Independent Versus Substance-Induced Major Depressive Disorder in Substance-Dependent Patients: Observational Study of Course During Follow-Up

Edward V. Nunes, M.D.; Xinhua Liu, Ph.D.; Sharon Samet, M.S.W.; Karen Matseoane, B.A.; and Deborah Hasin, Ph.D.

Objective: Clinicians frequently encounter patients presenting with both depression and substance abuse, and their diagnosis has been a source of controversy. The authors examined whether baseline and past diagnoses of DSM-IV primary (independent) or substance-induced depression or other psychiatric syndromes predict 1-year course of depression in substance-dependent patients.

Method: Inpatients with current DSM-IV major depressive disorder (MDD) and DSM-IV alcohol, cocaine, or opiate dependence (N = 110) were evaluated with the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) and followed for 12 months after discharge. Logistic regression for repeated measures modeled the odds of MDD and depressed mood over time as a function of baseline diagnoses and past independent depression, controlling for demographics, substance use, and antidepressant treatment during the follow-up. Subject recruitment was conducted from July 25, 1995 to May 14, 1997.

Results: Over the 12 months, 88% of the patients experienced depressed mood for at least 1 week, and 57% experienced MDD. Depression during follow-up was equally likely among patients with current (baseline) DSM-IV independent or substance-induced MDD; in the latter group, past independent MDD increased the likelihood of MDD during the follow-up. Panic attacks, posttraumatic stress disorder (trend), borderline personality, and antisocial personality also significantly predicted depression during the follow-up.

Conclusions: In substance-dependent patients, both DSM-IV primary and substance-induced MDD predict future depression, warranting consideration for specific treatment. The data suggest the importance of a careful psychiatric history that includes attention to past episodes of independent depression as well as anxiety and cluster B personality syndromes.

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Corresponding author and reprints: Edward Nunes, M.D., 1051 Riverside Dr. (Unit 51), New York, NY 10032 (e-mail: nunesed@pi.cpmc.columbia.edu).

Clinicians frequently encounter patients presenting with both depression and substance use disorders. Such depression has adverse prognostic implications for the outcome of substance abuse[1] and may respond to specific antidepressant treatment.[2] However, clinicians must decide how to manage depression in substance-dependent patients and whether to initiate specific antidepressant treatment, and diagnostic problems have hindered progress in the development of treatment guidelines. In the pre–DSM-IV era, depression among substance-dependent patients was shown to be common but often transient,[3–6] quite likely representing substance intoxication or withdrawal effects, and reliability and validity of the older diagnostic methods among substance abusers was poor.[7–13]

DSM-IV sought to improve diagnostic methods by defining primary (or independent) major depressive disorder (MDD), which begins prior to the onset of substance dependence or occurs during extended abstinence, and substance-induced depression, which occurs only during substance use but exceeds the expected effects of intoxication or withdrawal and "warrants clinical attention."[14(p371)] The substance-induced category marks recognition that depressive syndromes in active substance abusers may have prognostic implications and warrant specific treatment. However, to date, the predictive validity of these new categories has received little study. Further, the DSM-IV criteria for substance-induced mood disorders, particularly regarding what constitutes symptoms

in excess of those expected from substance intoxication or withdrawal, are not explicit, which would work against reliability and validity unless more specific criteria are operationalized.

We therefore developed the Psychiatric Research Interview for Substance and Mental Disorders (PRISM)[7,15] to diagnose psychiatric disorders in heavy users of alcohol or drugs. Using the PRISM, both independent (primary) and substance-induced depression have shown good to excellent test-retest reliability,[7,16] and both syndromes had adverse effects on the course of substance dependence during an 18-month follow-up.[17] We now address the question of most immediate concern to clinicians, namely whether a baseline diagnosis of independent or substance-induced depression predicts the future course of depression and should influence treatment decisions. Hospitalized substance-dependent patients with independent or substance-induced MDD diagnosed with the PRISM were followed for 1 year after discharge. It was predicted that DSM-IV independent MDD at baseline would predict greater likelihood of depression over the follow-up than baseline substance-induced depression. Other commonly co-occurring syndromes (panic attacks, posttraumatic stress disorder, and antisocial and borderline personality) were also predicted to impact adversely on the course of depression.

