Prospective Relations Between Melancholia and Substance Use Disorders

Adam M. Leventhal, Ph.D.,1 Peter M. Lewinsohn, Ph.D.,2 and Jeremy W. Pettit, Ph.D.3

1Center for Alcohol and Addiction Studies, Brown University, Providence, Rhode Island, USA
2Oregon Research Institute, Eugene, Oregon, USA
3Department of Psychology, University of Houston, Houston, Texas, USA

Abstract: Examining associations between subtypes of major depressive disorder (MDD) and substance use disorders (SUDs) might elucidate mechanisms of comorbidity between MDD and SUDs. This study evaluated prospective relations between SUDs and melancholic MDD. A cohort of community-dwelling participants with lifetime history of MDD (N = 460) were assessed for DSM-IV mental disorders using structured clinical interviews at ages 24 and 30. Stimulant use disorders and melancholic MDD were prospective risk factors for each other over the 6-year-period following the age-24 assessment. Associations were robust when controlling for clinical severity/chronicity. Alcohol and cannabis use disorders were not robustly associated with melancholia.

Keywords: Major depressive disorder, melancholic depression, nonmelancholic depression, substance use disorders, stimulant use disorders

INTRODUCTION

Major depressive disorder (MDD) and substance use disorders (SUDs) are highly overlapping and are prospective risk factors for each other (1). One potential barrier to understanding this relationship is MDD’s heterogeneity. Accordingly, several studies have examined the relationship between SUDs and different subtypes of MDD (2–4). This research approach may elucidate potential mechanisms of MDD–SUD comorbidity and shed light on the risk profiles of dual-diagnosis individuals.

The melancholic subtype of MDD (5), which is characterized by pervasive anhedonia and neurovegetative features, is associated with drug use disorders...
but not alcohol use disorders (2–4). These findings are interesting because both melancholic MDD and drug addiction are thought to be underpinned by dysregulation of the mesocorticolimbic dopamine and hypothalamic-pituitary-adrenal axis pathways (6, 7). Because previous data has examined relations between melancholia and the general category of drug use disorders (3), it remains unclear which classes of drug use disorders are most strongly associated with melancholia. Also, because previous data has primarily been cross-sectional (2–4), it is uncertain whether one (or both) of these disorders prospectively increases the risk of onset of the other disorder over extended periods of time.

The present report examined prospective associations between specific classes of SUDs (i.e., alcohol, cannabis, and stimulant use disorders) and melancholic vs. nonmelancholic MDD in unipolar depressed young adults participating in a longitudinal study. Given that the onset of MDD and SUDs are especially common young adulthood (8), we assessed whether history of one disorder at age 24 predicted risk of developing the other disorder over the subsequent 6-year period. We examined both the effects of melancholia on SUDs as well as the effects of SUDs on melancholia. To evaluate the possibility that chronicity, severity, comorbidity, and demographic characteristics might explain any associations, we conducted additional analyses that controlled for the effect of these variables. Given that cross-sectional associations between melancholia and SUDs in adult samples have been found for illicit drug use disorders but not alcohol use disorders (2–4), we expected that prospective relations in the current youth sample would be stronger for cannabis and stimulants than alcohol.

METHOD

Sample

The sample in the current report was drawn from the Oregon Adolescent Depression Project, a large, prospective, epidemiological study of psychiatric disorders that followed individuals from the general community through adolescence to early adulthood. The study’s procedures were approved by the Oregon Research Institute Human Subjects Committee. To date, this study has completed four waves of psychiatric assessment at mean ages of 16, 17, 24, and 30, with the first two being conducted in person and the last two over the phone. The procedures have been described in detail elsewhere (9). Briefly, 1,709 participants were randomly selected from nine senior high schools representative of urban and rural districts in western Oregon. All participants with history of psychopathology and a subset of those with no lifetime psychopathology at the second assessment were invited to participate in the third (T3) and fourth (T4) assessments [mean age: 24.6 ($SD = .61$) and 30.1 ($SD = .71$)]. The 816 T4
participants included 484 (59%) women and were mostly Caucasian (89%). Most participants were married (56%) or cohabitating (9%), with 25% never married and 10% separated or divorced. At the time of the T4 evaluation, 43% of the sample had received a bachelor’s degree or higher and 83% were employed.

