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Associations between subtypes of major depressive episodes and substance use disorders

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Abstract

The goal of this study was to examine whether certain subtypes of major depressive episodes (MDEs)—defined by their particular constellations of symptoms—were more strongly associated with substance use disorders (SUDs), compared to other subtypes of MDEs. Participants were adults in the National Comorbidity Survey-Replication sample who met DSM criteria for at least one lifetime MDE ($n=1829$). Diagnostic assessments were conducted using structured interviews. The following MDE subtypes were examined: atypical, psychomotor agitation, psychomotor retardation, melancholic, and suicidal. The results indicated that: (1) suicidal MDEs were associated with increased risk for all SUDs; (2) melancholic MDEs were associated with increased risk for alcohol use disorders; and (3) psychomotor agitation was associated with increased risk for alcohol dependence. These associations did not differ significantly by gender. Adjusting for age, the severity of the MDE, the age of onset of the first MDE, and psychiatric comorbidity did not substantially change the results. Supplemental analyses examining only diagnoses that occurred in the year prior to the assessment demonstrated a similar pattern (with MDEs characterized by psychomotor agitation being associated with drug use disorders as well). Exploratory order-of-onset analyses indicated that participants with lifetime MDEs and SUDs tended to report an MDE onset prior to the SUD onset, and those who experienced a suicidal MDE at some time in their lives were particularly likely to have had their first MDE prior to developing a SUD. Therefore, risk for lifetime SUDs differs according to the particular set of symptoms experienced during MDEs.

Keywords

major depression; substance abuse; substance dependence; alcohol; drug; comorbidity; order of onset

1. Introduction

Major depressive episodes (MDEs) are associated with substance use disorders (SUDs; Swendsen and Merikangas, 2000). However, not all people with MDEs experience a SUD, and this variability has led to research into factors that are associated with risk for SUDs among people who have had MDEs. One possibility that has received little attention is the

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fact that MDEs differ in the particular constellation of symptoms experienced by individuals. The goal of this study was to examine whether certain MDE subtypes were more strongly associated with SUDs (or particular types of SUDs), compared to other subtypes of MDEs, and whether these associations differed by gender.

MDE subtypes

Recently, researchers have suggested examining subtypes of depression in an effort to reduce the heterogeneity in this diagnosis, which could further our understanding of its etiology (Hasler et al., 2004). The DSM identifies several subtypes, including melancholic features (anhedonia, non-reactive mood, worsening symptoms in the morning, early morning awakening, psychomotor changes, loss of appetite/weight loss, excessive/inappropriate guilt) and atypical features (reactive mood, appetite increase/weight gain, hypersomnia, rejection sensitivity not limited to mood episodes, and leaden paralysis). Researchers examining subtypes of depression have, in addition to the DSM-defined subtypes, focused on the particular type of psychomotor change (agitation versus retardation; Leventhal et al., 2008a) and whether or not a MDE is characterized by suicidal ideation and/or attempts (Bostwick and Pankratz, 2000).

Associations between MDE subtypes and substance use disorders

There are several reasons that particular subtypes of MDEs could be differentially associated with SUDs. For example, people with MDEs that include symptoms relating to low motivation (e.g., anhedonia, the loss of interest of pleasure in activities previously enjoyed) and psychomotor retardation may simply not have the energy to obtain substances, or may not experience symptoms that motivate people to use substances (such as agitation and insomnia, which depressant substances may diminish). Alternatively, people with anhedonia may use substances in an effort to feel *something*, due to the fact that they are unable to derive pleasure from normal activities; in addition, anhedonia may be an effect of some SUDs (Kalechstein et al., 2002; Leventhal et al., 2008b). People with more activated depressions that involve psychomotor agitation and/or insomnia may seek out substances (such as alcohol and/or other depressants) to medicate those symptoms. Conversely, the increased risk for later depression experienced by people with SUDs may be due to physiological effects of heavy substance use. If this is the case, different substances may have different effects, resulting in different patterns of depressive symptoms. It is also possible that problems relating to the use of different substances tend to result in different negative life events (e.g., alcohol may relate to family and job problems, while drugs may relate to arrests), which may be associated with different MDE symptom constellations (Keller et al., 2007; Wadsworth et al., 2005).

