

# Differences Between Early-Phase Primary Psychotic Disorders With Concurrent Substance Use and Substance-Induced Psychoses

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**Context:** The distinction between a substance-induced psychosis and a primary psychotic disorder that co-occurs with the use of alcohol or other drugs is critical for understanding illness course and planning appropriate treatment, yet there has been little study and evaluation of the differences between these 2 diagnostic groups.

**Objective:** To identify key demographic, family, and clinical differences in substance-induced psychosis and primary psychotic disorders diagnosed according to DSM-IV criteria using a research diagnostic instrument for psychiatric and substance use comorbidity.

**Design:** Data on demographic, family, and clinical factors were gathered at baseline as part of a 3-year longitudinal study of early-phase psychosis and substance use comorbidity in New York, NY.

**Setting:** Psychiatric emergency department admissions.

**Participants:** The study is based on a referred sample of 400 subjects interviewed at baseline. Participants had at least 1 psychotic symptom assessed during administration of the research protocol, had used alcohol and/or other drugs within the past 30 days, and had no psychiatric inpatient history before the past 6 months. Subject

race included 43.5% black, 42.0% Hispanic, and 14.5% white or other.

**Main Outcome Measure:** Psychotic disorders defined by the DSM-IV.

**Results:** Overall, 169 (44%) were diagnosed as having substance-induced psychosis and 217 (56%), as having primary psychosis. Significant differences were observed in all 3 domains. Multivariate analysis using logistic regression identified the following 3 key predictors as being greater in the substance-induced group: parental substance abuse (odds ratio [OR], 1.69; 95% confidence interval [CI], 1.00-2.85), a diagnosis of dependence on any drug (OR, 9.41; 95% CI, 5.26-16.85), and visual hallucinations (OR, 2.13; 95% CI, 1.10-4.13). The key predictor of total positive and negative symptom score was greater in the primary psychosis group (OR, 0.96; 95% CI, 0.94-0.97).

**Conclusions:** Differences in demographic, family, and clinical domains confirm substance-induced and primary psychotic disorders as distinct entities. Key predictors could help emergency clinicians to correctly classify early-phase psychotic disorders that co-occur with substance use.

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**T**HE DISTINCTION BETWEEN A substance-induced psychosis and a primary psychotic disorder that co-occurs with the use of alcohol or other drugs is critical for understanding illness course and planning appropriate treatment, particularly when the psychotic disorder is of recent onset. Substances with psychotomimetic properties, such as alcohol,<sup>1</sup> cocaine,<sup>2-4</sup> amphetamine,<sup>5-7</sup> hallucinogens,<sup>8-10</sup> and cannabis,<sup>11-13</sup> are widespread, and their use or abuse can provoke psychotic reactions requiring crisis treatment in people otherwise free of serious mental illness.

The association between substance use and psychotic symptoms, however, is not simply due to substance-induced psychosis. The rate of substance abuse among people with severe mental illness far exceeds that in the general population,<sup>14-17</sup> even at the first onset of psychosis.<sup>18</sup> In persons with mental illness and at risk for mental illness, substance abuse is associated with a host of negative outcomes.<sup>19-25</sup> Although the rate of psychosis among people with a substance use disorder is not known, clinical reports suggest that substance-induced psychoses can also be chronic and disabling.<sup>7,26,27</sup>

The co-occurrence of psychosis and substance use is challenging diagnostically because people with primary psychotic disorders often present for treatment with signs and symptoms similar to those whose psychosis resulted from the use of substances alone.<sup>28</sup> An accurate diagnosis is a critical objective in treatment settings, because an error in diagnosis carries the risk of medical mismanagement. Despite the clinical significance of this issue, there has been surprisingly little study and evaluation of the differences between primary and substance-induced psychotic disorders.

This article is the initial report of a 3-year longitudinal study of 400 subjects with early-phase psychosis and concurrent substance use. Findings reported herein are from the baseline assessment. The aims of this aspect of the investigation were (1) to diagnose emergency department admissions with psychotic symptoms of recent onset and concurrent substance use according to *DSM-IV* criteria using a research diagnostic assessment for psychiatric and substance use comorbidity; (2) to determine whether there are differences in demographic, family, and clinical characteristics among those with a diagnosis of substance-induced psychosis compared with those with a diagnosis of primary psychotic disorder and concurrent substance use; and (3) to identify key predictors that could help emergency clinicians to correctly classify early-phase psychotic disorders that co-occur with substance use.

## METHODS

This study sought to identify subjects experiencing psychosis in an early phase. We followed the precedent established in previous research on early psychosis<sup>29</sup> by excluding those whose first hospitalization for psychosis occurred more than 6 months before the current admission. Moreover, we did not include individuals who had experienced an extended period of continuous psychotic symptoms in the absence of previous treatment. The Pearson product moment correlation between the age of onset of the first psychotic symptom and the age at the current admission was 0.85.

Study subjects were recruited from 5 psychiatric emergency departments serving approximately 900 000 residents of upper Manhattan in New York, NY. Many neighborhoods in this region have a low average income and high percentages of ethnic minorities. Subjects were typically identified during a crisis admission in the psychiatric emergency department and recruited for the study when they were clinically stable and able to give voluntary informed consent. For about three quarters of study subjects, this occurred after transfer to an inpatient service. Those treated in the emergency department and released to the community gave written informed consent before their discharge and were interviewed in their homes or in project offices shortly thereafter. Study subjects were English or Spanish speaking, were aged 17 to 45 years, had at least 1 psychotic symptom assessed during administration of the research protocol, and had used alcohol and/or other drugs within the past 30 days. Cases with delirium were not included in the study sample. In the few cases ( $n=6$ ) where the presence of a psychotic symptom was questionable, diagnosis-relevant data were reviewed by a senior research psychiatrist working with the research team who made the final determination.

All subjects meeting these criteria were considered for inclusion in the study. A total of 499 subjects were approached. Of

these, 38 refused, 58 initially agreed to be interviewed but could not be located after discharge, 2 were dropped from consideration because of dangerous behavior, and 1 died. Four hundred subjects consented to the study and were interviewed at baseline. This report is based on findings from interviews with these 400 subjects. The research protocol was approved by the institutional review boards of the New York State Psychiatric Institute/Columbia University Medical Center, New York, and the other institutions from which study subjects were recruited.

