

# Effects of Major Depression on Remission and Relapse of Substance Dependence

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**Background:** The effects of major depressive disorder (MDD) on the course of substance dependence may differ depending on the temporal relationship of depression to dependence. We investigated the effects of MDD on the outcome of substance dependence under 3 circumstances: (1) lifetime onset of MDD prior to lifetime onset of dependence, (2) current MDD occurring during a period of abstinence, and (3) current MDD during substance use that exceeded the expected effects of intoxication or withdrawal.

**Methods:** A sample of 250 inpatients with DSM-IV cocaine, heroin, and/or alcohol dependence were followed up at 6, 12, and 18 months. The Psychiatric Research Interview for Substance and Mental Disorders (PRISM) was used to make DSM-IV diagnoses. Using Cox proportional hazards models, stable remissions (those lasting at least 26 weeks) from DSM-IV cocaine, heroin, and/or alcohol dependence and from use were studied, as well as subsequent relapses of dependence and use.

**Results:** Patients with current substance-induced MDD were less likely to remit from dependence (adjusted hazards ratio, 0.11) than patients with no baseline MDD. A history of MDD prior to lifetime onset of substance dependence also reduced the likelihood of remission relative to the absence of such a history (adjusted hazard ratio, 0.49). Major depressive disorder during sustained abstinence predicted dependence relapse (adjusted hazards ratio, 3.07) and substance use after hospital discharge compared with those without abstinence MDD (adjusted hazards ratio, 1.45).

**Conclusion:** The timing of depressive episodes relative to substance dependence served as an important factor in the remission and relapse of substance dependence and substance use.

*Arch Gen Psychiatry.* 2002;59:375-380

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**M**AJOR DEPRESSIVE disorder (MDD) is common among substance abusers<sup>1-5</sup> and associated with considerable psychosocial disability,<sup>6-8</sup> suggesting that MDD may impede long-term remission from drug and alcohol dependence. Diagnostic problems have complicated research in this area, with efforts to resolve them largely relying on the temporal sequencing of depressive symptoms relative to substance abuse. In DSM-IV,<sup>9</sup> major depression is "primary" if "not due to the physiological effects of a substance," a causal relationship inferred largely from timing. Primary MDD is diagnosed when symptoms precede substance use or persist during extended periods of abstinence. A DSM-IV substance-induced disorder is diagnosed when clinically significant symptoms co-occur with substance use but clearly exceed the expected effects of intoxication or withdrawal. Little prospective research is available on whether these

aspects of timing affect the course of substance dependence or whether primary episodes starting prior to the lifetime onset of substance use have different effects from primary episodes occurring during periods of abstinence.

Many studies on MDD among alcoholics or drug addicts investigated lifetime depression, regardless of its timing. Rounsaville et al<sup>10</sup> found that lifetime MDD predicted poor alcoholism outcome among males, while others<sup>11,12</sup> did not. Given the lack of specificity about timing in these studies, inconsistencies are not surprising. Prospective studies offer clearer information. Among opiate addicts, baseline current MDD predicted subsequent heroin<sup>13</sup> and cocaine use.<sup>14</sup> Among alcoholic subjects, baseline MDD predicted drinking relapse.<sup>15</sup>

The lifetime order of onset of 2 disorders is fixed when the second disorder begins. Thus, a lifetime diagnosis of primary MDD with onset prior to substance dependence does not necessarily indicate current depression. However, the remitting and

## SUBJECTS AND METHODS

### SUBJECTS

Subjects were inpatients in a dual-diagnosis facility who were not severely psychotic or medically ill. Of 379 patients invited to participate, 349 (92%) participated in a baseline evaluation. Of these, 279 patients were of interest to the present analysis because they had a current diagnosis at baseline of *DSM-IV* alcohol, cocaine, and/or heroin dependence and never experienced mania or nonaffective psychosis. Of these patients, 250 (90%) participated in at least 1 follow-up interview. These are the patients described herein. Subjects were not required to meet criteria for MDD because we wanted to compare patients with and without this disorder.