Although research to date is sparse, there is some indication that different MDE symptom patterns may be differentially related to SUDs. Melancholic MDEs appear to be associated with drug use disorders, but not alcohol use disorders. Specifically, Leventhal and colleagues (2008b) found that among young adults, melancholic major depression was associated with stimulant use disorders, but not with alcohol or cannabis use disorders. Among outpatients with major depression, melancholic depression was related to drug use disorders, but not alcohol use disorders (Leventhal et al., 2008c); similarly, Melartin and colleagues (2004) did not find significant associations between melancholic MDEs and alcohol abuse or dependence in a different sample of outpatients. In addition, in a community-based sample of females, melancholic depression was not related to alcohol dependence (Kendler, 1997). Psychomotor agitation may be associated with both alcohol dependence and substance dependence overall (Leventhal et al., 2008a); in another study, psychomotor agitation and related symptoms were associated with substance dependence as well (Balazs et al., 2006). One study reported that atypical depression was associated with

increased risk for drug dependence (Matza et al., 2003), though others failed to find an association between atypical depression and SUDs (Posternak and Zimmerman, 2002; Leventhal et al., 2008c).

The goal of this study was to examine the associations between different subtypes of MDEs and alcohol and drug abuse and dependence. Based on previous research defining subtypes of MDE, we examined the following subtypes: atypical, psychomotor agitation, psychomotor retardation, melancholic, and suicidal. We examined alcohol and illicit drug abuse and dependence separately, as well as combined “any alcohol diagnosis,” “any drug diagnosis,” “any abuse diagnosis,” and “any dependence diagnosis” variables. We also examined whether these associations differed by gender, as well as whether adjusting for a variety of demographic and clinical correlates affected the results.

Our primary focus was on lifetime diagnoses—disorders that may have occurred at any point in a participant’s life. We also conducted supplemental analyses using only past-12 month diagnoses, in order to examine these associations among episodes/disorders that occurred in close temporal proximity.

We also examined the order of onset of each MDE subtype and each SUD, among people with lifetime histories of both disorders. Although the ages of onset were reported retrospectively, we did so to allow for an exploration of whether certain MDE subtypes are uniquely likely to precede or follow certain SUDs.

We expected that psychomotor agitation would be associated with increased risk for SUDs. We did not expect that psychomotor retardation would be associated with increased risk for SUDs because psychomotor slowing would likely make it more difficult or effortful to obtain substances. We considered it possible that atypical depression would be associated with increased risk for SUDs, although this hypothesis was considered tentative based on the conflicting nature of previous evidence. Based on prior evidence, we did not expect melancholic MDEs to be associated with alcohol use disorders, though it was considered possible that they would be associated with drug use disorders. We expected that suicidal MDEs would be associated with increased risk for SUDs, due to the association between SUDs and suicide (Brent, 1995). Due to the absence of empirical or theoretical reasons to expect that there would be gender differences, we predicted that these associations would not differ for males and females.

2. Methods

2.1 Participants

Participants were drawn from the National Comorbidity Survey-Replication (NCS-R), a cross-sectional sample of adults assessed in 2001–2003. All participants ($n=1829$) who reported a lifetime MDE were included. The sample is representative of English-speaking adult (age 18+) household residents in the coterminous United States, and the response rate was adequate (70.9%). Informed consent was obtained, and the study was approved by the IRBs of Harvard Medical School and the University of Michigan.

The weighted percentages of participants completing the entire assessment (including part II, as these participants did) were: male=47%, female=53%; non-Hispanic white=73%, non-Hispanic black=12%, Hispanic=11%, other=4%; age 18–34=32%, age 35–49=31%, age 50–64=21%, age 65+=17%; education less than or equal to 12 years=49%, education at least 13 years=51%. Detailed information about the study design, sample, and assessment procedures can be found in other publications [(Kessler et al., 2004; Kessler and Ustun, 2004).

2.2 Measures

Diagnoses of MDEs and SUDs were based on an in-person survey that was administered by trained, supervised interviewers using computer-assisted personal interview (CAPI) methods. The diagnoses were based on a modified version of the Composite International Diagnostic Interview (CIDI; World Health Organization; Kessler et al., 1998). This instrument is fully-structured for the use of trained lay administrators and assesses a wide variety of DSM-IV diagnoses. Lifetime diagnoses were used for the primary analyses; in supplemental analyses, only diagnoses that occurred in the 12 months prior to the interview were used. Specific information about the assessment of each diagnosis and MDE subtype is provided below.