## RESEARCH DIAGNOSTIC ASSESSMENTS

Research diagnoses were made using the Psychiatric Research Interview for Substance and Mental Disorders (PRISM),<sup>30</sup> which was developed to assess psychiatric and substance use comorbidity using *DSM-IV* criteria.<sup>31</sup> In the *DSM-IV*, a psychotic symptom must be persistent or repetitive and not an isolated experience. A primary diagnosis of psychosis is given only if there is no evidence of heavy substance use or withdrawal, if the full psychiatric syndrome is established before heavy substance use, or if the syndrome persists more than 4 weeks after the cessation of acute intoxication or withdrawal. In contrast, a substance-induced psychotic diagnosis is given for disorders occurring only during periods of heavy substance use or soon thereafter. During these periods, the psychotic symptoms must exceed the expected effects of intoxication or withdrawal and be sufficiently severe to warrant independent clinical attention. The *DSM-IV* lists the expected intoxication and withdrawal symptoms for each class of drug. For substance-induced psychotic disorders, the *DSM-IV* does not include minimum duration or symptom requirements as it does for a primary psychotic disorder.

In its implementation of *DSM-IV* criteria for psychotic disorders, the PRISM positions the substance use, abuse, and dependence sections before the other diagnostic sections so that the interviewer will already have ascertained the history of substance use when assessing primary and substance-induced psychiatric episodes. The substance abuse and dependence items assess criteria that are phenomenologically distinct from the psychotic items in later sections, so content on abuse and dependence is not relevant to psychotic symptomatology and not used in rating the psychotic items. However, the probing on substance use necessary to rate abuse and dependence items often reveals additional information about substance use history that is highly relevant to informed ratings of the later items on psychosis that pertain to the primary/substance-induced distinction.

In the psychotic module of the PRISM, primary and substance-induced psychotic disorders are differentiated according to the following guidelines. A diagnosis of primary psychosis (eg, independent of substance use) is assigned when there is no evidence of heavy substance use or withdrawal; when psychotic symptoms persisted for at least 4 weeks in the absence of heavy substance use; or when psychotic symptoms preceded onset of heavy use. For a substance-induced psychotic diagnosis, the following 2 criteria must be met: a primary psychotic episode has been ruled out owing to the absence of a substance-free period; and the psychotic symptoms must be in excess of the expected effects of intoxication or withdrawal. This follows *DSM-IV* criteria exactly. However, to increase reliability, the expected effects of intoxication or withdrawal are listed in detail in the PRISM for the interviewer to reference while making the ratings. A further unique PRISM specification to improve the diagnostic reliability of substance-induced psychotic disorders is that they must meet the symptom and duration requirements given for one of the primary *DSM-IV* psychotic diagnoses. In other words, although a full psychotic episode exists that meets *DSM-IV* criteria for a psychotic disorder (ie, schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or

psychotic disorder not otherwise specified), it cannot be diagnosed as primary because it occurs entirely during a period of substantial substance use.

The PRISM interview was administered in 1 to 2 sessions that took place as soon as subjects were clinically stable enough to participate. The multiple data sources for the PRISM included subject self-reports obtained during the interview, observations and diagnostic assessments of clinical staff, hospital medical charts, family/collateral reports of patterns of substance use and onset of psychosis, and results of urine toxicologic screens conducted routinely on all emergency department admissions. The PRISM diagnoses incorporated retrospective subject self-report data and retrospective collateral data collected during a period lasting from several days to 5 weeks. Symptoms and substance use were considered present when indicated by 1 or more of these data sources. If any source indicated that psychotic symptoms antedated heavy substance use or persisted during at least 4 weeks of abstinence, the PRISM assigned a primary diagnosis.

The DSM-III-R PRISM has shown good to excellent test-retest reliability across a variety of diagnoses in a substance-abusing patient sample, including current and lifetime psychotic symptoms ( $\kappa=0.63$  and  $\kappa=0.79$ , respectively).<sup>30</sup> Reliability for diagnoses relevant to this report (DSM-IV PRISM) was good to excellent for current and lifetime primary and substance-induced psychosis and schizophrenia ( $\kappa=0.59-0.86$ ) and for current and lifetime alcohol, cannabis, cocaine, and heroin dependence ( $\kappa=0.63-0.96$ ) (D.S.H., unpublished data; May 2004). The validity of the PRISM has been studied in relation to the Longitudinal, Expert, All Data (LEAD) criteria.<sup>32</sup> The PRISM/LEAD comparisons on substance-induced psychosis have produced excellent results, with  $\kappa$  statistics ranging from 0.76 to 0.81 (Michael B. First, MD, D.S.H., and W.B.S., unpublished data, May 2004).<sup>33</sup> The PRISM diagnostic assessments reported herein are based on computer-generated diagnostic algorithms applying DSM-IV criteria.

The PRISM interview was the source for information on the presence or absence of visual and auditory hallucinations, the age of onset of the first psychotic symptom, and the age at which a subject began using alcohol or other drugs on a regular basis, defined as 3 or more times per week for at least 1 month.

## DEMOGRAPHIC, FAMILY, AND CLINICAL CHARACTERISTICS OF STUDY SUBJECTS

Demographic data and information on living arrangements, education, employment, criminal justice contacts, out-of-home placement in childhood, current family support, and the subject's reports of family history were obtained using the Community Care Schedule.<sup>34</sup> Out-of-home placement was defined as living in a nonrelative setting before 18 years of age. Family support was assessed with a 4-point rating based on material support (eg, provision of housing, food, clothing, or money), companionship, and emotional support. Scores of fair (3) and inadequate (4) were classified as poor family support. Family history of mental illness was based on the subject's self-report of a parent's involvement in psychiatric treatment. Parental substance abuse was based on the subject's report of a parent's problems with alcohol or other drugs (treated or untreated).

Psychiatric symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS).<sup>35</sup> This instrument yields a total score on overall psychopathology (total PANSS) and has subscales yielding data on the positive symptoms of psychosis, negative symptoms, and overall general psychopathology. The  $\alpha$  coefficients of reliability for the PANSS subscale scores reported herein are as follows: for the positive subscale, 0.78; for the negative subscale, 0.81; and for the general psychopathology sub-

scale, 0.78. Symptoms experienced in the 7 days before the assessment are considered in determining PANSS ratings, which are made on 7-point scales ranging from none (1) to severe (7). The PANSS interview was the first assessment administered in implementing the study protocol to capture the subject's clinical status at admission to the emergency department. In 61% of cases, the PANSS assessment was completed within the 7-day window. The most common reason for a delayed PANSS assessment was that the subject was too ill to undergo voluntary informed consent procedures. There were no differences in the relationship of total PANSS scores to diagnostic classification between assessments made within 7 days compared with those made more than 7 days after admission to the emergency department.

