decreased appetite and marked psychomotor agitation were added to the model predicting nicotine dependence, the subtype effect was clearly eliminated (OR=0.96, $P = 0.85$). In the model predicting drug abuse/dependence, the effect of subtype was considerably reduced when weight loss/decreased appetite and marked agitation were added to the model (OR=1.82, $P = 0.17$). These results suggest that the effect of melancholic depression on nicotine dependence was fully carried by the influence of weight loss/decreased appetite and agitation and that the influence on drug abuse/dependence was partially carried by the effects of these two symptoms.

4. Discussion

There were modest differences in prevalence of some SUDs across depression subtypes in this sample. In comparison to undifferentiated and atypical depression, melancholic depression was associated with a significant 1.4- and 1.9-fold increase in risk of comorbid nicotine dependence, respectively. These associations were lowered when statistically controlling for MDD severity and chronicity variables, suggesting that part of the melancholia–nicotine relationship was explained by melancholia’s associated clinical characteristics. Indeed, melancholic patients had higher CGI-S scores than undifferentiated and atypical patients. Atypical-melancholic depression showed a similar incidence of nicotine dependence as melancholic depression; however, results comparing atypical-melancholic to the other subtypes were non-significant and were likely limited by low statistical power due to the infrequency of atypical-melancholic patients (they comprised only 8.5% of the sample). Additional comparisons between all depressed participants who met criteria for melancholia versus all of those who did not were generally consistent with the previous analyses. These findings are concordant with prior reports. Kendler (1997) showed that female twins with melancholic (vs. non-melancholic) depression in their most severe lifetime episodes had higher rates of lifetime nicotine dependence without adjusting for other clinical variables. The absence of differences between undifferentiated and atypical depression in nicotine dependence (as well as the lack of differences when all non-atypical and all atypical patients were compared) are congruent with previous findings. Indeed, Angst et al. (2006) showed similar rates of tobacco dependence in atypical and non-atypical depression in a sample of patients with MDD or bipolar-II disorder.

Rates of alcohol abuse/dependence did not differ across depression subtypes. Studies have shown no differences in alcohol use disorders when comparing atypical to non-atypical (Horwath et al., 1992; Levitan et al., 1997; Matza et al., 2003) and melancholic to non-melancholic (Kendler, 1997; Melartin et al., 2004; Leventhal et al., 2008a) depression. Taken together, it appears that the prevalence of alcohol use disorders does not differ across depression subtypes.

There was some differentiation in drug use disorders by subtype. Consistent with our hypotheses, melancholic depression had the highest rates of current drug use disorders and was associated with a greater than 2.5-fold increase in risk compared to undifferentiated depression. This effect was robust to control of demographic and clinical characteristics, suggesting that the association was specific to the qualitative features of the melancholic subtype. A previous study showed that melancholic versus non-melancholic MDD was associated with an increase risk of stimulant use disorders when statistically controlling for demographics, comorbid psychiatric disorders, and MDD severity and chronicity (Leventhal et al., 2007). Alternatively, atypical or atypical-melancholic depression was not significantly associated with drug use disorders in the present sample. Two previous studies of the *DSM-IV* definition of atypical depression showed that atypical versus non-atypical patients were not different in rates of comorbid stimulant and cannabis use disorders (Angst et al., 2006; Posternak and Zimmerman, 2002).

Previous research has shown increased rates of drug use disorders in individuals with reversed neurovegetative features (Horwath et al., 1992; Matza et al., 2003). However, symptom-level analyses showed no association between either of hypersomnia or hyperphagia and SUDs. Past studies of reversed neurovegetative symptoms have utilized lifetime rather than current diagnoses of drug use disorders and categorized subtypes based on symptom patterns during the worst episode (Horwath et al., 1992; Matza et al., 2003), making it difficult to compare these findings to the current study, which relied on current diagnoses. A study of the symptomatic expression of depressive episodes over the lifetime showed that individuals who had fluctuating neurovegetative symptoms (i.e., individuals who have increased appetite/

weight gain and hypersomnia in some MDD episodes and decreased appetite/weight loss and insomnia in other MDD episodes) had greater rates of sedative and stimulants use disorders (Levitan et al., 1997). Interestingly, that study found no differences in SUDs between individuals who had episodes with only typical neurovegetative symptoms and individuals with only atypical neurovegetative episodes, which may be applicable to the current findings.