The mean  $\pm$  SD age of subjects was 36.9  $\pm$  9.2 years, 66% were male, 57% were white, 15% did not complete high school, and 31% were married. At baseline, 75% met *DSM-IV* criteria for alcohol dependence, 58% for cocaine dependence, and 20% for heroin dependence.

### PROCEDURES

Following institutional review board requirements, clinical staff identified eligible, sequentially admitted patients (who had completed acute withdrawal, if applicable) and obtained their agreement to meet with research staff, at which time the study was explained. Consenting subjects participated in a baseline Psychiatric Research Interview for Substance and Mental Disorders (PRISM).<sup>20,21</sup> In the PRISM, the drug and alcohol sections are completed before assessment of psychiatric disorders. A PRISM test-retest study using the version for *DSM-IV* substance use disorders and *DSM-III-R* psychiatric disorders showed higher reliability than other diagnostic interviews in this type of sample.<sup>20</sup> Lifetime onset of any disorder was defined as the age when the full disorder was first present. Age at lifetime onset of MDD was used to create a prior-onset MDD diagnosis, representing major depression with onset before the lifetime onset of alcohol, cocaine, or heroin dependence. As a lifetime diagnosis, prior-onset MDD was diagnosed regardless of current status.

In the PRISM, abstinence MDD either occurred entirely during abstinence, began at least 2 weeks prior to a period of heavy drinking and/or drug use, or began during drinking and/or heavy drug use and continued more than 4 weeks after the substance use ended. Some baseline episodes were diagnosed as abstinence MDD in subjects currently dependent on alcohol or drugs because the depressive episodes began before the current substance dependence episodes or continued into the follow-up at least 4 weeks after cessation of substance use.

Substance-induced disorders in *DSM-IV* occur during periods of heavy substance use with symptoms *in excess of* (greater than the expected effects of) intoxication or withdrawal syndromes. PRISM episodes of substance-induced MDD included those occurring entirely during periods of substance use as well as episodes ending within a month of abstinence. To systematize this diagnosis, we required the same duration and number of symptoms as required for *DSM-IV* primary MDD. To systematize rating symptoms in excess of expected intoxication or withdrawal effects, we used the subject's own substance-using but nondepressed experience as a reference period (most often, a period of substance use immediately preceding onset of depressed mood). Symptoms during this reference period represented the subject's expected intoxication or withdrawal effects. Symptoms that began or became clearly worse only after the onset of depressed mood were counted toward a diagnosis of substance-induced MDD. Only depressive symptoms cross-listed as *DSM-IV* intoxication or withdrawal symptoms for substances used by the patient were rated this way.

Subjects could report past episodes of both abstinence and substance-induced MDD. However, we studied MDD current at baseline to provide close, prospective examination of its relationship to the course of substance dependence.

Follow-up interviews were conducted 6, 12, and 18 months after baseline. Subjects were paid US \$35. Subjects not interviewed when due were interviewed later whenever possible. Median length of follow-up was 91 weeks. Bias from loss to follow-up was unlikely because of the high follow-up rate and lack of differences between subjects followed up and not followed up for age ( $t_{274}=0.29$ ,  $P=.77$ ); sex ( $\chi^2_1=.004$ ,  $P=.95$ ); race ( $\chi^2_1=.71$ ,  $P=.40$ ); education ( $\chi^2_2=3.52$ ,  $P=.17$ ); baseline diagnoses of *DSM-IV* cocaine ( $\chi^2_1=.55$ ,  $P=.46$ ), heroin ( $\chi^2_1=.27$ ,  $P=.60$ ), and alcohol

recurring nature of major depression is important to address in longitudinal research. Time-varying MDD predicted failure to remit from alcoholism and relapse.<sup>16-18</sup> This study did not differentiate primary and substance-induced MDD or separate prior-onset from abstinence primary depressions. Furthermore, the study did not include polysubstance abusers, whose switching of substances<sup>14</sup> during follow-up can produce an inaccurate impression of remission if only 1 substance is studied.