Psychosocial, educational, and occupational functioning in childhood, adolescence, and adulthood were rated with the Premorbid Adjustment Scale.<sup>36</sup> The  $\alpha$  coefficient of reliability for the Premorbid Adjustment Scale was 0.87. The Scale to Assess Unawareness of Mental Disorders<sup>37</sup> was used to evaluate an individual's insight into having a mental illness. The instrument yields the following 2 scores: the unawareness of symptoms score ( $\alpha=0.68$ ) and the misattribution for symptoms score ( $\alpha=0.63$ ). The former assesses the awareness of the existence of a psychotic symptom, and the latter assesses the individual's understanding that a psychotic symptom is a manifestation of a mental illness. Subjects were given perfect scores on attribution for responses that indicated the individual knew that the symptom being rated was due to a mental illness or caused by the use of a substance (eg, "I saw a vision because of the PCP [phenylcyclidine hydrochloride] I smoked"). Near-perfect scores were also given for responses such as "my mind is playing tricks on me," "chemical imbalance," or "nervous breakdown." There was no requirement that the attribution had to match the DSM-IV diagnosis based on research diagnostic data.

## STATISTICAL METHODS OF ANALYSIS

The 400 study cases were classified as primary or substance induced on the basis of PRISM research diagnostic data applying DSM-IV criteria. Complete data were obtained on the 400 subjects, all of whom met the study's inclusion criteria. Fourteen cases (3.5%) were indeterminate, meaning that although these subjects met inclusion criteria, they did not meet minimal diagnostic criteria to be classified into the primary or substance-induced psychosis groups. These 14 cases were eliminated from the analysis reported herein.

The subjects with primary psychosis were compared with those with substance-induced psychosis on the demographic, family, clinical, and social domains outlined previously. Descriptive statistics are presented for selected variables by diagnostic category. Depending on whether the measurement of a variable was categorical or scaled, group differences were tested using either  $\chi^2$  or 2-tailed, unpaired *t* tests. Odds ratios (ORs) and 95% confidence intervals for selected variables and diagnostic categories were calculated using logistic regression. Logistic regression<sup>38</sup> was also used to examine a multivariate prediction model that included all potentially useful variables for discriminating the 2 diagnoses. All analyses were performed using SPSS software (SPSS Inc, Chicago, Ill). Statistical significance was determined using the .05 level and 2-tailed tests of significance.

## RESULTS

### DIAGNOSTIC CLASSIFICATION

Most of the study subjects (93.3%) initiated regular substance use before experiencing a first psychotic symp-

**Table 1. Demographic and Family Domain Variables for Overall Sample, Substance-Induced, and Primary Disorder Groups**

Variables	Subject Groups			P Value
	Overall (N = 386)	Primary Disorder (n = 217)	Substance-Induced Disorder (n = 169)	
Sex, %				
Male	72.0	70.0	74.6	.33
Female	28.0	30.0	25.4	
Age, y				
Mean	28.4	27.1	30.1	<.001
Median	27.0	25.0	29.0	
SD	8.3	8.0	8.4	
Marital status, %				
Single (never married)	75.1	81.3	67.1	.01
Married/conjugal (common-law)	10.8	7.0	15.6	
Separated/divorced	14.2	11.7	17.4	
Race, %				
Black	43.5	43.3	43.8	.14
Hispanic	42.0	39.2	45.6	
White/other	14.5	17.5	10.7	
Level of education, %				
No high school diploma	46.3	42.4	51.5	.18
High school diploma	20.7	23.0	17.8	
Some college	32.9	34.6	30.8	
Employment, %				
Employed	23.1	24.9	20.7	.30
Unemployed	76.9	75.1	79.3	
Homeless past 6 mo, %				
Yes	14.2	10.1	19.5	.01
No	85.8	89.9	80.5	
Jail/prison past 6 mo, %				
Yes	8.8	8.3	9.5	.69
No	91.2	91.7	90.5	
Out-of-home placement, %				
Yes	21.8	18.9	25.4	.12
No	78.2	81.1	74.6	
Poor family support, %				
Yes	24.7	20.7	29.8	.04
No	75.3	79.3	70.2	
Parental mental illness, %				
Yes	14.2	15.6	12.6	.41
No	85.8	84.4	87.4	
Parental substance abuse, %				
Yes	34.2	29.2	40.7	.01
No	65.8	70.8	59.3	

tom, consistent with the expected natural history of these 2 phenomena.<sup>39,40</sup> Overall, 169 (44%) of study subjects received a baseline PRISM diagnosis of substance-induced psychosis, and 217 (56%) received a diagnosis of primary psychotic disorder. Among those with a substance-induced psychotic disorder, the most common diagnoses were as follows: cannabis-induced psychosis (n=32 [18.9%]), alcohol-induced psychosis (n=29 [17.2%]), cocaine-induced psychosis (n=26 [15.4%]), hallucinogen-induced psychosis (n=7 [4.1%]), sedative-induced psychosis (n=4 [2.4%]), heroin-induced psychosis (n=2 [1.2%]), and stimulant-induced psychosis (n=1 [0.6%]). In 67 cases (39.6%) of substance-induced psychosis, 2 or more substances were involved, the most common of which were alcohol and cocaine, followed by alcohol and cannabis.

Among those with a diagnosis of primary psychotic disorder, the most common diagnoses were as follows: schizophrenia (n=80 [36.9%]), psychotic mood disorder

(n=73 [33.6%]), psychotic disorder not otherwise specified (n=32 [14.7%]), schizophreniform disorder (n=18 [8.3%]), schizoaffective disorder (n=8 [3.9%]), and delusional disorder (n=6 [2.8%]). The most common substances used by the primary psychotic disorder group were cannabis (n=120 [55.3%]), alcohol (≥5 drinks on a single occasion, n=109 [50.2%]; daily or near-daily use for at least 1 month, n=50 [23.0%]), cocaine (n=35 [16.1%]), and hallucinogens (n=11 [5.1%]).