METHOD

Participants

Subjects were recruited from July 25, 1995 to May 14, 1997, as described previously,[17] during an index hospitalization in a short-stay psychiatric unit specializing in patients with co-occurring substance use and psychiatric problems, situated within a private community-based psychiatric hospital. The hospital draws patients from a broad geographic region including the greater New York metropolitan area and Long Island, and patients are discharged to outpatient treatment in their local communities. The study was approved by the institutional review boards of New York State Psychiatric Institute and the hospital where the study took place; all subjects gave written informed consent. Of 379 patients asked 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 (i.e., bipolar I disorder) or nonaffective psychosis, and 250 participated in at least 1 follow-up interview. Out of this main sample, 110 patients (44%) had a current diagnosis of DSM-IV MDD and were the focus of the present report.

Procedures

Consecutively admitted, consenting patients were interviewed on the inpatient unit with the PRISM. Follow-up interviews were conducted approximately 6, 12, and 18 months after baseline. This was an observational study, and no control was exerted on the treatment received, although treatment was documented and covaried in analyses. Among the sample of 110 patients, 98% were successfully followed up at 6 months, and 88% at 1 year. The present analyses were restricted to the first year of follow-up, as data from this period were most complete. Interviewers had prior clinical experience, completed structured training, and participated in ongoing supervision conducted by experienced research supervisors who reviewed each case and conducted weekly interviewer meetings for case review and calibration to avoid interviewer drift.

Measures

The PRISM is a semistructured interview designed to address the poor reliability and validity found for psychiatric diagnosis among substance abusers.[9,10,12] The DSM-IV version of the PRISM showed good to excellent test-retest reliability for diagnoses relevant to this report, including primary (independent) and substance-induced MDD kappas ranging from 0.66 to 0.75, and kappas ranging from 0.50 to 0.69 for the other clinical conditions reported later.[7] In DSM-IV, criteria to distinguish between independent and substance-induced disorders are worded in a general fashion, particularly regarding what constitutes effects in excess of those expected from substance intoxication or withdrawal. Leaving this to interviewer judgment without more explicit criteria is likely to work against both reliability and validity. Therefore, the PRISM guides the interviewer in determining whether a current depressive episode is considered primary (independent) or substance-induced.

Independent MDD either antedates the current period of heavy substance use or persists throughout periods of abstinence lasting at least 4 weeks. Patients without such periods are evaluated for substance-induced MDD, in which each depressive criterion or symptom contributing to the diagnosis must exceed what would be the expected toxic or withdrawal effects of the substance(s) involved, based on the relevant DSM-IV criteria for intoxication and withdrawal. Only symptoms exceeding this threshold are counted toward a syndromal diagnosis. For symptoms occurring only in the context of depressed mood and active substance use, interviewers determine if the symptom occurred at a similar level during substance use but prior to the onset of depressed mood. If so, this suggests substance toxicity rather than a component of depression, and the symptom is not counted toward a diagnosis.

The PRISM also elicits past episodes of DSM-IV independent MDD. For the purposes of analysis, these were coded as "prior-onset MDD," defined as independent depressive disorder with initial onset predating the onset of alcohol, heroin, or cocaine abuse or dependence, or "past

independent MDD," defined as an episode of MDD that emerged or persisted during at least 4 weeks of abstinence. The purpose was to examine the independent contributions of these historical features to prognosis.

Follow-up interviews were conducted with the PRISM-L (longitudinal version), which establishes the presence or absence of substance use, substance dependence, subsyndromal depressed mood (i.e., the depressed mood criterion for MDD), MDD, and treatment, including antidepressant medication, on a weekly basis since the previous assessment. This involved charting a week-by-week timeline using memory aids like those used in other timeline-type measures.[18,19] Episodes of MDD during the 52-week follow-up were rated as independent or substance-induced by examining the onset and offset of episodes of MDD in relation to onset and offset of substance use and abstinence using the same PRISM procedures as described for the baseline assessment.

