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Agitated Depression in Substance Dependence

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Abstract

Background—Depression with psychomotor agitation (PMA; “agitated depression”) is a putative psychiatric phenotype that appears to associate with some forms of substance dependence. However, it is unclear whether such relationships extend across different substances and independent (I-MDE) versus substance-induced (SI-MDE) subtypes of major depressive episodes.

Method—We examined whether lifetime depression with (vs. without) PMA was associated with lifetime substance dependence across individuals with lifetime: (1) I-MDE only (n = 575); and (2) SI-MDE only (n = 1683). Data were pooled from several family and genetic studies of substance

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dependence in which participants received identical structured interviews to diagnose *DSM-IV* mental disorders.

Results—In I-MDE, PMA was significantly associated with alcohol, cocaine, opioid, other drug (hallucinogen, inhalant, speed-ball), and sedative dependence. After controlling for demographic and clinical co-factors, PMA's relationship to dependence on opioids, other drugs, and sedatives remained significant, but not its relationship to alcohol or cocaine. In SI-MDE, PMA was significantly associated with alcohol, cocaine, opioid, and other drug dependence. After adjusting for co-factors, associations remained significant for dependence on cocaine and opioids, but not alcohol or other drugs. Relationships between PMA and opioid dependence were stronger in I-MDE than SI-MDE. Depression subtype (I-MDE vs. SI-MDE) did not moderate relations between PMA and non-opioid forms of substance dependence.

Conclusions—Agitated depression associates with certain forms of substance dependence, particularly opioid dependence. MDE subtype did not alter most PMA-dependence associations, which suggests that the mechanisms underlying this comorbidity are complex and potentially bidirectional.

Keywords

Major Depression; Psychomotor Agitation; Substance Dependence; Agitated Depression; Substance-Induced Depression

1. Introduction

There is considerable evidence of an association between major depression and substance dependence (Davis et al., 2008; Nunes et al., 2006; Swendsen et al., 2000), but the reasons for their comorbidity are not entirely clear. The heterogeneity within depression may confound the understanding of its relationship to substance dependence. Studies of depression in substance dependence typically consider depression as a unitary phenotype. However, depression may be more aptly characterized as a complex set of numerous intermediate phenotypes (Hasler et al., 2004). It has been argued that by parsing depression into more narrow definitions based on individual key symptoms (depressed mood, anhedonia, memory impairment, appetite changes, diurnal variation in mood, executive dysfunction, psychomotor disturbance, and stress sensitivity), phenotypic markers representing more direct expressions of underlying genes, neurophysiology, and psychosocial processes might be isolated (Gottesman et al., 2003; Hasler et al., 2004). Accordingly, evaluating whether certain phenotypic expressions of depression are associated with substance dependence may help to clarify the mechanisms underlying the common co-occurrence of these disorders.

Psychomotor agitation (PMA; i.e., unintentional motor activity stemming from mental tension) is a symptom of several psychiatric disorders, including major depression (APA, 1994). PMA can be manifested as purposeless and stereotyped movements, such as fidgeting, pacing, and hand-wringing (APA, 1994; Parker et al., 1993). It is a marker of the melancholic subtype of depression (Leventhal et al., 2005) and may represent a unique psychopathologic depressive phenotype (Hasler et al., 2004; Leventhal et al., 2008b). Accordingly, there has been interest in exploring whether individuals with depression characterized by PMA (“agitated depression”) exhibit increased or decreased prevalence of substance dependence than those with non-agitated depression.

Extant research in epidemiologic and clinical samples indicates that depression with PMA is associated with higher rates of drug dependence, polysubstance use, and substance dependence (more broadly defined) than depression without PMA (Balázs et al., 2006;

Leventhal et al., 2008a; Leventhal et al., 2008b; Leventhal et al., 2010; Maremmani et al., 2007; Marmorstein, in press). Relationships between PMA and alcohol dependence have also been reported, but are less consistent across samples and analyses (Leventhal et al., 2008b; Leventhal and Zimmerman, 2010; Marmorstein, in press). Some of these associations extend across current and lifetime diagnoses and are robust even after controlling for demographics, comorbid psychiatric disorders, and depression severity, chronicity, and recurrence (Leventhal et al., 2008a; Leventhal et al., 2008b; Leventhal and Zimmerman, 2010; Marmorstein, in press). Although PMA is a diagnostic criterion for a manic episode (APA, 1994), evidence suggests that PMA and bipolar disorder have unique, non-overlapping relationships to substance dependence (Leventhal and Zimmerman, 2010).