2.2.1 MDE subtypes—MDEs were assessed according to DSM-IV criteria. Participants who endorsed more than one lifetime episode were instructed to report on the worst lifetime episode. Participants were considered to have atypical depression if they had hypersomnia (sleeping a lot more than usual) and increased appetite or weight gain (without trying to, and not during a period of pregnancy or growth). Participants were considered to have an MDE characterized by psychomotor agitation if they endorsed feeling so restless or jittery that they paced up and down or couldn't sit still *and* indicated that someone else noticed that they were restless. Participants were considered to have a MDE characterized by psychomotor retardation if they endorsed talking or moving more slowly than is normal for them *and* indicated that someone else noticed that they were talking or moving more slowly than usual. Participants were considered to have melancholic depression if they endorsed anhedonia (loss of interest in almost all things or loss of the ability to take pleasure in having good things happen); decreased appetite or weight loss (without trying to); insomnia (a lot more trouble than usual falling asleep, staying asleep, or waking too early); guilt (feeling totally worthless or feelings of extreme guilt); and psychomotor change (agitation [so restless or jittery that they paced up and down or couldn't sit still *and* someone else noticed that they were restless] or retardation [talking or moving more slowly than is normal *and* someone else noticed that they were talking or moving more slowly]). Participants were considered to have suicidal depression if they reported that they had thought about committing suicide, made a suicide plan, or made a suicide attempt during their MDE. Some participants fell into more than one category—for example, a particular MDE could have been coded as both melancholic and suicidal.

2.2.2 Gender—As part of the interview, the respondent's gender was recorded.

2.2.3 Age—As part of the interview, the respondent's age was recorded.

2.2.4 MDE age of onset—When a participant reported experiencing a MDE, he or she reported at what age the first MDE occurred.

2.2.5 MDE severity—The severity of a MDE was determined based on a combination of two questions, each with 4-point response scales. One asked participants to rate the severity of their emotional distress and the other asked how often their emotional distress was so severe that they could not carry out their daily activities. Severity was then rated on a 1–4 scale based on the participant's highest rating (4=very severe distress or often could not carry out daily activities; 3=severe distress or sometimes could not carry out daily activities; 2=moderate distress or rarely could not carry out daily activities; 1=mild distress and never could not carry out daily activities). The mean severity score was 3.12 (SD=.61), and the median was 3.

2.2.6 Substance use disorders—Alcohol abuse, alcohol dependence, drug abuse, and drug dependence were assessed according to DSM-IV criteria. Hierarchies were not applied; therefore, a participant who met criteria for dependence on a substance was still diagnosed with abuse of that substance if he or she met criteria for it. All illicit drugs were combined into the drug use disorder diagnoses; information on specific drugs was not available.

2.2.7 SUD age of onset—When a participant reported experiencing a SUD, he or she reported at what age that SUD first occurred.

2.2.8 Psychiatric comorbidity—Lifetime diagnoses of generalized anxiety disorder, conduct disorder, and attention-deficit disorder were assessed according to DSM-IV criteria.

2.2.9 Order of onset—When a participant reported experiencing both an MDE and a SUD, the ages of onset were examined and their age of onset pattern was categorized as “MDE before SUD,” “MDE concurrent with SUD” (the two disorders occurred first during the same year), or “MDE after SUD.”

2.3 Statistical Analyses

To address our primary hypotheses, we conducted logistic regression analyses. Sample weights were applied to adjust for differential nonresponse, residual differences between the sample and the population, and differential probabilities of selection of respondents within households, as appropriate with the NCS-R data (Alegrai et al., 2001–2003). Participant gender was entered into all analyses in order to adjust for gender differences in the rates of the disorders. For the first set of analyses, alcohol abuse was our dependent variable, with atypical MDE subtype and gender as the independent variables. We then repeated this analysis four times, substituting the other subtypes of depressive episodes (agitated, retarded, melancholic, and suicidal) for the atypical subtype in each subsequent analysis. We then repeated this set of analyses seven times, using the following dependent variables: alcohol dependence, drug abuse, drug dependence, any alcohol use disorder, any drug use disorder, any substance abuse diagnosis, and any substance dependence diagnosis.

Although some participants experienced MDEs that were characterized by two subtypes as defined in this study (e.g., melancholic and suicidal; all logically possible combinations of subtypes occurred at least occasionally), these analyses represented comparisons between participants with each MDE subtype and all other participants (all of whom had lifetime MDEs). Therefore, the results represent the increase in risk for the SUD that is associated with each MDE subtype, above and beyond the general association between MDEs and SUDs and ignoring any other subtype categorization that a given participant may have fallen into. When two different subtypes were both significantly associated with a certain SUD, we conducted follow-up analyses entering both subtypes into the model in order to examine whether one of the subtypes was carrying the weight of the association.