#### DIFFERENCES IN DEMOGRAPHIC CHARACTERISTICS

**Table 1** shows demographic characteristics for the sample as a whole and for the substance-induced and primary psychotic disorder groups. Nearly three quarters of subjects in both groups were male, reflecting the fact that substance use and substance use disorders are more common among men both in the general population and in

the population with severe mental illness.<sup>14,18,41,42</sup> When the substance-induced and primary psychotic disorder groups were compared on demographic characteristics, 3 important differences were noted. Subjects in the primary psychotic group were younger, having a median age of 25.0 years compared with 29.0 years for subjects in the substance-induced group. A greater proportion of those with a diagnosis of substance-induced psychosis had been involved in a marital or conjugal relationship (15.6%) compared with the primary psychosis group (7.0%). In addition, 19.5% of subjects in the substance-induced group were homeless in the 6 months before intake, compared with 10.1% in the primary psychotic disorder group. The 2 groups did not differ significantly on sex, race, level of education, employment, or jail/prison history.

### DIFFERENCES IN FAMILY CHARACTERISTICS

For the group as a whole, 21.8% experienced out-of-home placement in childhood, and 24.7% had poor family support. Also, 14.2% had at least 1 parent who had been treated for a mental illness, and 34.2% had at least 1 parent with an alcohol or other drug problem (Table 1). When substance-induced and primary psychotic disorder groups were compared on family characteristics, the substance-induced psychosis group had poorer family support (29.8% vs 20.7%) and a greater proportion of parents with alcohol and other drug problems (40.7% vs 29.2%).

### DIFFERENCES IN CLINICAL CHARACTERISTICS

**Table 2** shows scores on the Premorbid Adjustment Scale, PANSS, and the Scale to Assess Unawareness of Mental Disorders for the substance-induced and primary psychosis groups. The 2 groups did not differ on Premorbid Adjustment Scale scores or on age of onset of drug use, which averaged 17 years for both groups. However, important differences were observed on overall psychopathology as assessed by the PANSS. Compared with the substance-induced psychosis group, the primary psychosis group had significantly higher mean scores on the positive symptom subscale (18.62 vs 14.30), the negative symptom subscale (14.16 vs 11.67), and the general psychopathology subscale (33.29 vs 28.44). Differences were also observed in the Scale to Assess Unawareness of Mental Disorders. Subjects in the primary psychosis group were significantly less likely to be aware of psychotic symptoms (2.79 vs 1.98) and were less likely to interpret the symptoms as a manifestation of a mental disorder or substance abuse (2.99 vs 2.36), compared with the substance-induced psychosis group.

**Table 3** shows associated clinical characteristics of study subjects. The 2 diagnostic groups did not differ on auditory hallucinations, which were widespread in both groups (69.8% vs 68.7%), on violent behavior in the past year (14.7% vs 19.5%), or on lifetime suicide attempts (27.8% vs 24.0%). However, visual hallucinations were more common in the substance-induced group (23.7% vs 14.7%). The substance-induced group also had higher rates of suicidal ideation in the previous year (39.6% vs 27.6%).

**Table 2. Clinical Characteristics of Substance-Induced and Primary Psychotic Disorder Groups**

Finding	Baseline Findings by Diagnosis Category, Mean (SD)		P Value
	Primary Disorder (n = 217)	Substance-Induced Disorder (n = 169)	
PAS score	0.32 (0.14)	0.31 (0.14)	.34
PANSS			
Positive subscale score	18.62 (7.26)	14.30 (5.36)	<.001
Negative subscale score	14.16 (6.24)	11.67 (4.74)	<.001
General psychopathology score	33.29 (10.46)	28.44 (6.86)	<.001
SUMD			
Unawareness of symptoms	2.79 (1.52)	1.98 (1.74)	<.001
Misattributions for symptoms	2.99 (1.77)	2.36 (2.00)	<.001
Age of onset of drug use, y	17.17 (4.14)	16.83 (5.19)	.47

Abbreviations: PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale; SUMD, Scale to Assess Unawareness of Mental Disorders.

**Table 3. Associated Clinical Characteristics of Substance-Induced and Primary Psychotic Disorder Groups**

Characteristics	Subject Groups, %		OR (95% CI)
	Primary Disorder (n = 217)	Substance-Induced Disorder (n = 169)	
Auditory hallucinations	68.7	69.8	1.1 (0.7-1.6)
Visual hallucinations	14.7	23.7	1.8 (1.1-3.0)
Violent behavior, past 12 mo	14.7	19.5	1.4 (0.8-2.4)
Suicidal ideation, past 12 mo	27.6	39.6	1.7 (1.1-2.6)
Suicide attempt, lifetime	24.0	27.8	1.2 (0.8-1.9)

Abbreviations: CI, confidence interval; OR, odds ratio.

### AXIS II, POSTTRAUMATIC STRESS DISORDER, AND SUBSTANCE USE DISORDER COMORBIDITY

**Table 4** compares the substance-induced and primary psychotic disorders groups regarding diagnostic comorbidity. Those in the substance-induced psychosis group were more likely to have a diagnosis of antisocial personality disorder (17.2% vs 8.3%). Not surprisingly, the substance-induced psychotic group had higher rates of all substance use disorders except marijuana use/dependence (42.0% vs 37.3%). Differences were found for alcohol abuse/dependence (60.4% vs 34.1%), cocaine abuse/dependence (40.8% vs 9.2%), heroin abuse/dependence (10.7% vs 0.9%), hallucinogen abuse/dependence (5.9% vs 0.9%), and polydrug dependence (18.3% vs 5.1%). A current diagnosis of dependence on

**Table 4. Axis II, PTSD, and Substance Use Disorder Comorbidity**

Comorbidity	Subject Group, %		OR (95% CI)
	Primary Disorder (n = 217)	Substance-Induced Disorder (n = 169)	
Axis II disorders			
Borderline personality disorder	8.8	14.2	1.7 (0.9-3.3)
Antisocial personality disorder	8.3	17.2	2.3 (1.2-4.3)
PTSD	6.5	11.8	1.9 (0.9-4.0)
Substance use disorders			
Alcohol abuse/dependence	34.1	60.4	2.9 (1.9-4.5)
Marijuana abuse/dependence	37.3	42.0	1.2 (0.8-1.8)
Cocaine abuse/dependence	9.2	40.8	6.8 (3.9-11.8)
Heroin abuse/dependence	0.9	10.7	12.8 (2.9-56.0)
Hallucinogen abuse/dependence	0.9	5.9	6.8 (1.5-31.3)
Polydrug dependence*	5.1	18.3	4.2 (2.0-8.7)
Any drug dependence (including alcohol)	44.7	84.6	6.8 (4.1-11.2)

Abbreviation: CI, confidence interval; OR, odds ratio; PTSD, posttraumatic stress disorder.