Data Analysis

Likelihood of major depressive episodes during the 1 year of follow-up (independent only, substance-induced only, both, or neither) by baseline depression diagnosis (independent or substance-induced) was tested initially with a 2×4 χ^2 test. Then, generalized estimating equations (GEE) applied to logistic regression analyses with repeated measures[20] were used to estimate the odds of MDD (model 1), or depressed mood (model 2), over each of the 52 weeks of follow-up. This statistical method addresses within-subject correlations of the repeated outcome measures, uses all available data, is robust to the specification of the within-subject correlation structure, and admits time-dependent covariates. The effects of the predictors are presented as odds ratios and 95% confidence intervals. Using the same methods, the persistence of subsyndromal depressed mood was also examined as an outcome, because it may have adverse prognostic effects on a continuum with the adverse prognostic effects of full depressive syndromes.[21]

Predictors included time (weeks postdischarge), psychiatric syndromes current at baseline (current MDD classified as current independent [C-IND-MDD] or current substance-induced [C-SI-MDD], panic attacks, posttraumatic stress disorder [PTSD], borderline personality disorder, and antisocial personality disorder), lifetime prior-onset MDD, and past independent MDD (P-IND-MDD). To examine the prognostic implications of different patterns in the history of current and past depression, 4 categories were created to represent the combinations of current and past depression: current independent MDD with past independent MDD (C-IND-MDD with P-IND-MDD); current independent MDD without past independent MDD (C-IND-MDD without P-IND-MDD); current substance-induced MDD with past independent MDD (C-SI-MDD with P-IND-MDD); and current substance-induced MDD without past independent MDD (C-SI-MDD without P-IND-MDD), which was used as the reference group.

To examine whether the probability of depression differed over time by the presence or absence of the psychiatric predictors, interactions of time by each predictor were tested individually. Only significant interactions were retained in the final model. Panic attacks were examined rather than panic disorder because the latter was too rare to serve as a predictor with the sample size available. Age, gender, and race (white vs. nonwhite) were entered as control variables, as were time-dependent covariates: weekly presence/absence of antidepressant medication treatment and weekly presence/absence of clinically significant substance use. We included the latter to control for toxic or withdrawal effects of substances. Significance was set at $p = .05$ (trend, $p = .10$).

RESULTS

Sample Characteristics

Of the 110 patients with a DSM-IV diagnosis of current MDD at baseline, 48 (44%) were female; 66 (60%) were Caucasian, 28 (25%) African American and 14 (13%) Hispanic; 33 (30%) were married; 48 (44%) were employed or in school full time; and 67 (61%) had completed at least some college. The mean age of subjects was 37.1 years (SD = 9.1). Eighty-eight subjects (80%) met DSM-IV criteria for current alcohol dependence; 60 (55%), for cocaine dependence; and 22 (20%), for heroin dependence.

Fifty-four (49%) of the subjects were diagnosed as having current independent MDD (C-IND-MDD) and the remaining 56 (51%) were diagnosed as having current substance-induced MDD (C-SI-MDD). The mean number of MDD symptom criteria met was 7.1 (SD = 1.3). Thirteen (12%) of the patients also had a lifetime diagnosis of prior-onset MDD and 24 (22%) had past independent MDD (P-IND-MDD). Additional psychiatric syndromes were common, with 44 (40%) meeting DSM-IV criteria for PTSD; 12 (11%), for panic attacks; 14 (13%), for antisocial personality disorder; and 20 (18%), for borderline personality disorder.

One-Year Course of Depression in Relation to Substance Use

During the 12-month follow-up, 57.3% (63/110) met DSM-IV criteria for MDD (≥ 2 consecutive weeks meeting syndromal criteria); among these patients, the mean number of weeks spent in a major depressive episode was 25.6 (SD = 15.3). Persistent depressed mood most of the time for at least a week was experienced by most of the patients (88.2%, 97/110) with a mean number of weeks with persistent depressed mood of 29.6 (SD = 20.0). Substance use and dependence was found in about half the sample during the follow-up: 58.2% (64/110) used sub-

Table 1. Prevalence and Classification (independent vs. substance-induced) of DSM-IV MDD During the 52-Week Follow-Up Period as a Function of Classification of MDD Diagnosed With a PRISM Interview at Baseline Evaluation During an Index Hospitalization[a]

	MDD Diagnosis at Baseline	
MDD During 52-Week Follow-Up[b]	DSM-IV Independent (N = 54) N (%)	DSM-IV Substance-Induced (N = 56) N (%)
None	21 (38.9)	26 (46.4)
Independent	25 (46.3)	18 (32.1)
Substance-induced	5 (9.3)	8 (14.3)
Both independent and substance-induced	3 (5.6)	4 (7.1)

[a] $\chi^2 = 2.49$, df = 3, p = .48.
[b] MDD and substance abuse determined on a weekly basis during 52-week follow-up with the PRISM-L; MDD was classified as "independent" if an episode occurred during more than 4 consecutive weeks of no substance abuse and as "substance-induced" otherwise. Among patients with more than 1 episode of depression, each episode was classified separately.
Abbreviations: MDD = major depressive disorder, PRISM-L = Psychiatric Research Interview for Substance and Mental Disorders–Longitudinal version.

stances during at least 1 week (mean ± SD = 16.7 ± 14.1 weeks), and 48.2% (53/110) met criteria for substance dependence (mean ± SD = 10.9 ± 15.1 weeks).

