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Effects of independent and substance-induced major depressive disorder on remission and relapse of alcohol, cocaine and heroin dependence

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Abstract

Aims—Little is known about the differential effects of independent and substance-induced major depression on the longitudinal course of alcohol, cocaine and heroin disorders when studied prospectively.

Design—Consecutively admitted in-patients, evaluated at baseline, 6-, 12- and 18-month follow-ups.

Setting—Baseline evaluations in a short-stay in-patient urban community psychiatric hospital unit.

Participants—Adults (n = 250) with current DSM-IV cocaine, heroin and/or alcohol dependence at baseline.

Measurements—The Psychiatric Research Interview for Substance and Mental Disorders (PRISM), used to evaluate independent and substance-induced major depression, alcohol, cocaine and heroin dependence, and other psychiatric disorders. Outcomes for each substance: (i) time (weeks) from hospital discharge to first use; (ii) time from discharge to onset of sustained (≥26 weeks) remission from dependence; (iii) time from onset of sustained remission to relapse.

Findings—Substance-induced major depression significantly predicted post-discharge use of alcohol, cocaine and heroin (hazard ratios 4.7, 5.3 and 6.5, respectively). Among patients achieving stable remissions from dependence, independent major depression predicted relapse to alcohol and cocaine dependence (hazard ratios 2.3 and 2.7, respectively).

Conclusions—Substance-induced and independent major depressions were both related to post-discharge use of alcohol, cocaine and heroin. The findings suggest the importance of clinical attention to both types of depression in substance abusing patients.

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Declarations of interest
None.

Keywords

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INTRODUCTION

Major depressive disorder (MDD) is prevalent among individuals with substance dependence [1–7], and often accompanied by impairment [1,8] that may affect the effort to attain or maintain remission from alcohol or drug dependence [9–11]. Because MDD co-occurring with alcohol or drug dependence is responsive to treatment [12,13], its influence on the outcome of alcohol or drug dependence is of clinical interest.

Although DSM-IV definitions of independent and substance-induced disorders were published in 1994, little prospective information is available concerning the effects of DSM-IV independent and substance-induced major depression on the course of substance dependence. Previously, we examined these effects using a single outcome category indicating alcohol, cocaine and/or heroin dependence [14] designed to avoid misinterpretation due to substance 'substitution', i.e. shifts from one substance to another [15,16]. Life-time MDD beginning before the onset of substance dependence reduced the chances of remission from dependence during follow-up, as did substance-induced MDD at baseline. MDD during sustained remissions in dependence strongly predicted relapse to dependence. However, the relationship between major depression and alcohol, cocaine and heroin use disorders may involve distinct neurochemical processes [17,18] and distinct clinical trajectories. The impact of the time-varying status of independent and substance-induced major depression on the course of substance-specific dependence is unknown. Previous studies of depression and the course of specific substance disorders employed varied depression indicators and investigated one substance [19–21], rather than multiple substances within the same study. Investigating different substances simultaneously avoids between-study methodological variations (e.g. measures of predictors or outcomes, sample characteristics) that can compromise comparison of findings. The aim of this report was to investigate the prognostic influence of DSM-IV independent and substance-induced major depressive disorder on the course (use and dependence) of three substances: alcohol, cocaine and heroin.

METHODS

Participants

Patients were recruited during index hospitalizations in a short-stay unit for co-occurring substance use and psychiatric problems in a New York City community psychiatric hospital [14,22] from 1994 to 1999. Of 379 patients invited to participate, 349 (92%) consented and participated in baseline evaluation, 279 met inclusion criteria (current DSM-IV alcohol, cocaine and/or heroin dependence and no history of mania or non-affective psychosis. Of these, 250 (91%) participated in at least one follow-up interview, and comprise the present sample. Table 1 shows demographic and clinical characteristics of the patients. Many, but not all, patients were dependent on more than one substance.