\*Includes subjects with 3 or more drug dependence diagnoses

any drug (including alcohol) was found in 44.7% of subjects with a diagnosis of primary psychotic disorder and 84.6% of subjects with a diagnosis of substance-induced psychosis.

#### MULTIVARIATE ANALYSIS USING LOGISTIC REGRESSION

We next performed an analysis to determine the extent to which the differences reported between the groups are distinct as opposed to correlated features of the 2 groups. For these analyses, we entered into a logistic regression all the demographic variables, plus the family, clinical, and substance variables that appeared to distinguish the primary psychosis group from the substance-induced psychosis group. Model 1 in **Table 5** shows the ORs for each variable after being adjusted for all the variables in the model. When all the variables from Tables 2, 3, and 4 were considered together, only 3 remained significantly associated with the distinction between primary and substance-induced psychosis. These were total PANSS score, any diagnosis of substance dependence, and visual hallucinations. The first of these had an OR that was significantly less than 1.0, indicating that the PANSS score was lower for the substance-induced psychosis group, whereas the last 2 had ORs that were significantly greater than 1.0, indicating that they were more common among subjects with substance-induced psychosis. In addition to these 3 variables, the contrast between white and black subjects was significant in Table 5.

An additional analysis suggested that 1 more variable might also have discriminating power. We performed a forward stepwise analysis, which adjusts each variable for a smaller set of competing variables. When only total PANSS score and history of substance dependence and visual hallucinations were adjusted in addition to demographic variables, parental substance abuse also was significantly related to the distinction between primary and substance-induced psychosis. The results of this additional analysis are shown in model 2 in Table 5. Al-

though the primary psychosis and substance-induced groups of subjects appeared to differ on many other variables in Tables 1, 2, 3, and 4, these differences were largely accounted for by the 4 variables mentioned in this paragraph.

#### COMMENT

In this study of early-phase psychosis and substance use, we applied *DSM-IV* criteria to research diagnostic data to differentiate substance-induced psychoses from primary psychotic disorders that co-occurred with the use of alcohol and/or other drugs. This procedure allowed us to classify 96.5% of study subjects with combined substance use and psychosis into *DSM-IV* substance-induced and primary psychotic disorder groups. The use of a longitudinal observation period, multiple perspectives, and explicit decision rules resulted in classification of a high percentage of cases, contrary to earlier studies that found that many cases were difficult to classify.<sup>43,44</sup>

Substance-induced and primary psychotic disorders were distinguished from one another on several demographic, familial, and clinical characteristics. Compared with those with primary psychotic disorder, subjects with substance-induced psychosis had a significantly later age of onset of psychosis, greater conjugal ties, greater antisocial personality disorder comorbidity, more frequent homelessness, and poorer family support, and more subjects had a parent with a substance abuse problem.

Our results show that subjects with primary psychosis had more severe psychiatric symptoms associated with less insight, a finding that is not limited to positive symptoms but also includes negative symptoms and general psychopathology. In contrast, subjects with substance-induced psychosis had more severe forms of substance use disorders, characterized by long periods of substance use, multiple drugs, severe psychosocial problems, and greater dependence. These were not people whose substance-induced psychosis was associated with

**Table 5. Logistic Regression Results for Variables Distinguishing Primary Psychotic Disorder From Substance-Induced Psychosis**

Variables	Model 1*		Model 2†	
	$\beta$ (SE)	OR (95% CI)	$\beta$ (SE)	OR (95% CI)
Age	-0.001 (0.020)	1.00 (0.96-1.04)	-0.005 (0.019)	1.00 (0.96-1.03)
Sex	-0.030 (0.316)	0.97 (0.52-1.80)	-0.074 (0.293)	0.93 (0.52-1.65)
Race				
Hispanic	-0.412 (0.309)	0.66 (0.36-1.21)	-0.389 (0.291)	0.68 (0.38-1.20)
White/other	-0.847 (0.433)	0.43 (0.18-1.00)	-0.818 (0.418)	0.44 (0.19-1.00)
Marital status				
Married/conjugal	0.932 (0.481)	2.50 (0.99-6.50)	0.911 (0.466)	2.49 (1.00-6.19)
Separated	0.797 (0.430)	2.21 (0.96-5.15)	0.845 (0.415)	2.33 (1.03-5.25)
Education				
High school diploma	-0.507 (0.338)	0.60 (0.31-1.17)	-0.525 (0.330)	0.59 (0.31-1.13)
Some college	0.102 (0.334)	1.10 (0.58-2.13)	0.019 (0.319)	1.02 (0.55-1.91)
Poor family support	-0.251 (0.325)	0.78 (0.41-1.47)		
Parental substance abuse	0.441 (0.282)	1.55 (0.89-2.70)	0.524 (0.268)	1.69 (1.00-2.85)
Total PANSS	-0.043 (0.009)	0.96 (0.94-0.98)	-0.046 (0.008)	0.96 (0.94-0.97)
Onset of any drug use	-0.028 (0.031)	0.98 (0.92-1.03)		
Any drug dependence	2.18 (0.307)	8.86 (4.85-16.18)	2.24 (0.297)	9.41 (5.26-16.85)
Visual hallucinations	0.741 (0.347)	2.10 (1.06-4.14)	0.757 (0.337)	2.13 (1.10-4.13)
Unawareness of symptoms score	-0.131 (0.122)	0.88 (0.69-1.11)		
Misattribution of symptoms score	0.044 (0.106)	1.04 (0.85-1.29)		
Borderline personality	-0.005 (0.425)	1.00 (0.43-2.29)		
Antisocial personality	0.543 (0.402)	1.72 (0.78-3.79)		
PTSD	0.190 (0.450)	1.21 (0.50-2.92)		
Suicidal ideation	0.364 (0.288)	1.44 (0.82-2.53)		
Homelessness	0.397 (0.403)	1.49 (0.68-3.28)		

Abbreviations: CI, confidence interval; OR, odds ratio; PANSS, Positive and Negative Syndrome Scale; PTSD, posttraumatic stress disorder.

\*Includes all variables. The first category for sex, race, marital status, and education was coded as the reference group. Table 1 describes the category names.

†Includes variables that remain significant using stepwise selection. In addition, age, sex, race, marital status, and education were forced into the model because of their clinical importance on the outcome diagnosis.

a bad experience with recreational drug use. Another characteristic distinguishing the substance-induced psychosis group was visual hallucinations. Differences in hallucinatory behavior in the 2 diagnostic groups may reflect differences in the underlying mechanisms of psychosis, an issue requiring further study and evaluation.