As can be seen in Table 1, the prevalence and classification of MDD during the follow-up (i.e., no MDD, independent MDD, substance-induced MDD, or both independent and substance-induced MDD) did not differ between patients with independent vs. substance-induced MDD at baseline. Generally, patients with MDD during the follow-up had independent MDD, regardless of baseline diagnosis, and patients with substance-induced MDD at baseline tended to be recategorized to independent MDD.

Most patients (77.3%, 85/110) received treatment with an antidepressant during the follow-up. The treated patients received a median of 2 trials of different medications (range, 1–5). Selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline, and fluvoxamine) accounted for most trials (81 out of a total of 152, or 53.3%), followed by trazodone (25 trials), other new-generation agents (bupropion and venlafaxine, 10 trials each), tricyclics (17 trials), and others (9 trials). The mean number of weeks on antidepressant medication among the treated patients was 34.7 (SD = 18.1).

Table 2 presents the models predicting MDD (Model 1) and persistent depressed mood (Model 2) over the 52 weeks of follow-up. In Model 1, compared with the reference group with current substance-induced MDD without past independent MDD (C-SI-MDD without P-IND-MDD), current independent MDD (C-IND-MDD) did not affect the odds of follow-up MDD (with or without P-IND-MDD). In contrast, a history of past independent with current substance-induced MDD (C-SI-MDD with P-IND-MDD) significantly increased the odds of follow-up MDD. Figure 1 shows plots of the raw proportions of patients with MDD over each week of the 52 weeks of follow-up for each of the diagnostic subgroups, illustrating the increased rate of MDD in the C-SI-MDD with P-IND-MDD group compared with the other groups. In Model 1, panic attacks at baseline also increased the odds of follow-up MDD, with a trend in the same direction for borderline personality disorder. There was a main effect of time on MDD, indicating that the odds of MDD diminished over the 12 months. Antisocial personality disorder interacted with time at follow-up, indicating that patients with antisocial personality disorder became more likely to have MDD over time in the follow-up, compared with those without antisocial personality disorder.

In Model 2, compared with the reference group (C-SI-MDD without P-IND-MDD), C-IND-MDD without P-IND-MDD did not affect the odds of follow-up depressed mood, but a history of P-IND-MDD significantly increased the odds of depressed mood during the follow-up among patients with C-IND-MDD and of those with C-SI-MDD at a trend level. There were similar main effects of time, panic attacks, and borderline personality disorder, and a trend for PTSD to increase the odds of follow-up depressed mood as well. Time-varying substance use also increased the odds of depressed mood during the follow-up.

DISCUSSION

In this sample of substance-dependent patients with DSM-IV independent or substance-induced MDD diagnosed at an index hospitalization by PRISM interview, depression was prevalent during the 12 months after hospital discharge and manifested mostly as independent depression (i.e., emerged or persisted during at least 4 consecutive weeks of abstinence), regardless of whether the baseline diagnosis was independent or substance-induced depression. Thus, substance-induced MDD tended to be recategorized to independent MDD over the long run. Logistic regression modeling showed that in the absence of a past independent episode of MDD, MDD over the 12 months after hospital discharge was about equally likely among patients with baseline independent or substance-induced MDD. However, a past episode of independent MDD increased the risk of MDD during the follow-up when depression at baseline was classified as substance-induced and increased the risk of depressed mood when depression at baseline was classified as independent or substance-induced. The findings suggest that both independent and substance-induced MDD have important prognostic implications in predicting the future course of depression among substance-dependent patients.