Despite consistent evidence of an association between PMA and some forms of substance dependence, several points require further clarification. Due to the low prevalence of certain types of drug dependence in general population and psychiatric patient samples, prior analyses of PMA have mostly been limited to “combined drug dependence” categories, grouping multiple licit and illicit drug dependences together. In addition, prior research of PMA and substance dependence has not distinguished between a major depressive episode (MDE) occurring outside the context of substance use (i.e., independent from the substance use or “primary”) and an MDE that is a consequence of the direct physiological effect of a substance (“secondary”). These MDE subtypes can be diagnostically differentiated based on the onset and course of the mood disturbance in relation to substance use (APA, 1994). Examining whether the association between PMA and substance dependence extends across both independent (I-MDE) and substance-induced (SI-MDE) subtypes of major depressive episodes could shed light on the etiology and pathophysiology of this comorbidity.

The present report examined whether depression with (vs. without) PMA during the most severe MDE was associated with lifetime substance dependence diagnoses across two groups: (1) individuals with a history of I-MDEs only (n = 575); and (2) individuals with a history of SI-MDEs only (n = 1683). We examined these relationships in a combined sample of individuals participating in multi-center case-control or family studies of cocaine, opioid, and alcohol dependence (Covault et al., 2008; Gelernter et al., 2005; Gelernter et al., 2007; Gelernter et al., 2006), which capitalizes on recruitment strategies designed to sample individuals diagnosed with multiple types of substance dependence.

2. Method

2.1 Participants

2.1.1 Recruitment—Participants were recruited to take part in family-based and case-control genetic studies of substance dependence at five sites: Yale University School of Medicine (New Haven, CT; n = 976), the University of Connecticut Health Center (Farmington, CT; n = 915), the University of Pennsylvania School of Medicine (Philadelphia, PA; n = 155), the Medical University of South Carolina (Charleston, SC; n = 120), and McLean Hospital (Belmont, MA; n = 92). For family studies, families with sibling pairs concordant for a lifetime Diagnostic and Statistical Manual of Mental Disorders, 4th edition (*DSM-IV*; APA, 1994) diagnosis of opioid and/or cocaine dependence were recruited. For case-control studies, unrelated probands with lifetime opioid, alcohol, or cocaine dependence (cases) or with no lifetime diagnosis of substance use disorder (controls) were recruited. In addition, other family members of affected probands in family studies were invited to participate whenever possible, regardless of affection status. Substance-dependent individuals were recruited to participate in genetic studies primarily through advertisements in local media, but also directly from addiction treatment programs and from among participants in other clinical research projects. Controls were recruited through advertisements in local media. For the present report, the number of participants

from each of the three main sources of recruitment was as follows: (a) alcohol-, opioid-, and cocaine-dependent probands (n = 1834), (b) family members of affected probands regardless of affection status (n = 307), and (c) controls without a lifetime diagnosis of substance use disorders (n = 117).

Participants were excluded if they reported a primary clinical diagnosis of schizophrenia or schizoaffective disorder or evidenced cognitive impairment during the screening process. Participants with a lifetime diagnosis of substance abuse were included, but only if they also had a lifetime diagnosis of substance dependence. Participants provided informed consent, as approved by the institutional review board at each site, and Certificates of Confidentiality was obtained from the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism.

2.1.2 Sample—The current analysis included only probands and their self-identified full- and half-siblings from either family or case–control studies who met *DSM-IV* criteria for a lifetime history of at least one MDE occurring within the context of either unipolar or bipolar depression. Because we were interested in comparing motor agitation- substance dependence relations across I-MDE and SI-MDE, we excluded from the analyses, participants with a history of both types of MDEs across multiple episodes (n = 575). The final sample for analysis included 2258 participants split into two groups: (1) Individuals with a lifetime history of only I-MDEs (n = 575; 520 nuclear families with 1 - 3 participants per family); and (2) Individuals with a lifetime history of only SI-MDEs (n = 1683; 1315 nuclear families with 1 - 8 participants per family). Consistent with the diagnostic requirement of heavy substance use to classify SI-MDE, rates of substance dependence and comorbidity were higher for SI-MDE (0 dependence diagnoses: n = 19, 1%; 1 diagnosis: n = 236, 14%; 2 diagnoses: n = 530, 46%; 3 or more diagnoses: n = 858, 53%) than I-MDE (0 diagnoses: n = 107, 19%; 1 diagnosis: n = 132, 23%; 2 diagnoses: n = 125, 22%; 3 or more diagnoses: n = 211, 37%) participants, odds ratio (OR) = 2.15, $p < .0001$. Similarly, rates of PMA were higher in SI-MDE than I-MDE (65% vs. 52%), OR = 1.12, $p < .0001$. Demographic and psychiatric characteristics of these groups are reported in Table 1.