Although the 2 groups differed on many dimensions, only a few study variables can account for most of the differences. These are parental substance abuse (greater in the substance-induced psychosis group), higher levels of psychiatric symptoms (greater in the primary psychosis group), a concurrent diagnosis of drug dependence (more prevalent in the substance-induced psychosis group), and visual hallucinations (more common in the substance-induced psychosis group). This set of variables, represented as model 2 in Table 5, distinguish the substance-induced and primary psychosis groups from one another and may serve as guidelines for clinicians in acute care settings who are charged with the responsibility for diagnostic and treatment decisions.

The diagnostic distinction between a substance-induced and a primary psychotic disorder is critically important, because each disorder requires a different treatment. For example, subjects with drug-induced psychosis may need different medications, no medications, or brief medication therapy, and they may be more susceptible to the adverse effects of antipsychotic medications.<sup>45</sup> Although psychotomimetic drug use may precipitate a chronic schizophrenic illness,<sup>46</sup> an accurate diagnostic as-

essment is particularly significant in the early stages of psychotic disorder, when the diagnostic picture is often clouded by the presence of substance use and differential therapeutics are appropriate.

The 2 diagnostic groups did not differ on level of premorbid adjustment. Some previous studies of individuals with schizophrenia have found that those who abuse substances have better premorbid adjustment compared with people with schizophrenia who do not abuse substances.<sup>47-50</sup> It has been posited that more socially competent people with schizophrenia have greater exposure to substance use through their greater peer contacts. Because all of the people with primary psychotic disorders in our study also used substances, this "selection" factor may explain why no differences in premorbid functioning were observed in the primary and substance-induced psychosis groups. The 2 groups also shared a common preference for alcohol, cannabis, and cocaine, and a dangerous proclivity for violence and suicide attempts.

Although there were no differences by diagnostic classification, the finding that 14.2% of subjects in the overall sample had a parent with a mental illness suggests the possibility of a distinct vulnerability to psychosis among those with substance-induced psychosis that distinguishes them from other substance abusers and may predispose them to the development of chronic psychotic illness over time. Longitudinal follow-up will aid in clarifying this issue, as will comparison groups of heavy sub-

stance abusers who do not become psychotic. Moreover, substantial parental substance abuse in both diagnostic groups suggests that familial substance abuse should be studied further in relation to both types of psychosis and substance use comorbidity.

This study has several limitations. Diagnostic and symptom assessments are based on behavioral data. Future research should incorporate advances in neuroscience in the search for biological markers that might elucidate the distinction between primary and substance-induced psychotic disorders, a process that will be aided with the use of reliable and valid diagnostic assessments. Study subjects were drawn from upper Manhattan emergency departments serving low-income catchment areas. White subjects who selected these services were more likely to be diagnosed as having primary psychosis. Findings cannot be generalized to other settings, although further studies could contribute to this determination. Helping clinicians make more accurate early diagnoses is meant as a first step and does not supplant the need for longitudinal assessment. Subjects with psychosis and substance use must be followed up carefully and undergo reevaluation over time.<sup>51</sup> Finally, the application of *DSM-IV* criteria to the cross-sectional data reported herein permits neither an evaluation of diagnostic stability nor an assessment of the predictive validity of the diagnostic criteria. These issues will be addressed in the longitudinal follow-up to be reported subsequently.

To our knowledge, this is the first rigorous examination of the *DSM-IV* distinction between primary and substance-induced psychotic disorders. As such, it provides important insights into these disorders as the field moves toward an improved nomenclature with *DSM-V*. Study findings suggest future directions for interdisciplinary research aimed at a clearer understanding of the relationship of substance use and substance use disorders to psychotic illness, a comorbidity that continues to challenge effective treatment and management of severe and persistent mental illness.

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- Schuckit MA. *Drug and Alcohol Abuse*. 3rd ed. New York, NY: Plenum Publishing Corp; 1989.
- Lowenstein DH, Massa SM, Rowbotham MC, Collins SD, McKinney HE, Simon RP. Acute neurologic and psychiatric complications associated with cocaine abuse. *Am J Med*. 1987;83:841-846.
- Satel SL, Edell WS. Cocaine-induced paranoia and psychosis proneness. *Am J Psychiatry*. 1991;148:1708-1711.
- Ries RK. The dually diagnosed patient with psychotic symptoms. *J Addict Dis*. 1993;12:103-122.
- Mc Lellan AT, Woody GE, O'Brien CP. Development of psychiatric illness in drug abusers: possible role of drug preference. *N Engl J Med*. 1979;301:1310-1314.
- Sato M, Chen CC, Akiyama K, Otsuki S. Acute exacerbation of paranoid psychotic state of the long-term abstinence in patients with previous methamphetamine psychosis. *Biol Psychiatry*. 1983;18:429-440.
- Angrist B. Amphetamine psychosis: clinical variations of the syndrome. In: Cho AK, Segal DS, eds. *Amphetamine and Its Analogs*. Orlando, Fla: Academic Press Inc; 1994:387-414.
- Freedman DX. On the use and abuse of LSD. *Arch Gen Psychiatry*. 1968;18:330-347.
- Bowers MB, Swigar ME. Vulnerability to psychosis associated with hallucinogen use. *Psychiatry Res*. 1983;9:91-97.
- Vardy MM, Kay SR. LSD psychosis or LSD-induced schizophrenia: a multimethod inquiry. *Arch Gen Psychiatry*. 1983;40:877-883.
- Chopra G, Smith J. Psychotic reactions following cannabis use in East Indians. *Arch Gen Psychiatry*. 1974;30:24-27.
- Hollister LE. Health aspects of cannabis. *Pharmacol Rev*. 1986;38:1-20.
- Thomas H. Psychiatric symptoms in cannabis users. *Br J Psychiatry*. 1993;163:141-149.
- Kessler RC. Epidemiology of psychiatric comorbidity. In: Tsuang MT, Tohen M, Zahner GEP, eds. *Textbook of Psychiatric Epidemiology*. New York, NY: Wiley-Liss; 1995:179-197.
- Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. *JAMA*. 1990;264:2511-2518.
- Negrete JC. Clinical aspects of substance abuse in persons with schizophrenia. *Can J Psychiatry*. 2003;48:14-21.
- Jablensky A, McGrath J, Herrman H, Castle D, Gureje O, Evans M, Carr V, Morgan V, Korten A, Harvey C. Psychotic disorders in urban areas: an overview of the Study of Low Prevalence Disorders. *Aust N Z J Psychiatry*. 2000;34:221-236.
- Cantwell R, Brewin J, Glazebrook C, Dalkin T, Fox R, Medley I, Harrison G. Prevalence of substance misuse in first-episode psychosis. *Br J Psychiatry*. 1999;174:150-153.
- Strakowski SM, Tohen M, Stoll AL, Faedda GL, Mayer PV, Kolbrener ML, Goodwin DC. Comorbidity in psychosis at first hospitalization. *Am J Psychiatry*. 1993;150:752-757.
- Kovaszny B, Fleischer J, Tanenberg-Karant M, Jandorf L, Miller AD, Bromet E. Substance use disorder and the early course of illness in schizophrenia and affective psychosis. *Schizophr Bull*. 1997;23:195-201.
- Dixon L. Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. *Schizophr Res*. 1999;35(suppl):S93-S100.
- Drake RE, Wallach MA, Hoffman JS. Housing instability and homelessness among aftercare patients of an urban state hospital. *Hosp Community Psychiatry*. 1989;40:46-51.
- Susser ES, Lin SP, Conover SA, Struening EL. Childhood antecedents of homelessness in psychiatric patients. *Am J Psychiatry*. 1991;148:1026-1030.
- Caton CL, Shrout PE, Dominguez B, Eagle PF, Opler LA, Cournois F. Risk factors for homelessness among women with schizophrenia. *Am J Public Health*. 1995;85:1153-1156.
- Swanson JW, Swartz MS, Essock SM, Osher FC, Wagner HR, Goodman LA, Rosenberg SD, Meador KG. The socio-environmental context of violent behavior in persons treated for severe mental illness. *Am J Public Health*. 2002;92:1523-1531.
- Mendoza R, Miller BL, Mena I. Emergency room evaluation of cocaine-associated neuropsychiatric disorders. In: Galanter M, ed. *Recent Developments in Alcoholism: Alcohol and Cocaine: Similarities and Differences*. Vol 10. New York, NY: Plenum Press Inc; 1992:73-86.
- Boutros N, Bowers MB. Chronic substance-induced psychotic disorders: state of the literature. *J Neuropsychiatry Clin Neurosci*. 1996;8:262-269.
- Serper MR, Chou JC, Allen MH, Czobor P, Cancro R. Symptomatic overlap of cocaine intoxication and acute schizophrenia at emergency presentation. *Schizophr Bull*. 1999;25:387-394.