The current report included individuals who participated for all four waves of assessment and met lifetime diagnostic criteria for unipolar MDD by T4 \((N = 460)\). To reduce the number of comparisons performed (and probability of a type-I error), we combined substance abuse and dependence into an abuse/dependence category. As in Miles et al. (10), we used a stimulant abuse/dependence category to classify individuals who abused amphetamine, cocaine, or both substances to increase the rate of positive cases. Substance-induced mood disorders \((n = 7)\) and SUDs with low lifetime prevalence rates \(<1\%) and infrequent instances of disorder onset in the T3–T4 period \((n < 3)\) were excluded. For the remaining SUDs (alcohol, stimulant, and cannabis), lifetime SUD status (present vs. absent) at the T3 assessment and the T4 assessment was classified (Table 1).

**DSM-IV** criteria were applied to identify participants with depressive episodes that met the “with melancholic features” specifier. For both T3 and T4 assessments, participants with a lifetime history of at least one melancholic episode were classified as “melancholic,” and those with a history of MDD but no melancholic episodes were classified as “nonmelancholic” (Table 1). The **DSM-IV** melancholia criterion “distinct quality of mood” was not available for the T1 and T2 assessments.

**Diagnostic Assessment**

At T1, participants were interviewed with a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children that combined features of the Epidemiological Version (11) and the Present Episode Version. At T2, T3, and T4, participants were interviewed using the Longitudinal Interval Follow-up Evaluation (12), which elicited detailed information about the course of psychiatric symptoms since the previous evaluation. Diagnoses were made using **DSM-IV** criteria (5). Diagnostic information was available regarding the occurrence, onset age, duration, and individual symptoms of disorders prior to and during the course of the study. In addition to diagnostic interviews, the Hamilton Depression Rating Scale (HRSD) (13) was completed at each assessment as a measure of severity of depressive episodes experienced prior to and during each assessment. Information was also obtained at each assessment on smoking status (i.e., whether or not participants had ever engaged in daily smoking) (14). Reliability of MDD diagnoses and melancholic symptoms were adequate; see Lewinsohn et al., (9) for a more detailed description of interviewing procedures and reliability estimates.
Table 1. T3 and T4 lifetime prevalence of MDD subtypes and SUDs

<table>
<thead>
<tr>
<th>SUD</th>
<th>T3 Diagnostic Status</th>
<th></th>
<th>T4 Diagnostic Status</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Melancholic (n = 119)</td>
<td>Nonmelancholic (n = 280)</td>
<td>Melancholic (n = 181)</td>
<td>Nonmelancholic (n = 279)</td>
</tr>
<tr>
<td>Alcohol Abuse/Dependence,</td>
<td>47 (39.5%)</td>
<td>93 (33.2%)</td>
<td>80 (44.2%)</td>
<td>105 (37.6%)</td>
</tr>
<tr>
<td>$N(%)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulant Abuse/Dependence</td>
<td>21 (17.6%)</td>
<td>29 (10.4%)</td>
<td>35 (19.3%)</td>
<td>30 (10.8%)</td>
</tr>
<tr>
<td>$N(%)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis Abuse/Dependence,</td>
<td>34 (28.6%)</td>
<td>55 (19.6%)</td>
<td>54 (29.8%)</td>
<td>52 (18.6%)</td>
</tr>
<tr>
<td>$N(%)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SUD percentages are within MDD subtype groupings. Onset of melancholia during the T3–T4 period occurred for 66 participants. Some cases of new-onset melancholia occurred in individuals who had a history of nonmelancholic MDD at T3 and subsequently “crossed over” and had a melancholic episode in the T3–T4 period ($n = 44$). The other cases included individuals who had an onset of MDD during the T3–T4 period and at least one of the depressive episodes during that period was melancholic ($n = 22$). Some individuals had multiple SUDs (e.g., both alcohol and cannabis abuse/dependence). SUD = Substance Use Disorder; MDD = Major Depressive Disorder; T3 = Assessment at Time 3 (age 24); T4 = Assessment at Time 4 (age 30).
Statistical Analyses