2.2 Assessment and Diagnosis

Participants were interviewed using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA). The SSADDA is a computer-assisted interview that yields lifetime *DSM-IV* diagnoses of most substance use and Axis-I psychiatric disorders, as well as other demographic and clinical information. Detailed descriptions and the methods used to administer the SSADDA have been published previously (Pierucci-Lagha et al., 2007; Pierucci-Lagha et al., 2005).

2.2.1 Depression—Participants who endorsed lifetime anhedonia or depressed mood were administered the SSADDA major depression module. The module queries about the lifetime presence of *DSM-IV* MDE symptoms, including psychomotor agitation, experienced during the most severe episode. MDE symptoms were rated as present if they occurred daily or nearly every day for at least two weeks within the context of a depressive episode. Thus, transient symptoms that were not central to the depressive syndrome or reflective of epiphenomena, such as acute substance withdrawal symptoms that abated following sustained abstinence or drug use resumption, were not considered part of the MDE. Consistent with *DSM-IV*, an MDE diagnosis was made only in circumstances in which 5 or more depressive symptoms (with at least one being anhedonia or depressed mood) co-occurred during the same period lasting 2 weeks or longer. MDEs due to either to an underlying medical condition or bereavement were excluded from the analysis.

Psychomotor agitation was rated present (PMA+) or absent (PMA-) depending on endorsement of the SSADDA item, "Were you so fidgety or restless that you had a hard time sitting still (i.e., during a depressive episode lasting at least two weeks)?" Because symptom-level data were not assessed for every MDE within the SSADDA, agitation during most severe MDE was used to classify agitated depression status. Although this approach does not account for fluctuations in symptom expression across MDEs, prior research suggests that categorizing individuals on the basis of symptoms experienced during most severe episode can yield valid depressive phenotypes that associate with substance dependence (Leventhal et al., 2008b; Marmorstein, in press).

The module also includes a detailed set of queries to assess the etiological role of substance use in an MDE (Niciu et al., 2009). A diagnosis of independent MDE was assigned to episodes that occurred during periods with no concurrent heavy or frequent substance use or for episodes that preceded the onset of substance use. A diagnosis of substance-induced was assigned to episodes that occurred in strong temporal relation with heavy or frequent substance use, with the onset of the MDE following the onset of substance use. In contrast to the *DSM-IV* substance-induced mood disorder diagnosis that requires only clinically significant substance-induced dysphoria or anhedonia (APA, 1994), substance-induced MDE in the SSADDA requires full *DSM-IV MDE* temporal (2 weeks) and symptom criteria (≥ 5 symptoms with at least one being anhedonia or depressed mood). Thus, the minimum number and time-frame of symptom criteria across I- and SI-MDEs were equivalent.

Additional information regarding the number of symptoms experienced, onset date of and duration of the most severe episode, total number of MDEs experienced, history of receiving somatic treatment for depression, and other MDE characteristics was also collected

2.2.2 Substance Dependence—Lifetime *DSM-IV* substance dependence diagnoses were obtained for alcohol, amphetamine, cannabis, cocaine, opioid, and sedatives. We also created an "other drug" dependence category, which included dependence on any of the following substances: phencyclidine, hallucinogens, inhalants, solvents, or a combination of opioids and cocaine (i.e., "speedballs"). Substance abuse was not analyzed, given that PMA has been more strongly and consistently associated with dependence than abuse (Leventhal et al., 2008b; Marmorstein, in press).

2.2.3 Psychiatric disorders—Lifetime diagnoses of anxiety disorder (generalized anxiety disorder, posttraumatic stress disorder, panic disorder, social phobia), bipolar (I or II) disorder, schizophrenia, and disruptive behavior disorder (conduct, antisocial personality, or attention deficit/hyperactivity disorder) were assigned based on *DSM-IV* definitions.

The SSADDA-derived diagnoses relevant to the present study, including substance dependence diagnoses, generally showed adequate reliability (Pierucci-Lagha et al., 2005). The inter-rater and test–retest reliability estimates for independent MDE were $\kappa = 0.68$ and $\kappa = 0.76$, respectively, and for substance-induced MDE they were $\kappa = 0.46$ and $\kappa = 0.69$, respectively (Niciu et al., 2009). The inter-rater and test-retest reliabilities for agitation status were $\kappa = 0.53$ and $\kappa = 0.69$, respectively.