In order to examine whether these patterns differed for males and females, we repeated all analyses including an MDE subtype-by-gender interaction term. To ensure that our results were not accounted for by various demographic and clinical correlates, we then repeated all analyses adjusting for a series of factors: (1) age, (2) age of onset of first MDE, (3) severity of MDE, and (4) psychiatric comorbidity (generalized anxiety disorder, conduct disorder, and attention-deficit disorder).

Next, in order to examine whether MDE subtypes and SUDs that occur in close temporal proximity to each other exhibit similar patterns of association, we re-ran all analyses examining only diagnoses that occurred in the 12 months prior to the interview.

Finally, for those participants reporting both a particular MDE subtype and a particular SUD, we examined the pattern of onset using chi-square analyses comparing the proportion of participants with that MDE subtype who had an MDE onset prior to SUD onset, compared to the proportion of participants without that MDE subtype who had an MDE onset prior to SUD onset.

3. Results

Frequencies of each type of MDE and each SUD, by sex, are presented in Table 1 (along with the results of chi-square analyses indicating the significance of differences between males and females in the rates of each subtype/disorder). Agitated MDEs were more common among males, while retarded MDEs were more common among females. All types of SUDs were more common among males.

3.1 Associations between MDE subtypes and SUDs

Results of the logistic regression analyses examining lifetime diagnoses are presented in Table 2 (presented as odds ratios, along with significance levels from chi-square tests). These results indicated that: (1) MDEs characterized by psychomotor agitation were associated with increased risk for alcohol dependence; (2) melancholic MDEs were positively associated with alcohol abuse, any alcohol diagnosis, and any substance abuse diagnosis; and (3) suicidal MDEs were associated with increased risk for all SUD diagnoses.

Logistic regressions including a sex-by-MDE subtype interaction term (as well as main effects of sex and MDE type) were conducted, and none of the interaction terms was significant (all p -values $>.05$). Therefore, these associations did not vary significantly by gender.

For four of the SUDs, two different MDE subtypes were associated with the SUD (specifically, both melancholic and suicidal MDEs predicted alcohol abuse, any alcohol diagnosis, and any substance abuse diagnosis, and both agitated and suicidal MDEs predicted alcohol dependence). These MDE subtypes tended to be associated with each other (melancholic and suicidal: $\chi^2=31.6$, $df=1$, $p<.0001$; agitated and suicidal: $\chi^2=3.5$, $df=1$, $p=.06$). In order to examine whether the effects of each subtype were unique or whether the weight was disproportionately carried by the influence of one subtype, follow-up logistic regression analyses were conducted entering both subtypes into the equation (along with the main effect of sex). In three of the four instances (melancholic and suicidal MDEs predicting alcohol abuse and any alcohol diagnosis, and agitated and suicidal MDEs predicting alcohol dependence), both subtypes remained significant predictors of the SUD at the $p<.05$ level, indicating that each subtype predicted the SUD, net the effect of the other subtype. When melancholic and suicidal MDEs were both entered into the equation predicting any substance abuse, the effect of melancholic MDEs dropped to non-significance ($OR=1.28$, $CI=.93-1.77$, $p=.12$), indicating that in this case, the effect of suicidal MDEs was somewhat stronger.

3.2 Adjusting for Correlates

3.2.1 Age—It was considered possible that associations between MDE subtypes and SUDs could vary by age, perhaps because of differing MDE symptoms being more common among people of different ages, or because of cohort differences. There were significant negative correlations between age and atypical ($r=-.06$) and suicidal ($r=-.10$) MDEs, indicating that younger people were more likely to experience atypical and suicidal MDEs. When analyses were repeated adjusting for age, only one small difference in the pattern of results was found: the association between “any substance abuse” and melancholic MDEs

was non-significant. Therefore, age differences among participants do not account for these findings.

3.2.2 MDE Age of Onset—It was considered possible that an earlier age of onset of the first MDE could be associated with both MDE subtype and risk for SUDs, and therefore could account for these findings. MDE age of onset was negatively associated with atypical ($r=-.05$) and suicidal ($r=-.16$) MDEs, indicating that a later age of onset tended to be associated with increased risk for the atypical and suicidal subtypes. When age of onset was adjusted for, however, only one difference in the pattern of significant results emerged: the association between “any substance abuse” and melancholic MDEs was reduced to non-significance.