Surprisingly little study of the predictive validity of independent vs. substance-induced depression has taken place in the DSM-IV era. We had predicted that substance-

Table 2. Baseline and Follow-Up Predictors of MDD (Model 1) and Depressed Mood (Model 2) Over 12 Months in Patients (N = 110) With Substance Dependence and MDD at Baseline Inpatient Evaluation

Predictors	Model 1: MDD Odds Ratio (95% CI)[a]	Model 2: Depressed Mood Odds Ratio (95% CI)[b]
Baseline and prior		
Lifetime prior-onset MDD	1.21 (0.38 to 3.88)	0.47 (0.15 to 1.48)
Panic attacks	5.71 (1.90 to 17.22)**	3.62 (1.19 to 11.06)*
Posttraumatic stress disorder	1.52 (0.69 to 3.32)	1.91 (0.94 to 3.83)†
Borderline personality disorder	2.86 (1.01 to 8.11)†	3.88 (1.39 to 10.86)**
Antisocial personality disorder	1.47 (0.47 to 4.58)	1.43 (0.46 to 4.46)
Baseline current MDD interacting with past MDD		
C-IND-MDD with P-IND-MDD	0.51 (0.16 to 1.66)	4.97 (1.06 to 23.18)*
C-IND-MDD without P-IND-MDD	0.95 (0.37 to 2.45)	1.50 (0.66 to 3.41)
C-SI-MDD with P-IND-MDD	3.25 (1.08 to 9.79)*	3.00 (0.98 to 9.18)†
C-SI-MDD without P-IND-MDD (reference group)	1.00	1.00
Follow-up		
Time, wk	0.98 (0.97 to 0.99)**	0.97 (0.96 to 0.98)***
Time by antisocial personality disorder	1.04 (1.01 to 1.06)**	1.01 (0.98 to 1.05)
Substance use during follow-up	1.43 (0.94 to 2.19)	1.63 (1.17 to 2.27)**
Antidepressant treatment during follow-up	1.37 (0.78 to 2.42)	1.24 (0.85 to 1.80)

[a]Odds ratios (95% confidence intervals) were derived from repeated-measures logistic regression models using GEE estimation, MDD (yes/no) during each week of follow-up as outcome, controlling for age, gender, and race.
[b]Odds ratios (95% confidence intervals) were derived from repeated-measures logistic regression models using GEE estimation, persistent depressed mood (yes/no) during each week of follow-up as outcome, controlling for age, gender, and race.
†p < .10; *p < .05; **p < .01; ***p < .001.
Abbreviations: C-IND-MDD = current (baseline) independent MDD, C-SI-MDD = current (baseline) substance-induced MDD, GEE = generalized estimating equations, MDD = major depressive disorder, P-IND-MDD = past independent MDD.

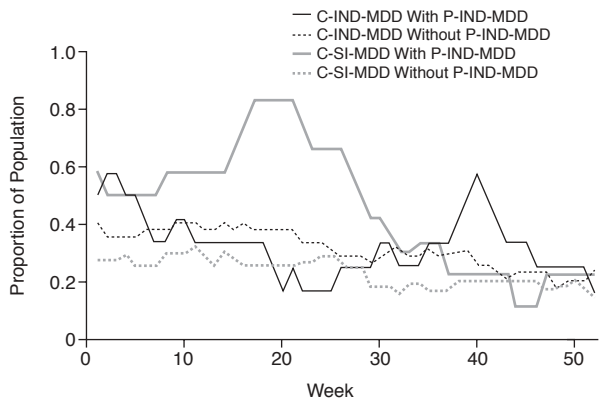
induced MDD would be associated with a lower likelihood of depression during follow-up on the basis of pre-DSM-IV studies.[3–6] While some more recent studies suggest that substance-induced depression is less associated than independent depression with family history of mood disorder, suicide attempts,[22] and depressogenic cognitions and coping styles,[23] other studies also reflect seriousness of substance-induced MDD by showing that substance-induced depressions are significantly associated with suicidality.[24–26] A recent study using the Structured Clinical Interview for DSM-IV (SCID; modified to resemble the PRISM for better specificity) also found that many DSM-IV substance-induced depressions were recategorized to independent MDD over a 1-year follow-up and that this recategorization was predicted by a history of an independent depression.[27] The PRISM operationalizes DSM-IV substance-induced depression by requiring that full criteria for MDD be met and, further, that each symptom contributing to the diagnosis exceeds what would be expected from the toxic or withdrawal effects of the particular substances a given patient is using. Thus, the PRISM criteria for substance-induced depression are clear and stringent. The findings suggest the approach of the PRISM fulfills the intent of DSM-IV that substance-induced depression represents a clinically significant syndrome, in excess of expected effects of substances, and calls for clinical attention.