2.3 Data Analysis

Generalized estimating equation (GEE) analysis was used to model within-family correlation in all models. In preliminary analyses, GEE-based logistic and linear regression models were used to examine whether agitation status (PMA+ vs. PMA-) was associated with the demographic, psychiatric, and MDE variables that served as covariates in primary analyses (see below). Primary analyses utilized GEE-based logistic regression models incorporating PMA status as the predictor and the presence (vs. absence) of substance

dependence as the outcome. We chose PMA status as the predictor and substance dependence as the outcome (rather than the reverse) because the adjusted models included covariates designed to partial out variance in the PMA status variable associated with non-specific psychiatric illness (see description of adjusted models below). Separate models were tested for each substance dependence diagnosis (alcohol, amphetamine, cannabis, cocaine, opioid, other, sedative). For each form of substance dependence, the model predicted the odds of having that particular dependence diagnosis (e.g., sedative dependence) with the reference category being those who did not meet criteria for that particular dependence diagnosis (e.g., no history of sedative dependence). This approach allows some participants in the no-dependence reference category to be dependent on a substance other than the one being predicted. Thus, the total sample size was consistent across the separate models predicting each of the different forms of substance dependence.

All models were recalculated after adjusting for demographics (sex, age, race, marital status, education), comorbid psychiatric disorders (lifetime anxiety, bipolar, schizophrenia, and disruptive behavior disorder), and depression characteristics (age of onset of most severe MDE, total number of MDEs, total number of symptoms in the most severe MDE, duration of the most severe MDE, and history of somatic treatment for depression). Adjusting for these variables was necessary given evidence that psychomotor agitation is associated with a unique demographic profile, higher rates of psychiatric comorbidity, and more severe, recurrent, chronic, and early-onset depression (Benazzi et al., 2002), and these variables may overlap with risk for substance dependence. The total number of symptoms in the most severe MDE serves as a proxy indicator of depression severity (APA, 1994), and controlling for this variable accounted for the possibility that agitation-dependence associations could be due a general tendency to endorse more symptoms rather than a specific effect attributable to experiencing PMA.

For each analysis, parallel tests were conducted across the two non-overlapping subsamples stratified by MDE subtype: (1) I-MDE (n = 575); and (2) SI-MDE (n = 1683). To evaluate whether agitation-dependence associations differed as a function of the subtype of MDE, we examined the interaction of MDE Subtype (I-MDE vs. SI-MDE) and PMA status (after controlling for those variables) in predicting dependence in the combined sample (N = 2258).

Analyses were conducted in SAS using the GENMOD procedure (SAS Institute Inc., 2003). Results are reported as *OR*s, with 95% confidence intervals (*CI*s). For all models, statistical significance was set at $p < 0.05$, and all tests were 2-tailed.

3. Results

3.1 Participant Characteristics

Demographics, psychiatric disorders, and MDE characteristics by PMA status within each of the MDE Subtype groups are reported in Table 1. PMA+ participants had less education, but were otherwise demographically comparable to PMA- participants. PMA+ participants had higher rates of anxiety disorders, bipolar disorder (SI-MDE group only), and disruptive behavior disorders (SI-MDE only) than PMA- subjects. PMA+ participants also evidenced longer MDE duration (I-MDE only) and more MDE symptoms (see Table 1).

3.2 Associations between PMA and Substance Dependence

In participants with lifetime I-MDE, PMA was significantly associated with alcohol, cocaine, opioid, other drug, and sedative dependence in unadjusted models (see Table 2). Relationships of PMA to opioid, other drug, and sedative dependence remained significant in adjusted models that controlled for demographic, psychiatric, and MDE characteristics (*p*s

≤ .01). However, relationships of PMA to alcohol and cocaine dependence were not statistically significant in adjusted models (see Table 2).

As illustrated in Table 3, PMA was associated with significantly higher rates of alcohol, cocaine, opioid, and other drug dependence in unadjusted models among participants with lifetime SI-MDE (see Table 3). After adjusting for demographic, psychiatric, and MDE characteristics, relationships involving alcohol and other drug dependence were no longer significant. Associations of PMA to opioid and cocaine dependence remained significant in adjusted models (*p*s ≤ .005).

As noted in section 2.1.2 there were high rates of comorbidity between different forms of substance dependence, which leaves unclear the specificity of associations between PMA and particular forms of substance dependence. To examine the specificity of associations, we re-ran each of the models and included an additional covariate that classified whether participants were diagnosed with any substance dependence disorder other than the form of dependence being predicted. For example, in analyses examining PMA as a predictor of opioid dependence, we included an additional covariate that classified whether or not participants met lifetime dependence on one or more of the following substances: alcohol, amphetamine, cannabis, cocaine, other drug, or sedative. The results of these supplemental analyses were consistent the original analysis; that is, there were no changes in the significance of any of the PMA-dependence associations.