3.2.3 MDE severity—In order to assess whether having a certain MDE subtype was associated with higher or lower levels of severity relative to other subtypes, point-biserial correlations between severity and each subtype were computed. All were significant ($p<.05$), with agitated ($r=.06$), retarded ($r=.14$), melancholic ($r=.19$), and suicidal ($r=.24$) being in the positive direction, indicating that these subtypes tended to be more severe than other MDEs. In contrast, the atypical subtype was negatively correlated with severity ($r=-.09$), indicating that it tended to be somewhat less severe than other MDEs. We repeated all analyses adjusting for severity, and the pattern of associations remained nearly identical. There were two changes: (1) the association between agitated MDEs and alcohol dependence was reduced to a trend level ($p<.10$), and (2) the association between “any substance abuse” and melancholic MDEs was non-significant.

3.2.4 Psychiatric comorbidity—It was considered possible that psychiatric comorbidity could have accounted for the associations between MDE subtypes and risk for SUDs that we found. Although a comprehensive examination of this possibility was beyond the scope of this project, we conducted the primary analyses adjusting for the presence of generalized anxiety disorder (which was associated with melancholic and suicidal MDEs, $r=.05$ and $r=.09$, respectively), conduct disorder (which was associated with agitated and suicidal MDEs, $r=.08$ and $r=.12$, respectively), and attention-deficit disorder (which was associated with suicidal MDEs, $r=.11$), because these disorders are commonly associated with MDEs and with SUDs. The pattern of significant results remained largely the same. The only differences were: (1) when adjusting for generalized anxiety disorder, the association between “any substance abuse” and melancholic MDEs was non-significant; (2) when adjusting for conduct disorder, the association between “any substance abuse” and melancholic MDEs was non-significant and the association between alcohol dependence and agitated MDEs was non-significant; and (3) when adjusting for ADHD, the association between “any substance abuse” and melancholic MDEs was non-significant. Therefore, the presence of comorbid generalized anxiety disorder, conduct disorder, and attention-deficit disorder do not generally account for these findings.

3.3 Past year diagnoses

We also examined whether MDE subtypes and SUDs that occurred in close temporal proximity to each other exhibited similar patterns of association (compared to lifetime associations). Therefore, we re-ran all analyses examining only diagnoses that occurred in the 12 months prior to the interview. Because these analyses included less than half of the sample ($n=805$), the statistical power was lower. The results were substantially the same (Table 3). The main difference was that there were stronger associations between agitated MDEs and SUDs: specifically, drug abuse, drug dependence, any drug use disorder, and any substance dependence were also associated with agitated MDEs ($p<.05$; alcohol dependence also remained significant, as in the lifetime analyses). Two other small differences were

found: (1) psychomotor retardation was negatively associated with alcohol dependence ($p < .05$), and (2) the associations between melancholic MDEs and SUDs were no longer significant, but were in the same direction and largely of similar magnitude as the lifetime analyses.

3.4 Order of Onset

Table 4 presents percentages of participants who reported the onset of their first MDE at an earlier age than, at the same age than, and at a later age than the onset of each SUD. Significance levels indicated in the “MDE before SUD” column are derived from chi-square analyses that compare the proportion of participants with that MDE subtype who had an MDE onset prior to SUD onset, compared to the proportion of participants without that MDE subtypes who had an MDE onset prior to SUD onset. These analyses should be considered exploratory due to the low prevalence of co-occurrence in some particular cases. Overall, participants more commonly reported an MDE onset prior to the SUD onset. The only differences by MDE subtype were with suicidal MDEs, which tended to have their onset prior to SUDs (except drug abuse), more than other MDE subtypes did. It is important to remember that these are lifetime diagnoses and participants reported on their worst MDE episode; therefore, this result should be interpreted as indicating that participants who had a suicidal MDE at some point in their lives were more likely than other participants to have had their first MDE prior to developing a SUD.

4. Discussion

The results of this study indicate that different subtypes of MDEs were associated with differing lifetime risk for SUDs. Specifically, (1) MDEs characterized by psychomotor agitation were associated with increased risk for alcohol dependence; (2) melancholic MDEs were positively associated with alcohol abuse, any alcohol diagnosis, and any substance abuse diagnosis; and (3) suicidal MDEs were associated with increased risk for all SUD diagnoses. When past-year diagnoses only were examined, the pattern of results remained similar, though MDEs characterized by psychomotor agitation were associated with a broader range of SUDs. These significant associations are striking because the increased risk associated with certain MDE symptom constellations was relative to other people who also have MDEs—not relative to people without MDEs.

These results did not vary substantially by gender, and adjusting for the age of the participant, the severity of the MDE, the age of onset of the MDE, and psychiatric comorbidity (conduct disorder, generalized anxiety disorder, and attention-deficit disorder) did not change the results substantially. This indicates that these results were not due to these demographic or clinical correlates of these disorders.