Symptom-level analyses indicated that marked psychomotor agitation was associated with increased prevalence of nicotine and drug use disorders, even in models controlling for clinical characteristics. Prior reports have shown that depression with mixed manic/depressive episodes, which highly overlaps with psychomotor agitation, and agitated depression are associated with increased incidence of substance dependence (Balzais et al., 2006; Leventhal et al., 2008b). Weight loss/decreased appetite was also related to nicotine and drug use disorders, when adjusting for clinical characteristics. The relationship between weight loss/decreased appetite and nicotine dependence was especially robust and could be explained by the psychopharmacological effects of nicotine, which includes appetite suppression (Frankham and Cabanac, 2003). However, interviewers in this study provided detailed queries of all depressive symptoms to elucidate whether they are central to the syndrome or merely epiphenomena. Follow up analyses demonstrated that associations between these two melancholic features and nicotine and drug use disorders accounted for part or all of melancholia–SUD relationships. On the other hand, the two key criteria of melancholia (anhedonia and lack of mood reactivity; American Psychiatric Association, 1994) were not associated with any SUDs.

In addition, we found that no patients with marked psychomotor retardation were positive for alcohol or drug use disorders. Findings involving agitation and retardation should be considered in respect to past data showing that these two forms of motor disturbance are rarely concurrent in the same episode (Zimmerman et al., 2006). Thus greater rates of drug use disorders in agitated patients may be driven by a lack of retardation or lower rates in retarded patients may be driven by a lack of agitation. Either way, these findings are interesting and have implications to understanding the role of psychomotor disturbance in patients with comorbid MDD and drug use disorders.

The limitations of our study should be considered. First, there were low rates of alcohol and drug use disorders in this sample, which precluded our investigation of the relationship between subtypes and specific drugs (cocaine, amphetamine, sedatives, cannabis, opioids) and may have provided insufficient power to detect true associations that might have been present. Indeed, it is notable that the incidence of alcohol and drug abuse/dependence in this sample (5.0% and 7.7%, respectively) was slightly lower than those typically indicated in the literature. It is possible that the low rates of active alcohol and drug use disorders were due to the nature of this sample, which included individuals interested in outpatient psychiatric treatment in general (rather than primarily substance abuse treatment). Thus, future investigations of individuals in inpatient or substance abuse treatment programs may be useful in order to increase rates of active SUDs. Second, it is difficult to determine the causal or temporal nature of MDD–SUD comorbidity because these associations are cross-sectional. Accordingly, longitudinal designs might be indicated.

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Table 1
Demographic and clinical characteristics by depression subtype