3.3 Do PMA-Dependence Associations Differ by MDE Subtype?

The MDE Subtype (I-MDE vs. SI-MDE) × PMA status (PMA+ vs. PMA-) interaction was significant in models predicting opioid dependence (Unadjusted: $Z = 2.2$, $p = .03$; Adjusted $Z = 2.2$, $p = .03$). Inspection of *OR*s in Tables 2 and 3 indicate that the interaction signifies that the association between PMA and opioid dependence was significantly stronger among individuals with I-MDE than those with SI-MDE. Interactions were not significant in models predicting any of the non-opioid forms of substance dependence.

4. Discussion

The present report adds to a growing literature examining the relationship between agitated depression and certain types of substance dependence. Results showed that PMA was associated with higher rates of lifetime alcohol dependence, but these relationships did not remain significant after adjusting for demographics, psychiatric comorbidity, and MDE characteristics. These findings are relatively consistent with prior analyses of adult epidemiologic and clinical samples indicating a significant relationship between PMA and lifetime alcohol dependence that is no longer significant after controlling for these co-factors (Leventhal and Zimmerman, 2010; Marmorstein, in press). Participants with PMA in this study exhibited less education, higher comorbidity, and more severe and chronic MDEs, which is important because each of these characteristics is associated with alcohol dependence (Gilman et al., 2008; Hasin et al., 1993; Hasin et al., 2007; Lynskey, 1998). Thus, the overall pattern of findings in this analysis and prior studies suggests a possible relationship of PMA to alcohol dependence in adults that is not entirely divisible from its overlap with non-specific demographic and clinical factors.

Analyses of the association between PMA and drug dependence diagnoses illustrated an interesting pattern. We found a clear relationship between PMA and opioid dependence that remained after adjusting for co-factors and was consistent across both I-MDE and SI-MDE samples. PMA was associated with cocaine dependence in both samples; however, after adjusting for co-factors, this relationship remained significant in SI-MDE participants, but not in I-MDE participants. Similarly, PMA was significantly related to the category of other

drug dependence (i.e., phencyclidine, hallucinogens, inhalants, solvents, cocaine-heroin combination use) across all samples and analyses with the exception of adjusted models in participants with SI-MDE; this is of particular interest because these substances, unlike alcohol, opioids, and cocaine, were not considered in subject recruitment. Finally, both unadjusted and adjusted results showed that PMA was significantly associated with sedative dependence in I-MDE participants, but not SI-MDE participants. PMA was not significantly associated to amphetamine or cannabis dependence. These findings extend prior studies examining associations between depression with PMA and a combined category of drug dependence (Leventhal et al., 2008a; Leventhal and Zimmerman, 2010; Marmorstein, in press) and illustrate that this relationship is complex and non-equivalent across different forms of drug dependence.

Examination of the role of MDE subtype indicated that the relationship between PMA and opioid dependence was more robust in I-MDE than SI-MDE, although both relations were significant. As noted above, the pattern of significant relations of PMA to cocaine, other drug, and sedative dependence were somewhat inconsistent across MDE type. However, MDE diagnostic subtype did not moderate the relation of PMA to dependence for any of the other types of substance dependence. It is possible that dividing the sample into two groups may have left some of the tests underpowered, resulting in relations to cocaine, other drug, and sedative dependence that did not satisfy statistical significance criteria in some circumstances (*p*s = .07 - .09; see Tables 2 and 3). Indeed, post-hoc analyses not reported in the results section that combined the two samples yielded significant effects in adjusted models (cocaine: *OR* = 1.85, $p < .0001$; other: *OR* = 1.47, $p = .002$; sedative: *OR* = 1.59, $p = .008$), although these results should be interpreted with caution, given their post-hoc nature.

It is important to note that the mechanisms used to recruit some of the substance-dependent individuals were different that the mechanisms for recruiting control participants, which may have impacted the present findings. For example, the recruitment strategies might have produced substance-dependent participants who had unique demographic characteristics that could overlap with PMA. However, adjusted models controlled for a variety of demographic factors that could have differed by recruitment mechanism and potentially impacted the findings, and the primary associations remained significant. It is also possible that because a portion of substance-dependent participants were recruited from addiction treatment centers or clinical studies, some substance-dependent participants may have been experiencing more distress, which could have generally increased the endorsement of any psychiatric symptoms (including PMA). To address this, we adjusted statistically for a host of clinical variables indicative of more severe general distress, and the main results remained significant. Thus, although we cannot definitively rule out an impact of recruitment strategies on the findings, it is unlikely that they had a major impact on the associations in the adjusted models.