Panic attacks, PTSD, and cluster B personality syndromes at baseline predicted MDD and/or depressed mood during follow-up. We previously suggested that other co-occurring psychiatric syndromes might be important in the evaluation of depression among substance-dependent patients.[8,28] Such syndromes may serve as markers of clinically significant psychopathology in substance-dependent patients. Panic attacks and PTSD are distinctive anxiety syndromes that also respond to antidepressant medications, suggesting shared pathophysiologic mechanisms with depression.[29,30] Borderline and antisocial personality disorders both involve affective dysregulation and are associated with elevated rates of depression and suicide risk.[31,32] These co-occurring disorders might suggest distinct treatment implications, e.g., evidence-based cognitive-behavioral interventions for panic disorder,[33] PTSD,[34] and borderline personality[35] and antidepressants[36] or mood stabilizer medications[37–39] for the impulsivity and irritability associated with borderline and antisocial personality.

Limitations

Since the sample was drawn from an inpatient unit, it represents patients with relatively severe psychiatric and substance use disorders. Future research is needed to determine whether the findings generalize to other common treatment settings such as outpatient programs or to untreated individuals. Also, our choice of predictors was limited to syndromes measured by the PRISM that occurred with sufficient prevalence to be useful as predictors. Future studies with larger samples should examine

Figure 1. Prevalence of Major Depressive Disorder (MDD) in Patients With Independent Versus Substance-Induced MDD During Follow-Up[a]



[a]Proportion of patients with major depressive disorder (MDD) over 52 weeks after hospital discharge for 4 diagnostic subgroups: current independent MDD with past independent MDD (C-IND-MDD with P-IND-MDD); current independent MDD without past independent MDD (C-IND-MDD without P-IND-MDD); current substance-induced MDD with past independent MDD (C-SI-MDD with P-IND-MDD); and current substance-induced MDD without past independent MDD (C-SI-MDD without P-IND-MDD).

a broader array of predictors, including nicotine use/dependence, and a broader array of other Axis I disorders and personality disorders.

The data are observational, and thus direct control was not exerted over treatment or substance use during the follow-up period, either of which could influence the course of depression. Our statistical control for these factors suggests that the effects of diagnostic predictors on depression outcome were not explained by differing levels of ongoing substance use or of postdischarge treatment for depression. As would be expected, substance use during the follow-up period increased the likelihood of depressed mood but fell short of significance in predicting MDD. The lack of association of antidepressant treatment with reduced depression could indicate poor compliance, which has been observed in clinical trials in such populations,[40] inadequate dosing, or greater likelihood of receiving medication among more chronic, treatment-resistant patients. Further, serotonin reuptake inhibitors, the most common type of medication given to this sample, have unclear efficacy among substance-dependent patients with some clinical trials showing medication superior to placebo[41,42] but more of the trials showing no advantage of medication over placebo.[40,43–46]

Implications

Clinicians need guidelines for evaluating depression among substance-dependent patients and deciding when to initiate antidepressant treatment. By showing that both independent and substance-induced MDD, as operationalized by the PRISM, predict a similar likelihood of future depression, and that such depression usually presents as independent of substance use during follow-up, the present data suggest that both syndromes should be taken seriously when diagnosed at baseline evaluation. The finding that a history of episodes of independent MDD predicts increased likelihood of future depression among patients with substance-induced MDD further suggests the utility of the DSM-IV typology and the importance of a thorough lifetime history in the evaluation of patients presenting with both substance abuse and depression.

The term *substance-induced* may actually be somewhat misleading, since the term suggests depressive symptoms caused by substance use. This probably reflects a common clinical concept of the term. However, such a concept is more consistent with what DSM-IV would call "expected effects" of substances (that do not contribute to a diagnosis of mood disorder), as opposed to the DSM-IV requirement that symptoms of substance-induced depression be "in excess of expected effects of substances." The findings also suggest the importance of attention in the psychiatric evaluation to a history of anxiety disorders and borderline and antisocial personality disorders, since these increased the risk of depression over the long term and may suggest distinct treatment strategies. Future research should include clinical trials to directly examine the treatment implications of DSM-IV primary and substance-induced depression and co-occurring anxiety and personality disorders among substance-dependent patients.

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), trazodone (Desyrel and others), venlafaxine (Effexor and others).

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