To address these issues, we studied the effects of MDD on substance dependence prospectively. Primary MDD beginning prior to the lifetime onset of substance dependence was not predicted to affect the outcome of current substance dependence because primary MDD usually occurs long in the past and also because of potential memory problems. Proximal abstinence and substance-induced MDD were predicted to impede remission from substance dependence. Abstinence MDD was predicted

to increase the chance of relapse into substance dependence when studied in time-varying fashion, since drinking to cope with negative emotions predicts onset of alcohol dependence.<sup>19</sup>

## RESULTS

### DEPRESSION DIAGNOSES

Of the 250 patients, 37 (15%) received a lifetime diagnosis of prior-onset MDD. At baseline, 18 (49%) of 37 patients with prior-onset MDD had current abstinence MDD, while 12 (32%) of 37 had current substance-induced MDD. Thus, most patients with prior-onset MDD had a current diagnosis of MDD. The average age at onset of prior-onset MDD was 16.7 years. Since the average age of the 37 patients with prior-onset MDD was 36.0 years, MDD first occurred on average 19.3 years previously.

dependence ( $\chi^2_1 = .038$ ,  $P = .85$ ); antisocial personality disorder ( $\chi^2_1 = 1.09$ ,  $P = .30$ ); prior-onset MDD ( $\chi^2_1 = .01$ ,  $P = .94$ ); baseline abstinence-induced MDD ( $\chi^2_1 = 1.14$ ,  $P = .29$ ); or baseline substance-induced MDD ( $\chi^2_1 = .65$ ,  $P = .42$ ).

At follow-up, subjects participated in a PRISM-L (longitudinal),<sup>21</sup> a version of the PRISM covering the period since the previous interview. The PRISM-L includes elements of the Longitudinal Interval Follow-up Evaluation<sup>22</sup> and also substance abuse timeline follow-back methods.<sup>23,24</sup> PRISM-L timeline grids allow rating the course of separate conditions (including substance use, dependence, and depression) by week after study entry. Interviewers obtain a history since the previous interview and then assess the timing of alcohol and drug use, dependence and abuse symptoms, and psychiatric syndromes, referring to the timing of life events as needed. When the relative timing of substance and psychiatric disorders was unclear, semistructured probes aided systematic exploration.

Interviewers had clinical experience and received extensive, systematic training. Two supervisors with several years of research experience conducted training and supervision. They reviewed each case, conferred occasionally with members of Columbia's Department of Psychiatry and conducted weekly interviewer calibration meetings. Supervisors occasionally blindly reviewed each other's cases to ensure review consistency. After data entry and cleaning, computer programs produced diagnoses as well as the follow-up onset and offset variables.

#### OUTCOME MEASURES USED IN THE ANALYSIS

*Remission of substance dependence* was defined as 26 or more weeks during follow-up with no symptoms of dependence on heroin, cocaine, or alcohol, a definition that guarded against substance substitution and provided periods with stability.<sup>16</sup> The start date of a remission was the first of the 26 or more required weeks. *Relapse* was defined as 1 or more weeks when patients experienced symptoms of DSM-IV dependence or abuse for alcohol, cocaine, or heroin dependence after the 26th week of remission from dependence.

We also investigated 3 outcomes defined by use. The first was remission for 26 or more weeks in any use of alcohol, cocaine, or heroin. The second included relapse from

such remission, meaning any use of alcohol, cocaine, or heroin any time after 26 weeks or more of remission. The third was time from discharge to first use of alcohol, cocaine, or heroin.