Analyses modeled the degree to which lifetime history of one disorder at the T3 assessment predicted onset of the other disorder during the T3–T4 interval. To test the effects of melancholia on SUDs, logistic regression models that examined the probability of SUD onset between T3 and T4 (expressed as an Odds Ratio [OR] with 95% Confidence Interval) by predicting T4 SUD status from T3 melancholic status while controlling for T3 SUD diagnostic status were conducted. This analysis was repeated while including relevant demographic (age and gender), psychiatric (T3 lifetime histories of anxiety disorders, disruptive behavior disorders, and cigarette smoking), and MDD characteristics (T3 age of first onset MDD, number of previous MDD episodes, total duration of previous MDD episodes, and HRSD-rated severity of the worst episode MDD). Separate models were run for presence vs. absence of each class of SUD at T3 and analyses included only subjects with a T3 lifetime history of MDD (n = 399).

To test the effects of SUDs on melancholia, logistic regression models that examined the probability of melancholic episodes between T3 and T4 by predicting T4 melancholic status from T3 SUD status while controlling for T3 lifetime history of MDD (MDD vs. no MDD) and T3 melancholic status. These models were run with and without including T4 covariates (demographic, psychiatric, and MDD characteristics) and were restricted to subjects with a T4 lifetime history of MDD (n = 460).

It should be noted that in models predicting T4 melancholic status from T3 SUDs, some cases of new-onset melancholia occurred in individuals who had a history of nonmelancholic MDD at T3 and subsequently “crossed over” and had a melancholic episode in the T3–T4 period (n = 44). The other cases included individuals who had an onset of MDD during the T3–T4 period and at least one of the depressive episodes during that period was melancholic (n = 22).

SPSS 10.0 for Windows was used for data analysis. All tests were two-tailed and significance was defined at the .05 level.

RESULTS

The lifetime prevalence of MDD and SUD subtypes at T3 and T4 are displayed in Table 1.

Effects of Melancholia on SUDs

The influence of T3 melancholia on onset of SUDs is displayed in the left portion of Table 2. There was no effect of melancholia on alcohol abuse/
<table>
<thead>
<tr>
<th>SUD</th>
<th>Effects of T3 Melancholic Status on T4 SUDs&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Effects of T3 SUDs on T4 Melancholic Status&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alcohol Abuse/Dependence</td>
<td>1.39 (.91–2.15)</td>
<td>1.56 (.58–4.22)</td>
</tr>
<tr>
<td>Stimulant Abuse/Dependence</td>
<td>2.20** (1.25–3.85)</td>
<td>4.46* (1.07–18.59)</td>
</tr>
<tr>
<td>Cannabis Abuse/Dependence</td>
<td>1.83* (1.13–2.95)</td>
<td>3.65 (.78–17.04)</td>
</tr>
</tbody>
</table>

All results presented as Odds Ratios with 95% Confidence Intervals. SUD = Substance Use Disorder; MDD = Major Depressive Disorder; T3 = Assessment at Time 3 (age 24); T4 = Assessment at Time 4 (age 30).

<sup>a</sup> Analyses include only individuals with a history of MDD by T3 (N = 399) and control for respective T3 SUDs (alcohol, cannabis, stimulant) in order to model SUD onset between the T3 to T4 period.

<sup>b</sup> Models additionally adjusted for age, gender, T3 lifetime histories of Anxiety Disorders, Disruptive Behavior Disorders, and cigarette smoking, age of first onset MDD, and number of previous MDD episodes, total duration of previous MDD episodes, and severity of worst MDD episode by T3.