The finding that suicidal MDEs were particularly associated with increased risk for lifetime SUDs is not surprising, given that SUDs are associated with suicidal behavior (Brent, 1995). This study indicates that people who have had a suicidal MDE are particularly likely to experience a SUD during their lifetime.

MDEs with melancholic features tended to be associated with increased risk for alcohol use disorders (particularly abuse). Similarly, psychomotor agitation was associated with alcohol dependence. Perhaps people with these symptom constellations are particularly likely to use alcohol, a depressant, in an effort to self-medicate their “keyed-up” feelings (insomnia, psychomotor agitation). The concurrent link between psychomotor agitation and SUDs was particularly striking: analyses of past-year diagnoses indicated that psychomotor agitation was associated with a broad range of SUDs. It is possible, however, that heavy substance—use and/or the effects of withdrawal—may cause these symptoms. Either way, clinicians

should be aware that people whose MDEs involve melancholic features and/or psychomotor agitation may be at particular risk for maladaptive substance use.

Retrospective reports of order of onset indicated that although overall, more people tended to report an onset of MDE prior to SUD, there were minimal subtype differences in this pattern. The main exception to this was that participants who had a suicidal MDE at some point in their lives were more likely than other participants to have had their first MDE prior to developing a SUD (except drug abuse). This is consistent with the possibility that early-onset MDEs tend to predict a more severe course of disorder (perhaps involving suicidal ideation and/or behavior), though evidence indicates that the presence of major depression may not worsen the course of drug use disorders (Darke et al., 2009). In addition, inspection of the percentages indicates that people with atypical MDEs were relatively unlikely to experience their MDE onset prior to the onset of alcohol use disorders; although the chi-square analysis was non-significant, more research into this possibility would be interesting.

Post-hoc exploratory analyses examining different subtypes of MDEs together (when more than one subtype was associated with a particular SUD) indicated that the effects of each MDE subtype tended to be unique. This evidence argues against the possibility that, for example, melancholic MDEs appear to be associated with SUDs only because they are sometimes characterized by suicidality as well.

These findings are somewhat consistent with the existing literature on links between MDE subtypes and SUDs. Like Leventhal and colleagues (2008a), we found that psychomotor agitation was associated with alcohol dependence. When only past-year diagnoses were considered, we found an association between psychomotor agitation and drug use disorders, similar to Baslasz and colleagues (2006). Like other studies, we did not find a significant association between atypical depression and SUDs (Posternak and Zimmerman, 2002; Leventhal et al., 2008c). However, other studies found that melancholic depression was not associated with alcohol use disorders (Kendler, 1997; Melartin et al., 2004; Leventhal et al., 2008b and 2008c), whereas we found a significant link between these disorders. This discrepancy may be because these other studies examined young adults only (Leventhal et al., 2008b), clinical samples (Melartin et al., 2004; Leventhal et al., 2008c), or only alcohol dependence (Kendler, 1997). In contrast, our sample was community-based and included a range of ages; in addition, we found stronger associations for alcohol abuse than for alcohol dependence. This difference could also be due to the slightly different definitions of melancholic MDEs used. Future research into the links between melancholic MDEs and alcohol use disorders are needed to help clarify for whom these disorders are associated.

This study has limitations. We did not have information on which drugs participants may have abused or been dependent on; the associations between MDE subtypes and drug use disorders may differ by type of drug. Information about MDEs due to physical causes or bereavement was not available; therefore, some of the MDEs reported may have been related to these factors. Some of the MDEs occurred as part of lifetime major depressive disorders, while others occurred as part of bipolar disorder (11.6% of this sample reported experiencing a manic episode at some point in their lives). In particular, some of the MDE subtypes used in this study may overlap with subthreshold bipolar episodes, which appear to be related to SUDs (Merikangas et al., 2008; for example, it is possible that some instances of MDE with psychomotor agitation in this study were actually subthreshold bipolar or mixed mood episodes). Due to sample size limitations and limitations in the subtleties of the assessment, we did not distinguish between different lifetime mood episode patterns. Future research examining related questions among people with different lifetime mood episode patterns would be useful. Finally, the NCS-R employed skip patterns that only assessed

substance dependence when abuse was present; this may have resulted in an underestimate of the rate of substance dependence in this sample.