#### STATISTICAL ANALYSIS

Survival analysis was used to investigate these outcomes: weeks from hospital discharge to remission of dependence and remission of use as defined already, weeks from establishment of stable remission (ie, the 26th week of remission) to subsequent relapse into dependence and relapse into use, and weeks from inpatient discharge to first use of alcohol, cocaine, or heroin after discharge. The cumulative probabilities of remission and survival curves of relapse were obtained with Kaplan-Meier estimates. Cox proportional hazard models were used to examine the effect of time-invariant and time-varying predictors. Cases were censored if they did not experience an event by the end of the follow-up, including those lost to death or follow-up. Time-invariant predictors used in the Cox models included age, sex, race, education, baseline DSM-IV diagnoses of alcohol, cocaine, and heroin dependence, antisocial personality disorder with symptoms in the year prior to the interview, and prior-onset MDD. Note that prior-onset MDD was tested independently of current MDD status. Thus, it characterized an unchanging aspect of lifetime history, regardless of current status. The models compared the effects of prior-onset MDD to the absence of such a history.

Time-varying predictors indicated the effects of change in MDD on subsequent outcome of dependence. The 2 time-varying predictors were the status of substance-induced MDD (present or absent) and the status of abstinence MDD (present or absent). These 2 types of depression were mutually exclusive at any point in time and were examined separately to determine their unique effects on remission. The basis of comparison for each type of depression was the absence of depression. Only abstinence MDD was tested in relation to relapse, since substance-induced MDD could not start during remission. Tests were 2-tailed with  $\alpha = .05$ . Because time in a restrained environment is not remission, the follow-up period for the 138 patients hospitalized longer than a week after their baseline interview began the week of discharge.

Of the 213 patients with no lifetime diagnosis of prior-onset MDD, 60 (28%) had baseline diagnoses of abstinence MDD and 50 (24%) had current substance-induced MDD. Subjects with prior-onset MDD were more likely to have any current diagnosis of MDD at baseline than those without prior-onset MDD ( $\chi^2_1 = 4.41$ ,  $P = .04$ ) and also were more likely to have baseline abstinence MDD ( $\chi^2_1 = 6.16$ ,  $P = .01$ ). Those with and without prior-onset MDD did not differ on substance-induced MDD ( $\chi^2_1 = 1.36$ ,  $P = .24$ ). The Cox proportional hazards models (below) allowed us to study the effects of current depression controlling for prior-onset MDD.

#### REMISSION FROM DEPENDENCE

Among the 250 patients, 133 (53%) had a remission of all dependence symptoms lasting at least 26 weeks. **Figure 1** shows the Kaplan-Meier estimates of cumulative prob-

abilities of remission from dependence. The cumulative probability curve reached its plateau of 57.1% at week 100. Prior-onset MDD decreased the likelihood of stable remission from substance dependence compared with patients without such a history (**Table**). Time-varying substance-induced MDD decreased the likelihood of stable remission from substance dependence compared with subjects with no current MDD. Abstinence MDD was not related to remission of dependence.

#### REMISSION FROM USE

Among the 250 patients, 117 (47%) remitted from alcohol, cocaine, and/or heroin use for at least 26 consecutive weeks. Figure 1 shows the Kaplan-Meier estimates of cumulative probabilities of remission from use. The MDD diagnoses were not associated with time to remission in substance use (Table).

## RELAPSE INTO DEPENDENCE

Among the 133 patients who remitted from dependence, 45 relapsed during the follow-up, leaving only 88 (35%) of the 250 patients with dependence remission from all 3 substances throughout the follow-up. **Figure 2** shows the Kaplan-Meier estimates of survival probabilities of relapse into dependence. As shown in the Table, abstinence MDD increased the risk of relapse into dependence by a factor of about 3, thus constituting an important risk factor for dependence relapse.

## RELAPSE INTO USE

Among the 250 patients, 205 (82%) reported substance use after discharge. Of the 117 with remission of use lasting 26 weeks or more, 52 relapsed into use of alcohol, cocaine, and/or heroin, leaving only 65 (26%) of the 250 patients with stable remission from use lasting 26 weeks or more. Figure 2 shows the Kaplan-Meier estimates of cumulative probabilities of relapse into use. As shown in the Table, neither prior-onset MDD nor abstinence MDD was associated with relapse into use. However, abstinence MDD was related to risk of use after hospital discharge. **Figure 3** shows the Kaplan-Meier estimates of survival probabilities of substance use after hospital discharge.