Procedures

Patients participated in a baseline interview while in the in-patient unit. In-person follow-up interviews were conducted approximately 6, 12 and 18 months later. The study was approved by the Institutional Review Boards of New York State Psychiatric Institute and the community hospital; all subjects gave written informed consent. Bias from loss to follow-up

was unlikely due to the high follow-up rate (91%) and lack of significant differences between participants followed, and not followed on age, sex, race, education and diagnoses of DSM-IV cocaine, heroin and alcohol dependence, antisocial personality disorder or depressive disorders at baseline [14]. Interviewers completed structured training; experienced research supervisors reviewed each case and conducted weekly interviewer meetings for case review and calibration to avoid interviewer drift.

Baseline measures

The Psychiatric Research Interview for Substance and Mental Disorders (PRISM) [23,24] was used to collect baseline demographic, treatment and diagnostic information. The PRISM is a semi-structured interview designed to evaluate current and life-time DSM-IV disorders with improved reliability and validity of psychiatric diagnosis among substance abusers. The PRISM showed good to excellent test–retest reliability for independent and substance-induced major depression with kappa ranging from 0.66 to 0.75 [23].

Substance dependence—Alcohol and drug disorders were diagnosed with DSM-IV criteria. PRISM diagnoses of substance dependence have high test–retest reliability [23,24] and validity [25].

Independent and substance-induced major depressive disorder (MDD)—We designated three categories of MDD: prior-onset independent MDD, independent MDD and substance-induced MDD. For clarity due to the different time-frames, we divided independent major depression into prior-onset independent MDD and independent MDD:

1. *Prior-onset independent MDD* indicates a history of episodes of DSM-IV independent major depression beginning prior to the life-time onset of substance dependence. Prior-onset independent MDD is a past diagnosis.
2. *Independent MDD* indicates DSM-IV independent major depression occurring at baseline or during the follow-up period. Independent MDD could occur during periods lasting at least 1 month without heavy substance use (thereby ruling out intoxication and withdrawal); *or* beginning at least 2 weeks prior to heavy substance use. Some baseline episodes were diagnosed as independent MDD in subjects currently dependent on alcohol or drugs because the depressive episodes began before the current substance dependence episode or continued into the follow-up at least 4 weeks after substance use ceased.
3. *Substance-induced MDD* could occur at baseline or during follow-up. These were episodes of MDD occurring during periods of heavy substance use, with symptoms in excess of the expected effects of intoxication or withdrawal from the substances the patients were using. These episodes could occur entirely within periods of substance use or end within 4 weeks after substance use ceased. To ensure reliability, episodes of substance-induced MDD were required to meet the duration and symptom requirements of DSM-IV independent MDD [22,23].

Follow-up measures

The PRISM-L (longitudinal) [26] was used to collect data at each follow-up evaluation. The PRISM-L combines elements of the Longitudinal Interval Follow-up Evaluation (LIFE) [27] and the time-line follow-back method [28–30], widely used instruments in psychiatric and substance abuse research that use similar memory aids to improve reporting on the longitudinal course, by week, of different conditions. PRISM-L test–retest reliability is excellent [26]. The PRISM-L also collects detailed information on treatment, by type, across each follow-up period.

We created three outcome measures for each substance. (i) *Time (weeks) from hospital discharge to first use* of each substance [11] is readily comparable to many other clinical reports, including randomized clinical trials [31–34]. (ii) *Remission of dependence* on a specific substance was defined as ≥26 consecutive weeks (6 months) with no dependence or abuse symptoms of that substance among those meeting current dependence criteria for it at baseline. The 6-month period was selected to indicate a meaningful degree of stability [35–37]. The start date of the remission was the first of the ≥26 weeks. *Relapse to dependence* could occur only after the 26th week of remission, and was defined as ≥1 week with any DSM-IV dependence or abuse symptom, following the guidelines in the DSM-IV course specifiers for substance dependence (DSM-IV-TR p195–196 [38]).