<sup>c</sup> Analyses include only individuals with a history of MDD by T4 (N = 460) and control for T3 lifetime history of MDD and T3 Melancholic Status in order to model melancholia onset between the T3 to T4 period.

<sup>d</sup> Models additionally adjusted for age, gender, T4 lifetime histories of Anxiety Disorders, Disruptive Behavior Disorders, and cigarette smoking, age of first onset MDD, and number of previous MDD episodes, total duration of previous MDD episodes, and severity of worst MDD episode by T4.

** p < .001; * p < .05.
Melancholia and Substance Use 265

dependence. Lifetime melancholic status at T3 predicted onset of stimulant use disorders by T4 (with and without controlling for demographic, psychiatric, and MDD characteristics). There was also an effect of T3 melancholic status on T4 cannabis use disorders. However, this effect fell below significance when demographic covariates were included in the model.

Effects of SUDs on Melancholia

The influence of T3 SUDs on onset of melancholia is displayed in the right portion of Table 2. Alcohol abuse/dependence had no effect. T3 history of stimulant use disorders predicted onset of melancholic MDD by T4 (with and without controlling for demographic, psychiatric, and MDD characteristics). Participants with T3 histories of cannabis use disorders showed a significant increase in risk for melancholic MDD by T4 that was eliminated after controlling for covariates.

Supplemental Analyses

To examine whether there were differential effects for amphetamine and cocaine use disorders within the stimulant abuse/dependence category, we conducted additional analyses of amphetamine and cocaine use disorders separately. These results were similar to findings with the combined category (ORs > 4.52), although sample sizes for cocaine use disorders were small and led to nonsignificant effects for these models.

To account for the fact that some participants were positive for multiple SUDs (e.g., stimulant and cannabis use disorders), we recalculated each analysis while including total number of substance abuse/dependence disorders in logistic regression models as a covariate. The results of these analyses did not substantially change any of the findings (more detailed results available upon request).

DISCUSSION

The aim of this study was to examine whether melancholia and SUDs increased risk for one another during a 6-year period of development in young adulthood. We found that melancholia and stimulant use disorders were prospective risk factors for each other, even when accounting for the effects of demographic factors, psychiatric comorbidity, and features of previous MDD. Melancholic MDD also showed increased prospective risk for cannabis use disorders. However, this effect dropped below significance after explanatory variables were
included in the model, suggesting that the effects were nonspecific. There was no association between melancholia and alcohol use disorders.

These findings are generally consistent with previous investigations of melancholia-SUD associations in samples of adults (2–4) and extend these results to young adult populations. These data also extend previous research by examining whether relations between melancholia and SUDs are persistent over time (i.e., whether they evidence prospective associations). The bi-directional prospective associations between stimulant use disorders and melancholia are consistent with literature suggesting that chronic stimulant exposure might dysregulate mesocorticolimbic dopamine and hypothalamic-pituitary-adrenal axis pathways, which could in turn provoke expression of melancholic symptoms (6, 7). They are also consistent with data showing that individuals with melancholic symptoms, such as anhedonia, are more sensitive to the reinforcing effects of amphetamine (15, 16), which could increase stimulant abuse liability.

Several limitations should be considered. First, the relatively low SUD prevalence rates in this community sample restricted our analyses of other forms of SUDs (e.g., opiates, hallucinogens, inhalants) and prevented examination of abuse and dependence categories separately. Second, psychiatric symptoms were evaluated retrospectively by self-report telephone interviews. Our assessment of symptoms like psychomotor disturbance might differ from those used in clinical studies that rely partially on behavioral observation. Accordingly, future studies that evaluate the clinical features in currently depressed individuals at risk for future SUDs may be informative.

ACKNOWLEDGMENTS

This research was supported in part by NIMH awards MH40501, MH50522, MH 52858, and DA 12951 awarded to Dr. Lewinsohn.

REFERENCES