### COMMENT

Under all 3 temporal circumstances studied, major depression was related to the course of substance dependence, including lifetime onset prior to substance de-

pendence, during periods of abstinence and periods of substance use when symptoms clearly exceeded the effects of intoxication and/or withdrawal. However, the effects of MDD were not uniform across the outcomes and circumstances. Prior-onset MDD was associated with reduced likelihood of remission of substance dependence, as was substance-induced MDD current at baseline. No depression variable was associated with stable remission in use. Abstinence MDD was associated with substance use after hospital discharge and relapse into dependence after a stable remission. Prior-onset MDD was not related to relapse.

The data support the DSM-IV primary and substance-induced distinctions as well as distinction between prior-onset and abstinence depressions because different types of depression were related to different aspects of outcome. While we did not predict the association of prior-onset MDD with remission from substance dependence because of its distal nature, prior-onset MDD reduced the likelihood of dependence remission even with current MDD in the model. As noted, prior-onset MDD began at about age 16 years. This early MDD may cause distinct psychosocial disability, contributing to difficulties in achieving remission from substance dependence. The time-varying course of substance-induced MDD also decreased the likelihood of dependence remission. Substance-induced MDD may place an additional proximal burden on individuals trying to recover from dependence that may interfere with activities or efforts needed to achieve sustained remission.

The effects of abstinence MDD on relapse might occur several ways. It may reduce energy needed to refrain from drug and/or alcohol use. Feeling worse during ab-

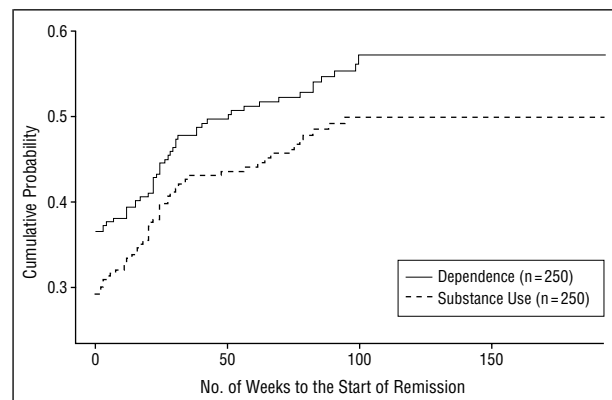


Figure 1. Time to remission, cumulative probabilities.

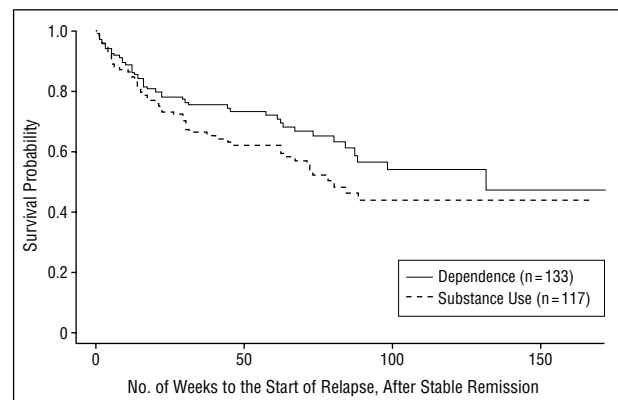


Figure 2. Relapse after stable remission, survival curves.

### Association of Major Depression With Time to Outcome of Substance Dependence or Use for 250 Patients\*

Outcome	Prior-Onset MDD (n = 37)	Abstinence MDD (n = 78)	Substance-Induced MDD (n = 62)
Remission of substance dependence ( $\geq 26$ wk)	0.49 (0.27-0.89)	0.96 (0.61-1.52)	0.11 (0.02-0.82)
Remission of substance use ( $\geq 26$ wk)	0.56 (0.31-1.03)	0.76 (0.46-1.25)	0.39 (0.12-1.24)
Relapse into dependence after remission	0.99 (0.32-3.07)	3.07 (1.28-7.32)	...
Relapse into use after remission	1.18 (0.43-3.21)	2.21 (0.90-5.42)	...
Time from hospital discharge to first use	1.37 (0.93-2.03)	1.45 (1.03-2.03)	...