Statistical analysis

Survival analysis was used to investigate time (weeks) from hospital discharge to the occurrence of a substance-specific event. These included (i) time to first post-discharge use of the substance (alcohol, cocaine or heroin); (ii) time to the onset of sustained remission from dependence; and (iii) time from start of sustained remission to relapse. The cumulative probability of remission was obtained with Kaplan–Meier estimates. Cox proportional hazards models [39–41] were used to examine the effect (hazard) of the three types of MDD as predictors of the substance outcomes. Similar to an odds ratio, a hazard ratio (HR) >1.0 indicates a positive association between the predictor and outcome, with greater HRs indicating stronger relationships. HRs of 1.0 indicate no association, and HRs < 1.0 indicating inverse relationships between predictor and outcome; for HRs <1.0, the closer the HR is to zero, the stronger the inverse relationship. We assessed for violations of the proportional hazard assumptions of the Cox model with standard methods, including multiple Kaplan–Meier curves of the survival function versus the survival time and the log[-log(survival)] versus log of survival time for the MDD predictors in each model [42,43]. This indicated that Kaplan–Meier curves of the survival function versus the survival time and the log[-log(survival)] versus log of survival time for the MDD predictors in each model were approximately parallel, meeting the proportional hazard assumptions. SAS PROC PHREG was used to conduct all aspects of the survival analyses [44].

Time-invariant predictors do not change during follow-up. The main time-invariant predictor was a binary variable indicating presence or absence of prioronset independent MDD, diagnosed in 14.8% of the patients and considered independently of current depression status at baseline because current status does not alter this aspect of life-time history.

We controlled for several psychiatric disorders present at baseline using time-invariant control variables. These were binary variables indicating the presence or absence of the diagnoses, and included panic, generalized anxiety, specific and social phobia, post-traumatic stress disorder and antisocial personality disorder. In addition, because some patients were dependent on more than one of the three substances at baseline, each substance-specific analysis controlled for time-invariant past-month baseline dependence (coded as present or absent) on the other two substances. Analyses of independent and substance-induced major depression also controlled for prior-onset independent MDD. We further controlled for demographic characteristics assessed at baseline: age (years; continuous), sex (male; female), race (white; other) and education (≤12 years; >12 years). Finally, a time-invariant binary control variable for treatment during the follow-up was included in each model to control for treatment effects. This variable was created by combining the detailed information on psychiatric, psychological and substance abuse treatment collected in the PRISM-L.

Time-varying predictors allow modeling the effects of change in the status of the predictors during follow-up on the outcome variable. The time-varying predictors we studied were independent MDD and substance-induced MDD. These were defined as present or absent, by week, during the period of the follow-up. These two types of MDD were mutually exclusive and examined separately to determine their unique effects. The comparison condition for each type of depression was the absence of depression. In models of relapse we analyzed time-varying independent MDD only, because an episode of substance-induced MDD cannot begin during sustained remission from dependence. Significance was set at $P < 0.05$; all tests were two-tailed.

RESULTS

Descriptive substance outcomes

Among the 188 patients with current alcohol dependence at baseline, 80.9% had at least one drink during the follow-up, but 71.8% (135) remitted from alcohol dependence for ≥26 weeks (Table 2). Of those who remitted, 31.1% (42) subsequently relapsed. Among the 144 patients with current cocaine dependence at baseline (Table 2), 67.4% used cocaine at least once during the follow-up, but 74.3% (107) remitted from cocaine dependence for ≥26 weeks. Of these, 27.1% (29) subsequently relapsed. Among the 49 patients with current heroin dependence at baseline (Table 2), 71.4% used heroin at least once during the follow-up, but 79.6% (39) remitted from heroin dependence for ≥26 weeks, and of these, 30.8% (12) subsequently relapsed.

Effects of prior-onset independent MDD

The Cox proportional hazards models (Table 2) showed that patients with prior-onset independent MDD had significantly increased hazard of cocaine use after hospital discharge (HR: 2.1), and significantly decreased risk of sustained remission of cocaine and heroin dependence (HRs: 0.4 and 0.3, respectively). Prior-onset independent MDD was unrelated to the alcohol outcomes.

Effects of independent MDD

Among patients with alcohol or heroin dependence, independent MDD significantly increased the risk of post-discharge use of alcohol and heroin (HRs: 1.5 and 2.6, respectively). Independent MDD was also related to relapse after a sustained remission from alcohol dependence (HR: 2.3) and cocaine dependence (HR: 2.7).

Effects of substance-induced MDD

Substance-induced MDD strongly and significantly increased the hazard of post-discharge use by patients dependent on that substance at baseline: alcohol (HR: 4.7), cocaine (HR: 5.3) and heroin (HR: 6.5) (Table 2). Substance-induced MDD also adversely affected the chances of remission from heroin dependence (HR: 0.1).