It is important to note that our definitions of melancholic and atypical MDEs differed somewhat from those in the DSM, due to the information that was available. Specifically, for melancholic MDEs, the anhedonia reported by participants in this study may not have been “pervasive” as required by the DSM definition of melancholia; mood reactivity was not included in our definition; there was no assessment of a “distinct quality of depressed mood”; depression may not have been worse in the morning; the insomnia might not have been early morning awakening; and the psychomotor change may not have been “marked.” Because of these somewhat looser definitions for each symptom, we required anhedonia, insomnia, guilt, psychomotor change, *and* appetite decrease/weight loss, even though the DSM requires fewer symptoms. For the atypical subtype, mood reactivity was not assessed (note, however, that some research has shown that mood reactivity is not related to other symptoms of atypical MDEs and may not be an appropriate symptom for this subtype; Posternak and Zimmerman, 2002) and this study did not assess leaden paralysis or impairing rejection sensitivity, so we required appetite increase/weight gain and hypersomnia. Therefore, although we used reasonable approximations of these DSM subtypes, it is possible that participants categorized as having a melancholic or atypical MDE in the current study may not have met DSM criteria for those subtypes, or the reverse. This could explain differences between these results and the results of other studies.

As noted in the Methods section, we used the symptoms experienced during the most severe lifetime MDE to categorize MDE subtype. However, participants may have experienced additional episode(s) with other symptom constellations. Because all of the subtypes examined except for atypical MDEs were positively associated with severity, this may have minimized the apparent associations between atypical and “uncategorized” (not assigned to any subtype in this study) MDEs and SUDs. Future research more closely examining symptoms experienced during each lifetime MDE, and each episode’s temporal relation with SUD onset and symptom exacerbations and decreases, would be useful in furthering our understanding these associations.

Overall, these results indicate that the particular pattern of symptoms within an MDE is an important correlate of risk for SUDs. Clinicians should be aware of the strong links between melancholic MDEs and alcohol use disorders, between MDEs characterized by psychomotor agitation and alcohol dependence (as well as possibly other SUDs), and between suicidal MDEs and all SUDs. The presence of these particular symptom combinations in a patient with an MDE should trigger a thorough assessment of past and current SUDs. In addition, assessment of current substance use patterns among these patients may provide useful information for helping to prevent current use from progressing into clinically-significant SUDs.

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University Dresden and Max Planck Institute of Psychiatry). A complete list of NCS publications and the full text of all NCS-R instruments can be found at <http://www.hcp.med.harvard.edu/ncs>.

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Table 1

Lifetime prevalence of subtypes of major depressive episodes and substance use disorder diagnoses, by sex

	N ^a	Males	Females	Chi-square ^b
Subtypes of Major Depressive Episodes:				
Atypical	44	2.9%	4.5%	2.56
Agitated	115	14.6%	9.3%	11.48***
Retarded	458	35.8%	45.5%	15.85***
Melancholic	264	22.0%	25.3%	.12
Suicidal	176	15.4%	15.8%	.06
Substance Use Disorder Diagnoses:				
Alcohol abuse	275	37.4%	15.8%	107.27***
Alcohol dependence	139	18.3%	8.2%	41.07***
Drug abuse	188	25.6%	11.1%	64.53***
Drug dependence	91	10.7%	5.6%	15.58***
Any alcohol abuse or dependence	275	39.6%	16.6%	71.87***
Any drug abuse or dependence	189	27.6%	11.2%	47.97***
Any abuse	301	42.1%	18.9%	68.91***
Any dependence	168	23.8%	10.4%	35.34***

p<.001

^aTotal number of participants with this diagnosis/subtype. Because analyses were weighted, estimated frequencies were rounded to the nearest whole number.

^bChi-square values derived from analyses comparing the percentages of males and females with and without each major depressive episode subtype and each substance use disorder (N=1829).

Odds ratios (95% confidence intervals) representing risk for lifetime substance use disorders associated with different types of lifetime major depressive episodes^a