\*All values are hazards ratio (95% confidence intervals) based on Cox proportional hazards model. The hazards ratio is derived from models that controlled for age, sex, education, race, type of baseline substance dependence, and antisocial personality disorder. MDD indicates major depressive disorder.

stinence than when using substances due to depression may reduce motivation to continue abstinence efforts. Depression may lead to self-medication.<sup>25,26</sup> Aspects of MDD may become conditioned cues for drug use, continuing to prompt drug cravings during abstinence.<sup>27</sup> Abstinence MDD may also reflect preexisting negative thinking that presents a common risk for depression and relapse. Consistent with this, antidepressants for depression during treatment for alcoholism<sup>28-32</sup> or drug addiction<sup>29,33</sup> improve depression and modestly improve substance abuse.

We analyzed abstinence and substance-induced MDD as separate variables, finding distinct effects. Combining them would have attenuated the ability to show an effect. This supports the utility of the *DSM-IV* primary vs substance-induced distinction. Our approach also supported differentiation between lifetime primary-onset and abstinence MDD. If these types of depression are truly different, combining them limits the ability to understand each one. Note that effects were found controlling for baseline dependence on all 3 substances, using an outcome defined by remission from all 3 substances. This eliminated questions about substance switching.

Several methodological limitations warrant comment. Our results were based on naturalistic findings in treated inpatients. To generalize the results, untreated subjects and different types of patients need to be studied. Also, this study did not include urine samples or informant reports. However, in the absence of sanctions, reports of drug use tend to be accurate.<sup>34</sup> Only a few patients reported sustained remission from alcohol and/or drug use without relapse, so the scope of disclosure suggests relatively accurate reporting. Finally, we analyzed remissions lasting at least 26 weeks because we wanted periods with stability. Analyzing longer remissions would require longer follow-ups.

Investigators differ on the best outcome indicators in substance abuse research. We separated remission from relapse to study whether their predictors differed. We also analyzed dependence and use separately. Individuals can stop manifesting dependence symptoms while decreasing but not ceasing use, as indicated by the proportion of untreated drinkers with past-only alcohol dependence.<sup>35</sup> However, in the clinical sphere, many think that a harm reduction strategy leaves patients vulnerable for relapse. Therefore, investigating predictors of sustained abstinence is important.

Difficulty diagnosing MDD in alcohol and drug patients has led to inconsistencies in the relationship of depression to substance outcome. This study presented evidence of differential effects of major depression occurring under different temporal relationships to substance dependence. Research on the reasons for differences in the effects (for example, effects of different levels or types of disability) may yield clinically useful information. We suggest that future studies on these issues be conducted.

Accepted for publication August 13, 2001.

The study was supported by grant R01 DA 08409 from the National Institute on Drug Abuse, Bethesda, Md, grant

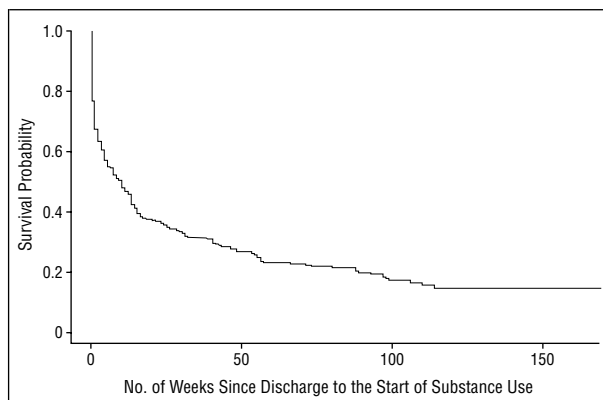


Figure 3. Time from discharge to substance use, survival curve.

AA K02 AA00151 from the National Institute on Alcohol Abuse and Alcoholism, Bethesda, and by the New York State Psychiatric Institute.

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