Summary

Substance-induced MDD predicted post-discharge use of all three substances among patients dependent on the substances at baseline. Independent MDD predicted relapse to alcohol and cocaine dependence after sustained remissions, as well as post-discharge use of alcohol and/or heroin among those dependent on these substances at baseline. Prior-onset independent major depression (preceding the life-time onset of substance use disorders) reduced the chances of stable remission from cocaine and heroin dependence.

DISCUSSION

In this study, we examined the prognostic effects of independent and substance-induced depressions on the specific outcomes of alcohol, cocaine and heroin dependence, extending our prior research on effects of independent and substance-induced MDD when these substances were combined [11]. Key findings were that substance-induced MDD increased the risk of post-discharge first use of all three substances among patients dependent on them at baseline, independent MDD increased the risk of relapse to alcohol and cocaine dependence among those with sustained remissions, and prior-onset independent MDD decreased the likelihood of sustained remission from cocaine or heroin dependence.

Substance-induced MDD posed a strong risk for reduced time to post-discharge substance use across all substances.This finding was robust to substance disorder comorbidity, which we controlled in the analyses. The finding that risk for first use associated with substance-induced MDD was of a similar magnitude across the substances is noteworthy, given differences in the neurobiology of intoxication, chronic exposure and withdrawal.

Substance-induced MDD, as defined in the PRISM, is a rigorous diagnosis that requires a full major depressive episode, each symptom exceeding the expected effects of intoxication or withdrawal. Our findings suggest that substance-induced depression defined in this manner was not specific to a particular substance, but may instead represent a general vulnerability to depression. Clinicians may minimize the importance of MDD occurring during periods of heavy substance use, as many such episodes resolve within a month of abstinence. However, the findings suggest that among patients with alcohol, cocaine or heroin dependence, such episodes of MDD have unrecognized prognostic importance for post-discharge substance relapse. This could occur because the substance-induced MDD episodes persist after abstinence, meriting re-categorization as independent depressive episodes [22,45], or because substance-induced MDD has lingering residual impairment even after it resolves, a topic warranting future study. In either case, the findings are consistent with research on the neurobiology of addiction, suggesting that changes in the brain during substance dependence expressed as depressed affect during withdrawal continue to operate long afterwards, even into abstinence after withdrawal ends [46,47] (i.e. ‘protracted abstinence’).

In our earlier study, independent MDD was associated with relapse into dependence following sustained remission using a combined-substance outcome. In the present study, independent MDD predicted relapse only of alcohol and cocaine dependence. While results did not reach statistical significance in the smaller heroin-dependent group, taken as a whole the findings are consistent with emerging evidence on the clinical relevance of negative mood states for relapse long after heavy drug use has stopped [46–49], and underscore the importance of clinical attention to MDD during substance dependence remissions as a potent risk for relapse.

Prior-onset independent MDD predicted outcomes for cocaine- and heroin-dependent but not for alcohol-dependent patients. This is consistent with epidemio-logical findings that, after control for demographic characteristics and other psychiatric comorbidity, independent MDD is associated with drug [4], but not alcohol [2] dependence. The difference between alcohol and drug dependence in comorbidity results has received little attention thus far, and warrants explanation.

Some investigators address post-treatment substance outcomes entirely in terms of use, rather than in terms of remission and relapse of dependence. To address whether this affected our findings, we conducted sensitivity analyses re-analyzing our remission and relapse outcomes substituting use for dependence. Thus, we analyzed achieving sustained

abstinence from the substance for ≥26 weeks among those dependent on the substance at baseline, and relapse to any use of the substance after sustained abstinence. We found that the results (not shown) were very similar in terms of direction and magnitude of effect and in significance levels.

Study findings support the diagnosis of major depressive episodes full requirements for duration and number of symptoms are met, even if they occur during periods of heavy substance use. This definition of substance-induced MDD, which allows for a reliable [23] and valid diagnosis [25], has been influential in the proposed definition for DSM-5 [50]. While making the diagnoses in such cases may take time for busy clinicians, user-friendly computer-assisted diagnostic aids are now available (e.g. a computer-assisted version of the PRISM), and these greatly increase the ease of the diagnostic process.