29. Bromet EJ, Schwartz J, Fennig S, Geller L, Jandorf L, Kovasznay B, Lavell J, Miller A, Pato C, Ram R. The epidemiology of psychosis: the Suffolk County Mental Health Project. *Schizophr Bull.* 1992;18:243-255.
30. Hasin DS, Trautman KD, Miele GM, Samet S, Smith M, Endicott J. Psychiatric Research Interview for Substance and Mental Disorders (PRISM): reliability for substance abusers. *Am J Psychiatry.* 1996;153:1195-1201.
31. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.* Washington, DC: American Psychiatric Press; 1994.
32. Spitzer RL. Psychiatric diagnosis: are clinicians still necessary? *Compr Psychiatry.* 1983;24:399-411.
33. Torrens M, Serrano D, Astals M, Perez-Dominguez G, Martin-Santos R. Diagnosing comorbid psychiatric disorders in substance abusers: validity of the Spanish versions of Psychiatric Research Interview for Substance and Mental Disorders and the Structured Clinical Interview for *DSM-IV.* *Am J Psychiatry.* 2004;161:1231-1237.
34. Caton CLM. *The Community Care Schedule.* Rev ed. New York: New York State Psychiatric Institute; 1997.
35. Kay SR, Opler LA, Fiszbein A. *The Positive and Negative Syndrome Scale Manual.* Toronto, Ontario: Multi-Health Systems Inc; 1992.
36. Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in schizophrenia. *Schizophr Bull.* 1982;8:470-484.
37. Amador XF, Strauss DH, Yale S, Gorman JM, Endicott J. The assessment of insight in psychosis. *Am J Psychiatry.* 1993;150:873-879.
38. Kleinbaum DG, Kupper LL, Muller KE, Nizam A. *Applied Regression Analysis and Other Multivariate Methods.* 3rd ed. Pacific Grove, Ga: Duxbury Press; 1998.
39. Grant BF. Prevalence and correlates of alcohol use and *DSM-IV* alcohol dependence in the United States: results of the National Longitudinal Alcohol Epidemiologic Survey. *J Stud Alcohol.* 1997;58:464-473.
40. Keith SJ, Regier DA, Rae DS. Schizophrenic disorders. In: Robins LN, Regier DA, eds. *Psychiatric Disorders in America.* New York, NY: Free Press; 1991:33-52.
41. Sim K, Swapna V, Mythily S, Mahendran R, Kua EH, McGorry P, Chong SA. Psychiatric comorbidity in first episode psychosis: the Early Psychosis Intervention Program (EPIP) experience. *Acta Psychiatr Scand.* 2004;109:23-29.
42. Brunette M, Drake RE. Gender differences in patients with schizophrenia and substance abuse. *Compr Psychiatry.* 1997;38:109-116.
43. Lehman AF, Myers CP, Corty E, Thompson JW. Prevalence and patterns of "dual diagnosis" among psychiatric inpatients. *Compr Psychiatry.* 1994;35:106-112.
44. Rosenthal RN, Hellerstein DJ, Miner CR. Integrated services for treatment of schizophrenic substance abusers: demographics, symptoms, and substance abuse patterns. *Psychiatr Q.* 1992;63:3-26.
45. Cornish JW, McNicholas LF, O'Brien CP. Treatment of substance-related disorders. In: Schatzberg AF, Nemeroff CB, eds. *Textbook of Psychopharmacology.* 3rd ed. Washington, DC: American Psychiatric Publishing Inc; 2004:1009-1029.
46. Bowers MB Jr, Mazure CM, Nelson JC, Jatlow PI. Psychotogenic drug use and neuroleptic response. *Schizophr Bull.* 1990;16:81-85.
47. Mueser KT, Yarnold PR, Levinson DF, Singh H, Bellack AS, Kee K, Morrison RL, Yadalam KG. Prevalence of substance abuse in schizophrenia: demographic and clinical correlates. *Schizophr Bull.* 1990;16:31-56.
48. Caton CL, Shrout PE, Eagle PF, Opler LA, Felix A. Correlates of codisorders in homeless and never homeless indigent schizophrenic men. *Psychol Med.* 1994;24:681-688.
49. Arndt S, Tyrrell G, Flaum M, Andreasen NC. Comorbidity of substance abuse and schizophrenia: the role of pre-morbid adjustment. *Psychol Med.* 1992;22:379-388.
50. Sevy S, Robinson DG, Holloway S, Alvir JM, Woerner MG, Bilder R, Goldman R, Lieberman J, Kane J. Correlates of substance misuse in patients with first-episode schizophrenia and schizoaffective disorder. *Acta Psychiatr Scand.* 2001;104:367-374.
51. Weiss RD, Mirin SM, Griffin ML. Methodological considerations in the diagnosis of coexisting psychiatric disorders in substance abusers. *Br J Addict.* 1992;87:179-187.