This study had several limitations. First, given the cross-sectional correlational design and reliance on lifetime diagnoses, we cannot comment on the causal or temporal aspects of the relationships demonstrated herein. That is, PMA may precipitate substance dependence, substance dependence may itself cause PMA, the two may be associated via common etiology, or unmeasured extraneous variables that correlate with both conditions may account for their relationships. Although we cannot definitively rule out the latter explanation, rigorous statistical control of demographic and clinical features reduces the likelihood that external factors account for the relationships identified. Second, the sample included participants recruited for family and case-control studies of the genetics of substance dependence, which provided the advantage of ample rates of various dependence diagnoses, but may limit the degree to which some findings will extend to other groups. While we expect that the associations between PMA and dependence will likely generalize,

the raw rates of substance dependence in this sample are higher than those in the general population. Thus, readers should not be left with the assumption that most PMA occurs in the context of substance dependence, as many individuals with agitated depression have no history of substance dependence (Marmorstein, in press). Third, there was substantial comorbidity of substance dependence diagnoses in this sample, which precluded analyses to explore whether PMA associated with "pure" cases including only one substance dependence diagnosis; but comorbidity is common in clinical and community samples, and selecting "purely" diagnosed subjects could have biased our findings away from the direction of clinical realism. Supplemental analyses that statistically adjusted for the effect of comorbid substance dependence diagnoses did not substantially change any of the results, suggesting that the PMA-dependence relations identified may be specific to the forms of dependence demonstrated in this report. Nonetheless, future research in restricted samples with a single dependence diagnosis is warranted to clarify the exact substance specificity of these associations. Fourth, although I- and SI-MDE diagnoses evidenced adequate reliability, the validity of retrospectively diagnosing these subtypes is unknown, which raises the possibility for diagnostic overlap or misclassification. Fifth, because a diagnosis of SI-MDE requires heavy substance use to be present, rates of substance dependence and PMA may have been inflated in the SI-MDE group, which complicates comparisons to I-MDE. Sixth, although using PMA during the most severe MDE to identify agitated phenotypes of depression has received some prior support (Leventhal et al., 2008b; Marmorstein, in press), some individuals who had an agitated episode outside of their most severe MDE could have been misclassified. Seventh, given the focus on lifetime PMA, interviewers were unable to use behavioral observation to rate PMA, which is the clinical standard in the assessment of psychomotor disturbance. Eighth, given the retrospective and interview limitations, it cannot be determined whether individuals with SI-MDE might have been in substance withdrawal during their index depression, which could have impacted manifestations of their depression. Ninth, the assessment of PMA was based on a single item, which has psychometric limitations. Although past research provides support for the use of single-item measures of PMA in this context (Leventhal et al., 2008a; Leventhal et al., 2008b; Leventhal and Zimmerman, 2010; Marmorstein, in press), future research using multiple-item clinical rating scales (Parker, 2000; Sobin et al., 1998), may be warranted. Tenth, although the SSADDA requires that symptoms experienced during an MDE occur daily or nearly daily for at least two weeks, are central to a depressive syndrome, and are not merely epiphenomena, it is still possible that substance withdrawal manifested as PMA could have been misclassified as an agitated MDE for some individuals. Because the PMA-dependence associations were consistent across SI-MDE and I-MDE (which requires the depressive symptoms to occur outside of periods of heavy substance use), it is unlikely that misclassified agitation related to substance withdrawal had a major impact on the current findings. Finally, we analyzed seven outcomes without adjusting the alpha level, which raises the probability of type-I error.

Limitations notwithstanding, this study extends the literature on the comorbidity of depression and substance dependence by demonstrating that agitated depression—a putative psychopathologic depressive phenotype—is associated with certain forms of substance dependence. For most classes of dependence, the MDE subtype did not alter the strength of PMA-dependence associations, which is inconsistent with the view that this comorbidity is solely accounted for by a unidirectional mechanism whereby drug use induces agitated depression. Rather, it is possible that these relationships are bi-directional or accounted for by variables other than demographics, comorbid psychiatric disorders, or depressive severity, chronicity, and recurrence. Both I-MDE and SI-MDE were associated with opioid dependence, with stronger relationships evident in I-MDE. This pattern is concordant with an unbalanced bidirectional relationship, with a greater proportion of cases being due to agitated depression increasing the risk for opioid dependence. Additional research using

longitudinal designs is warranted to clarify the mechanisms and nature of the PMA-dependence relationship.

The present findings may be useful for practitioners. Given PMA's relationships to particular types of substance dependence, clinicians should be aware that patients with agitated forms of depression may be especially likely to have a comorbid substance dependence disorder and may benefit from a formal addiction assessment. Likewise, depressed patients with substance dependence may have higher rates of agitated depression, which is important to consider for treatment planning. Agitation is a particularly distressing symptom of depression that is associated with suicidal ideation (Olgiati et al., 2006). Evidence suggests that depression with melancholic features, such as PMA, is more responsive to somatic versus behavioral interventions (Leventhal and Rehm, 2005). Furthermore, emerging preliminary data suggest that augmentation of antidepressant treatment with atypical antipsychotics may be particularly effective for depression with PMA (Baune et al., 2007; Dannlowski et al., 2008). Thus, it may be important to assess this often-overlooked symptom in the context of substance abuse treatment.