Study limitations are noted. Patients were recruited from an in-patient facility. To generalize the results, patients from other types of facilities and untreated individuals should also be studied. Also, this study did not include urine samples or collateral information. However, in the absence of sanctions, reports of drug use tend to be accurate [30,51–56]. Because very few patients in our study reported sustained remission from alcohol and/or drug use throughout the *entire* follow-up, the scope of disclosure suggests relatively accurate reporting. A standard quantitative depression scale was not included in the study, which may have enabled us to replicate a finding that more severe MDD is predictive of less abstinence following alcohol treatment [57]. However, the PRISM depression diagnoses were made carefully and conservatively and the patients were hospitalized in a psychiatric unit at baseline, suggesting severity of the episodes diagnosed. Future studies should include a quantitative depression scale. Along the same lines, aside from time to first post-discharge use, our substance measures were in diagnostic terms rather than quantitative indicators of quantity and/or frequency of substance use. While beyond the scope of the present report, a future study using quantitative indicators could be informative and useful. We did not analyze the effects of specific depressive symptoms on outcome, which could be a valuable project in future research. We controlled for treatment using a dichotomous treatment variable. When we refined that variable to represent substance abuse treatment only or psychiatric treatment only, the results were unchanged, but a future study could investigate more detailed information about treatments received. Finally, we analyzed remissions lasting at least 26 weeks to study periods with stability. Analyzing longer remissions could be informative in future studies.

In this study, we focused on major depression, as the association between major depression and substance use disorders has been replicated extensively [1–4,10,58], and a causal relationship between alcohol dependence and depression has been established [5,20]. We did not investigate other psychiatric disorders that are also associated with substance use disorders (i.e. panic, generalized anxiety, specific and social phobia, post-traumatic stress disorder and antisocial personality disorder) [2,4,59,60], as the added complexity is beyond the scope of this paper. However, we controlled for these disorders to clarify the nature of the findings on major depression.

Strengths of the study are also noted. The follow-up rate was very high, and included patients remaining in treatment as well as those dropping out. Remission and relapse were studied separately, a strategy supported by the fact that their predictors differed. Furthermore, the diagnostic procedures had higher reliability and validity than other available procedures. The reliability and validity of the PRISM [23–25] and PRISM-L [26] for drug dependence and MDD diagnoses is good to excellent. Relapse to substance use immediately after detoxification or end of treatment is a frequently studied, clinically important outcome [61–64]. However, this outcome may not be an appropriate measure of

the impact of depression on the course of substance dependence, given the unstable nature of early-stage remission [38]. Therefore, we studied the relationship of major depression to stable remissions lasting 6 months or longer.

The findings from this study have important clinical implications. First, clinicians should be aware of the risk for post-discharge substance use posed by substance-induced MDD. In addition, providers should inform their alcohol- and drug-abusing patients of their risk for relapse if they experience depression during sustained remissions, which may improve treatment outcomes. In addition, careful assessment of depressive symptoms at treatment entry and at repeated intervals is necessary to distinguish expected effects of withdrawal and substance-induced MDD [65]. When independent or persistent substance-induced major depressions are detected they could be treated with antidepressant medications, which have evidence of effectiveness among drug and alcohol patients [12], or addressed with evidence-based psychosocial treatments for substance abusers such as cognitive–behavioral therapy-relapse prevention [66], whose modules on coping with mood problems could be emphasized in such patients. Finally, because MDD increases the risk of relapse even in individuals in remission for 6 or more months, ongoing supportive services during periods of stable remission may prevent future relapse.

In summary, the present study examined whether independent and substance-induced depressive episodes had specific effects on the post-discharge course of alcohol, cocaine or heroin dependence. For the most part, the relationship of substance-induced and independent depression to outcome was similar across substances, with similar clinical implications for each substance. Little has been published on independent versus substance-induced major depression, an important issue in substance abusers that makes the study findings novel and an important contribution to the literature. Results support the DSM-IV division of independent and substance-induced major depressive disorders. They also support clinical attention to each of these aspects of depression in the context of substance abusers. Finally, the findings suggest that future studies to address the most effective types of interventions for the types of major depression in the context of heavy drinking or drug use may offer clinically useful and important information.