23. Suzuki WA, Amaral DG. The perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. *J Comp Neurol*. 1994;350:497-533.
24. Burwell RD. The parahippocampal gyrus: corticocortical connectivity. *Ann N Y Acad Sci*. 2000;911:25-42.
25. Aggleton JP, Brown MW. Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav Brain Sci*. 1999;22:425-489.
26. Murray EA, Bussey TJ, Hampton RR, Saksida LM. The parahippocampal region and object identification. *Ann N Y Acad Sci*. 2000;911:166-174.
27. Bohbot VD, Allen JJ, Nadel L. Memory deficits characterized by patterns of lesions to the hippocampus and parahippocampal cortex. *Ann N Y Acad Sci*. 2000;911:355-368.
28. Vann SD, Brown MW, Erichsen JT, Aggleton JP. Fos imaging reveals differential patterns of hippocampal and parahippocampal subfield activation in rats in response to different spatial memory tests. *J Neurosci*. 2000;20:2711-2718.
29. Suzuki WA, Miller EK, Desimone R. Object and place memory in the macaque entorhinal cortex. *J Neurophysiol*. 1997;78:1062-1081.
30. Eichenbaum H. A cortical-hippocampal system for declarative memory. *Nat Rev Neurosci*. 2000;1:41-50.
31. Hasselmo ME, Wyble BP. Free recall and recognition in a network model of the hippocampus: simulating effects of scopolamine on human memory function. *Behav Brain Res*. 1997;89:1-34.
32. Meeter M, Murre JMJ, Talamini LM. A computational approach to memory deficits in schizophrenia. *Neurocomputing*. 2002;44-46:929-936.
33. Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Paesschen WV, Mishkin M. Differential effects of early hippocampal pathology on episodic and semantic memory. *Science*. 1997;277:376-390.
34. O'Reilly RC, McClelland JL. Hippocampal conjunctive encoding, storage, and recall: avoiding a trade-off. *Hippocampus*. 1994;4:661-682.
35. Murre JMJ, Berg RJ. Walnut/Nutshell, version 1.0.255 [computer program]. 2000. Available at: <http://www.neuromod.org/nutshell>.
36. Oja E. A simplified neuron model as a principal component analyzer. *J Math Biol*. 1982;15:267-273.
37. Levy WB, Colbert CM, Desmond NL. Elemental adaptive processes in neurons and synapses: a statistical/computational perspective. In: Gluck MA, Rumelhart DE, eds. *Neuroscience and Connectionist Theory*. Hillsdale, NJ: Lawrence A Erlbaum Assoc; 1990:187-235.
38. Hasselmo ME, Bradley P, Wyble BP, Wallenstein GV. Encoding and retrieval of episodic memories: role of cholinergic and GABAergic modulation in the hippocampus. *Hippocampus*. 1996;6:693-708.
39. Meeter M, Murre JMJ, Talamini LM. Mode shifting between storage and recall based on novelty detection in oscillating hippocampal circuits. *Hippocampus*. 2004;14:722-741.
40. Godden DR, Baddeley AD. Context-dependent memory in two natural environments: on land and underwater. *Br J Psychol*. 1975;66:325-331.
41. Raaijmakers JGW, Shiffrin RM. Search of associative memory. *Psychol Rev*. 1981;88:93-134.
42. Law AJ, Weickert CS, Hyde TM, Kleinman JE, Harrison PJ. Reduced spinophilin but not microtubule-associated protein 2 expression in the hippocampal formation in schizophrenia and mood disorder: molecular evidence for a pathology of dendritic spines. *Am J Psychiatry*. 2004;161:1848-1855.
43. Spitzer M. A cognitive neuroscience view of schizophrenic thought disorder. *Schizophr Bull*. 1997;23:29-50.
44. Reed JM, Squire LR. Impaired recognition memory in patients with lesions limited to the hippocampal formation. *Behav Neurosci*. 1997;111:667-675.
45. Rempel-Clower NL, Zola SM, Squire LR, Amaral DG. Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *J Neurosci*. 1996;16:5233-5255.
46. Elvevåg B, Egan MF, Goldberg TE. Paired-associate learning and memory interference in schizophrenia. *Neuropsychologia*. 2000;38:1565-1575.
47. O'Carroll RE, Murray C, Austin MP, Ebmeier KP, Goodwin GM, Dunan J. Proactive interference and the neuropsychology of schizophrenia. *Br J Clin Psychol*. 1993;32:353-356.
48. Marr D. Simple memory: a theory for archicortex. *Philos Trans R Soc Lond B Biol Sci*. 1971;262:23-81.
49. McGlashan TH, Hoffman RE. Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Arch Gen Psychiatry*. 2000;57:637-648.
50. Mandler G. Recognizing: the judgment of previous occurrence. *Psychol Rev*. 1980;87:252-271.
51. Norman KA, O'Reilly RC. Modeling hippocampal and neocortical contributions to recognition memory: a complementary learning systems approach. *Psychol Rev*. 2003;110:611-646.
52. Yonelinas AP. The nature of recollection and familiarity: a review of 30 years of research. *J Mem Lang*. 2002;46:441-517.

### Correction

**Error in Byline.** In the Original Article by Caton et al titled "Differences Between Early-Phase Primary Psychotic Disorders With Concurrent Substance Use and Substance-Induced Psychoses," published in the February issue of the ARCHIVES (2005;62:137-145), an error occurred in the byline on page 137. The byline should have read as follows: Carol L. M. Caton, PhD; Robert E. Drake, MD, PhD; Deborah S. Hasin, PhD; Boanerges Dominguez, MS; Patrick E. Shrout, PhD; Sharon Samet, MSW; Bella Schanzer, MD." The journal regrets the error.