	Undifferentiated (n=365)	Atypical (n=117)	Melancholic (n=245)	Atypical-melancholic (n=68)	All groups F/ χ^2
<i>Demographics</i>					
Female, no. (%) #	225 (61.6)	97 (82.9)	157 (64.1)	50 (73.5)	20.16***
Age, M (S.D.)	38.7 (12.4)	37.2 (11.6)	38.7 (12.9)	37.4 (9.5)	0.64
Race: white, no. (%)	317 (86.9)	94 (80.3)	201 (82.0)	57 (83.8)	4.09
Marital status, no (%)	—	—	—	—	11.77
Single	105 (28.8)	38 (32.5)	59 (24.1)	17 (25.0)	
Married/living together	173 (47.4)	43 (36.8)	124 (50.6)	37 (54.4)	
Divorced/separated	76 (20.8)	33 (28.2)	58 (23.7)	14 (20.6)	
Widowed	11 (3.0)	3 (2.6)	4 (1.6)	0 (0.0)	
Level of education, no. (%) #	—	—	—	—	18.39*
Less than high school diploma	37 (10.1)	20 (17.1)	31 (12.7)	15 (22.1)	
High school graduate	92 (25.2)	33 (28.2)	59 (24.1)	14 (20.6)	
At least some college	108 (29.6)	41 (35.0)	79 (32.2)	23 (33.8)	
College degree or higher	128 (35.1)	23 (19.7)	76 (31.0)	16 (23.5)	
<i>Lifetime psychiatric comorbidity</i>					
Dysthymia	36 (9.9)	14 (12.0)	17 (6.9)	9 (13.2)	3.83
Any anxiety disorder	259 (71.0)	91 (77.8)	171 (69.8)	57 (83.8)	7.36
<i>MDD characteristics</i>					
CGI-S: M (S.D.)	2.97 (.59) ^{a,b}	3.09 (.58) ^b	3.26 (.67) ^{cd}	3.38 (.65) ^d	15.43 [†]
Duration of current episode: wk., median δ	40 ^{a,b}	54 ^a	24 ^b	104 ^a	11.85***
Number of episodes: m (S.D.) ##	3.13 (5.87)	3.74 (8.97)	4.20 (9.30)	3.59 (5.06)	3.69
Age of onset, yrs, m (S.D.)	26.1 (13.5) ^{a,b}	23.3 (11.9) ^{a,b}	27.7 (14.7) ^a	22.7 (11.5) ^b	4.23**

Note. N = 795. All participants meet criteria for current major depressive disorder. CGI-S—Clinical Global Impression—Severity. Letters with different superscripts indicate that groups are significantly different from each other in two-group comparisons controlling for age, sex, race, level of education, and marital status ($P < 0.05$). Groups with shared superscripts are not significantly different in these analyses. (e.g., for CGI-S ratings, atypical depression has a “b” superscript and melancholic depression has “c” and “d” superscripts indicating significant differences due to different letter superscripts for these groups. In contrast, undifferentiated depression has “a” and “b” superscripts and atypical depression has a “b” superscript, indicating no significant differences due to the common “b” superscript).

* $P < 0.05$;

** $P < 0.01$,

 $P<0.001$;[†] $P<0.0001$.[#] Two-group χ^2 contrasts of all groups indicated that atypical depression was significantly different from undifferentiated and melancholic depression ($P\leq 0.0003$).[‡] Two-group χ^2 contrasts of all groups indicated that undifferentiated depression was significantly different from atypical and atypical-melancholic depression ($P<0.02$).[§] Median one-way analysis.^{##} Kruskal–Wallis Test

Table 2
Prevalence of current substance use disorders across depression subtypes

	Undifferentiated (n=365)	Atypical (n=117)	Melancholic (n=245)	Atypical-melancholic (n=68)	All groups	
					χ^2	P
Nicotine dependence, no. (%)	95 (26.0) ^a	29 (24.8) ^a	83 (33.9) ^b	24 (35.3) ^{ab}	6.70	0.08
Alcohol abuse/dependence, no. (%)	34 (9.3) ^a	7 (6.0) ^a	19 (7.8) ^a	1 (1.5) ^a	5.56	0.15
Drug abuse/dependence, no. (%)	12 (3.3) ^a	6 (5.1) ^{ab}	19 (7.8) ^b	3 (4.4) ^{ab}	6.18	0.10

Note. N =795. All participants meet criteria for current major depressive disorder.

Letters with different superscripts indicate that groups are significantly different from each other in two-group comparisons controlling for age, sex, race, level of education, and marital status. Groups with shared superscripts are not significantly different in these analyses. (e.g., for Drug Abuse/Dependence, undifferentiated depression has only an “a” superscript and melancholic depression has only a “b” superscript, indicating significant differences due to different letter superscripts for these groups. In contrast, atypical depression has “a” and “b” superscripts and melancholic depression has a “b” superscript, indicating no significant differences due to the common “b” superscript).