Table 2

	Major Depressive Episode Subtype				
	Atypical	Agitated	Retarded	Melancholic	Suicidal
Alcohol Abuse	1.15 (.56–2.33)	1.31 (.85–2.02)	.92 (.69–1.23)	1.52** (.10–2.09)	1.96*** (1.37–2.81)
Alcohol Dependence	.61 (.20–1.86)	1.71* (1.04–2.83)	.76 (.52–1.11)	1.35 (.90–2.03)	2.67*** (1.75–4.05)
Drug Abuse	1.73 (.84–3.59)	1.19 (.73–1.94)	.89 (.64–1.23)	.91 (.62–1.34)	2.33*** (1.60–3.43)
Drug Dependence	1.42 (.53–3.82)	1.53 (.84–2.79)	.88 (.56–1.38)	1.04 (.63–1.73)	2.65*** (1.63–4.31)
Any Alcohol	1.15 (.56–2.33)	1.31 (.85–2.02)	.92 (.69–1.23)	1.52** (.10–2.09)	1.96** (1.37–2.81)
Any Drug	1.73 (.83–3.57)	1.19 (.73–1.93)	.88 (.63–1.23)	.91 (.62–1.33)	2.32*** (1.57–3.41)
Any Abuse	1.19 (.60–2.35)	1.24 (.81–1.89)	.94 (.71–1.25)	1.37* (1.00–1.87)	1.90*** (1.34–2.71)
Any Dependence	1.05 (.45–2.46)	1.50 [§] (.92–2.42)	.84 (.60–1.19)	1.19 (.81–1.74)	2.50*** (1.66–3.67)

[§] p<.10;

* p<.05;

** p<.01;

*** p<.001

^a All odds ratios are adjusted for main effects of gender (N=1829).

Table 3

Odds ratios (95% confidence intervals) representing risk for past-12-month substance use disorders associated with different types of past-12-month major depressive episodes^a

	Atypical	Major Depressive Episode Subtype			
		Agitated	Retarded	Melancholic	Suicidal
Alcohol Abuse	.42 (.02–8.32)	1.32 (.50–3.49)	.67 (.33–1.38)	1.12 (.53–2.38)	2.41* (1.67–4.97)
Alcohol Dependence	--	3.00* (1.19–7.60)	.39* (.15–.98)	1.12 (.47–2.68)	3.47*** (1.54–7.79)
Drug Abuse	2.12 (.25–18.13)	3.01* (1.09–8.31)	.75 (.29–1.92)	.85 (.30–2.40)	2.85* (1.13–7.19)
Drug Dependence	1.65 (.09–30.39)	6.31*** (1.84–21.64)	.65 (.19–2.28)	.94 (.25–3.58)	5.23*** (1.59–17.22)
Any Alcohol	.37 (.02–7.24)	1.83 (.78–4.30)	.63 (.32–1.25)	1.47 (.74–2.91)	2.46*** (1.24–4.88)
Any Drug	1.92 (.23–16.18)	3.44*** (1.30–9.13)	.68 (.27–1.71)	.78 (.28–2.19)	2.59* (1.05–6.40)
Any Abuse	1.20 (.20–7.05)	1.33 (.55–3.18)	.76 (.40–1.45)	1.07 (.54–2.13)	2.09* (1.07–4.09)
Any Dependence	.56 (.03–9.89)	3.30*** (1.39–7.82)	.38* (.16–.90)	.97 (.42–2.23)	3.23*** (1.51–6.90)

* p<.05;

** p<.01

^a All odds ratios are adjusted for main effects of gender (N=805).

Table 4

Order of onset of major depressive episode subtypes and substance use disorders, among participants with both disorders^a

MDE Subtype	SUD	Percentages of Participants With:		
		MDE first	Concurrent	SUD first
Atypical	Alcohol abuse	35.1	6.5	58.4
	Alcohol dependence	16.2	49.5	34.3
	Drug abuse	44.6	12.8	42.6
	Drug dependence	68.9	0.0	31.1
Agitated	Alcohol abuse	54.1	18.2	27.7
	Alcohol dependence	57.2	19.3	23.5
	Drug abuse	54.9	6.1	39.0
	Drug dependence	59.1	6.0	34.9
Retarded	Alcohol abuse	58.8	6.2	35.0
	Alcohol dependence	74.1 [§]	9.8	16.1
	Drug abuse	55.0	7.5	37.5
	Drug dependence	69.8	2.4	27.8
Melancholic	Alcohol abuse	57.3	7.6	35.1
	Alcohol dependence	68.1	15.7	16.2
	Drug abuse	56.0	5.9	38.1
	Drug dependence	69.6	2.2	28.2
Suicidal	Alcohol abuse	65.7 [*]	15.2	19.1
	Alcohol dependence	78.9 [*]	17.5	3.6
	Drug abuse	59.4	15.3	25.3
	Drug dependence	81.6 [*]	6.2	12.2

[§] p<.10;

^{*} p<.05;

MDE=major depressive episode; SUD=substance use disorder.

^a Significance tests derived from chi-square tests comparing the proportion of people with the indicated MDE subtype who experienced MDE prior to that SUD, compared to the proportion of people with other MDE subtypes who experienced MDE prior to that SUD.