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Table 1

Sociodemographic and Psychiatric Characteristics by Agitation Status and MDE Subtype Group

	Independent MDE[a]			Substance-Induced MDE[b]		
	PMA- (*n* = 275)	PMA+ (*n* = 300)	Contrast *p*-value	PMA- (*n* = 597)	PMA+ (*n* = 1086)	Contrast *p*-value
Sociodemographics						
Female, %	61.8	56.3	*ns*	47.2	41.1	*ns*
Age, *M(SD)*	39.1 (10.7)	39.3 (10.1)	*ns*	38.9 (9.5)	39.7 (9.0)	*ns*
Race/Ethnicity, %	-	-	*ns*	-	-	*ns*
Native American/American Indian	1.4	0.7		0.7	1.1	
Asian	0.7	0.3		0.0	0.0	
Pacific Islander	0.0	0.7		0.0	0.0	
Black/Non-Hispanic	40.7	42.0		42.9	44.4	
Black/Hispanic	0.7	2.3		1.2	3.6	
White/Non-Hispanic	45.5	34.3		44.7	34.4	
White/Hispanic	4.0	8.3		4.9	7.7	
Other	6.9	11.3		5.7	8.8	
Education, %	-	-	<.0001	-	-	.0002
Less than high school	24.4	41.7		38.2	44.4	
Completed high school	21.8	21.3		27.3	31.0	
Attended some post high school education	53.8	37.0		34.5	24.6	
Marital Status, %	-	-	*ns*	-	-	*ns*
Married	15.6	16.7		10.9	10.5	
Widowed	2.6	4.7		1.5	2.8	
Separated	7.3	7.7		8.4	7.3	
Divorced	20.4	23.7		18.4	19.9	
Never married	54.2	47.3		60.8	59.6	
Comorbid Disorders (Lifetime), %						
Anxiety Disorders	26.8	39.3	.006	25.1	33.7	<.0001
Bipolar Disorder	5.1	7.7	*ns*	4.0	8.3	.0003
Schizophrenia	0.4	0.3	*ns*	0.2	0.1	*ns*

	Independent MDE[a]			Substance-Induced MDE[b]		
	PMA- (*n* = 275)	**PMA+ (*n* = 300)**	**Contrast *p*-value**	**PMA- (*n* = 597)**	**PMA+ (*n* = 1086)**	**Contrast *p*-value**
Disruptive Behavior Disorder	19.6	26.0	*ns*	21.1	29.5	<.0001
MDE Characteristics						
Number of MDE in lifetime, *M(SD)*	2.1 (5.5)	3.3 (10.8)	*ns*	3.8 (12.2)	4.1 (12.3)	*ns*
No. of symptoms in most severe MDE, *M(SD)*	7.3 (1.2)	7.9 (1.2)	<.0001	7.2 (1.3)	8.0 (1.1)	<.0001
Age of onset of most severe MDE, *M(SD)*	29.6 (11.8)	29.8 (12.1)	*ns*	31.6 (10.1)	31.8 (9.9)	*ns*
Duration of most severe MDE in wks, *M(SD)*	60.2 (139.0)	112.7 (221.1)	.0007	59.4 (119.6)	65.0 (133.0)	*ns*
Received somatic treatment for depression, %	44.0	54.3	*ns*	53.2	54.5	*ns*

Note. All participants had a lifetime history of at least one MDE as either part of unipolar or bipolar depression. Percentages indicate rates of respective substance dependence diagnosis by psychomotor agitation status in most severe MDE. Contrast signifies results of statistical comparison of PMA+ vs. PMA- on respective characteristic (*ns* = non-significant). PMA+ = Psychomotor agitation present in most severe MDE; PMA- = Psychomotor agitation absent in most severe MDE; MDE = Major Depressive Episode.

[a] *N* = 575 probands and full biological siblings with lifetime history of only independent MDEs (520 nuclear families, with 1 - 3 participants per family).

[b] *N* = 1683 probands and full biological siblings with lifetime history of only substance-induced MDEs (1315 nuclear families, with 1 - 8 participants per family).