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Table 1

Baseline patient characteristics (n = 250).

	%			
		Dependence type (past 12 months)		
	Total (n = 250)	**Alcohol (n = 188)**	**Cocaine heroin**	**(n=144)(n = 49)**
Male	66.0	66.5	70.1	69.4
Caucasian	56.8	60.1	49.3	57.1
Education <HS	15.2	14.4	18.1	20.1
Married	31.2	26.6	28.5	12.2
Prior-onset independent MDD	14.8	11.7	13.2	20.4
Independent MDD	31.2	33.5	28.5	28.6
Substance-induced MDD	24.0	22.3	22.2	36.7
Follow-up treatment at any point	54.0	55.9	64.6	63.3
Age: mean (SD)	36.88 (9.16)	37.16 (9.49)	35.23 (7.43)	33.67 (8.69)

HS: high school; MDD: major depressive disorder; SD: standard deviation.

Table 2

Type of major depression and time (number of weeks after hospital discharge) to substance outcome events.

		Hazards ratios (95% CI)[a] Type of major depression		
	%	Prior-onset Independent (n = 37)	Independent (n = 78)	Substance-induced (n = 62)
Alcohol-dependent patients (n = 188)[b]				
Time from discharge to 1st use of alcohol		0.83 (0.48–1.44)	**1.52 (1.02–2.26)** *	**4.66 (2.02–10.79)** **
Remission of dependence (26+ weeks)	71.8	1.12 (0.63–1.99)	0.76 (0.47–1.21)	0.40 (0.12–1.29)
Relapse to dependence (after 26-week remission)	31.1	1.04 (0.35–3.06)	**2.25(1.05–4.87)** *	–
Relapse to use (after 26-week remission)	46.0	2.01 (0.60–6.79)	1.26 (0.46–3.47)	–
Cocaine-dependent patients (n = 144)[c]				
Time from discharge to 1st use of cocaine		**2.10(1.16–3.75)** *	1.61 (0.96–2.71)	**5.30 (1.82–15.46)** **
Remission of dependence (26+ weeks)	74.3	**0.43 (0.22–0.85)** *	1.22 (0.70–2.11)	0.20 (0.03–1.47)
Relapse to dependence (after 26-week remission)	27.1	1.38 (0.40–4.68)	**2.66 (1.07–6.62)** *	–
Relapse to use (after 26-week remission)	34.6	1.61 (0.58–.46)	**3.01 (1.23–7.67)** **	–
Heroin-dependent patients (n = 49)[d]				
Time from discharge to 1st use of heroin		1.20 (0.51–2.81)	**2.56 (1.12–5.85)** *	**6.47 (1.58–26.56)** *
Remission of dependence (26+ weeks)	79.6	**0.27 (0.08–0.88)** *	0.81 (0.31–2.12)	**0.09 (0.01–0.77)** *
Relapse to dependence (after 26-week remission)	30.8	0.46 (0.11–3.72)	4.85 (0.83–28.53)	–
Relapse to use (after 26-week remission)	35.9	1.05 (0.23–.80)	3.46 (0.71–16.86)	–

[a] Hazard ratios derived from Cox proportional hazard models controlling for age, gender, education, race, other psychiatric disorders (panic, generalized anxiety, specific and social phobia, post-traumatic stress, antisocial personality) and any follow-up treatment.

[b] Controlling for baseline (past-month) cocaine and/or heroin dependence.

[c] Controlling for baseline (past-month) alcohol and/or heroin dependence.

[d] Controlling for baseline (past-month) alcohol and/or cocaine dependence. Hazard ratios <1.0 indicates decreased likelihood of the event (e.g. remission).

* $P < 0.05$

** $P < 0.01$. –: In models of relapse, we analyzed time-varying abstinence MDD only, as an episode of substance-induced MDD cannot begin during abstinence/remission. Remission is defined as 26+ consecutive weeks with no substance-specific dependence or abuse symptoms. Relapse could only occur after the 26th week of remission. Bold type indicates significant values. CI: confidence interval.