Table 2

Associations between Agitated vs. Non-agitated Independent Major Depressive Episodes and Lifetime Substance Dependence

	PMA- (*n* = 275)	PMA+ (*n* = 300)	Baseline Model[a]		Adjusted Model[b]	
	%	%	*OR* (95% CI)	*p*	*OR* (95% CI)	*p*
Alcohol dependence	45.5	59.7	1.78 (1.27-2.49)	.0009	1.30 (0.89-1.93)	.17
Amphetamine dependence	4.0	8.0	2.07 (1.00-4.30)	.051	1.97 (0.87-4.46)	.10
Cannabis dependence	24.0	30.3	1.39 (0.96-2.02)	.08	1.15 (0.74-1.78)	.54
Cocaine dependence	54.9	70.0	1.91 (1.37-2.67)	.0001	1.41 (0.95-2.09)	.09
Opioid dependence	24.0	42.3	2.30 (1.62-3.28)	<.0001	2.32 (1.49-3.60)	.0002
Other drug dependence[c]	10.6	21.0	2.24 (1.39-3.59)	.0009	1.96 (1.13-3.40)	.02
Sedative dependence	3.3	8.3	2.67 (1.22-5.81)	.01	3.32 (1.41-7.65)	.005

Note. N = 575 probands and full biological siblings (520 nuclear families, with 1 - 3 participants per family). All participants had a lifetime history of at least one independent MDE as either part of unipolar or bipolar depression, and no history of substance-induced MDEs. Percentages indicate rates of respective substance dependence diagnosis by psychomotor agitation status in most severe MDE. *OR*s indicate association of psychomotor agitation with respective substance dependence diagnosis outcome (dependent vs. non-dependent) in Generalized Estimating Equation logistic regression models accounting for familial clustering. PMA+ = Psychomotor agitation present in most severe MDE; PMA- = Psychomotor agitation absent in most severe MDE; MDE = Major Depressive Episode; *OR* = Odds Ratio; *CI* = Confidence Interval.

[a] Baseline model including psychomotor agitation as the sole predictor

[b] Adjusted for sex, age, race, marital status, education, history of anxiety, bipolar, schizophrenia, and disruptive behavior, age of onset of most severe MDE, total number of MDEs, total number of symptoms in most severe MDE; duration of most severe MDE, and history of somatic treatment for depression.

[c] Other substance dependence includes dependence on phencyclidine, hallucinogens, inhalants, solvents, or a combination of opioids and cocaine (i.e., “speedballs”)

Table 3

Associations between Agitated vs. Non-agitated Substance-Induced Major Depressive Episodes and Lifetime Substance Dependence

	PMA- (*n* = 597)	PMA+ (*n* = 1086)	Baseline Model[a]		Adjusted Model[b]	
	%	%	*OR* (95% CI)	*p*	*OR* (95% CI)	*p*
Alcohol dependence	66.5	71.6	1.28 (1.03-1.59)	.03	1.06 (0.83-1.36)	.64
Amphetamine dependence	6.7	8.5	1.29 (0.88-1.88)	.19	1.47 (0.96-2.27)	.08
Cannabis dependence	37.4	41.2	1.17 (0.95-1.44)	.15	0.97 (0.76-1.23)	.78
Cocaine dependence	81.9	90.5	2.11 (1.56-2.85)	<.0001	1.75 (1.25-2.45)	.001
Opioid dependence	39.4	48.4	1.45 (1.18-1.78)	.0004	1.44 (1.12-1.86)	.005
Other drug dependence[c]	16.6	21.9	1.44 (1.11-1.88)	.006	1.32 (0.98-1.77)	.07
Sedative dependence	9.4	12.3	1.35 (0.96-1.88)	.08	1.41 (0.95-2.09)	.09

Note. N = 1683 probands and full biological siblings (1315 nuclear families, with 1 - 8 participants per family). All participants had a lifetime history of at least one substance-induced MDE as either part of unipolar or bipolar depression, and no history of independent MDEs. Percentages indicate rates of respective substance dependence diagnosis by psychomotor agitation status in most severe MDE. *OR*s indicate association of psychomotor agitation with respective substance dependence diagnosis outcome (dependent vs. non-dependent) in Generalized Estimating Equation logistic regression models accounting for familial clustering. PMA+ = Psychomotor agitation present in most severe MDE; PMA- = Psychomotor agitation absent in most severe MDE; MDE = Major Depressive Episode; *OR* = Odds Ratio; *CI* = Confidence Interval.

[a] Baseline model including psychomotor agitation as the sole predictor

[b] Adjusted for sex, age, race, marital status, education, history of anxiety, bipolar, schizophrenia, and disruptive behavior (i.e., conduct, antisocial personality, or attention deficit/hyperactivity disorder), age of onset of most severe MDE, total number of MDEs, total number of symptoms in most severe MDE; duration of most severe MDE, and history of somatic treatment for depression.

[c] Other substance dependence includes dependence on phencyclidine, hallucinogens, inhalants, solvents, or a combination of opioids and cocaine (i.e., “speedballs”)