Pergamon

J. psychiat. Res., Vol. 30, No. 1, pp. 59–68, 1996

Printed in Great Britain
0022-3956/96 $15.00 + .00

0022-3956(95)00044-5

THE EFFECTS OF ANTECEDENT SUBSTANCE ABUSE ON THE DEVELOPMENT OF FIRST-EPISODE PSYCHOTIC MANIA

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(*Received* 5 *July* 1995; *revised* 11 *September* 1995; *accepted* 15 *September* 1995)

Summary—We examined associations of antecedent drug and alcohol abuse with age of onset of bipolar disorder and the time to hospitalization in a sample of 59 patients presenting with their first episode of psychotic mania. Patients with first-episode manic or mixed bipolar disorder with psychotic features were recruited from consecutive hospitalizations and evaluated using structured diagnostic instruments. Antecedent alcohol abuse was present in 12 patients (20%), and antecedent drug abuse in 19 (32%). Antecedent alcohol abuse was associated with a later age of onset of the bipolar disorder, although antecedent drug abuse was not associated with age of onset. Patients with antecedent drug or alcohol abuse required hospitalization sooner than those without. These preliminary findings suggest that patients with bipolar disorder and antecedent alcohol abuse may have a later onset of their affective illness, perhaps representing a subgroup of patients in whom previous alcohol abuse is necessary to precipitate an affective episode. Regardless, the presence of antecedent substance abuse leads to more rapid hospitalization in these patients. Our results should be considered preliminary, given the small sample size and the *post-hoc* design of the study. Additional prospective studies of patients with new onset bipolar disorder and antecedent substance abuse syndromes are needed to further clarify the complex relationships between substance abuse and bipolar disorder.

Introduction

Substance abuse is common in bipolar disorder, affecting up to 60% of patients (see Strakowski et al., 1994 for review). High rates of substance abuse have been observed in bipolar patients even at the time of hospitalization for a first manic episode, suggesting it is not simply a consequence of long-term illness (Strakowski et al., 1992, 1993, 1994, 1995a). Moreover, these high rates of substance abuse are not simply an artifact of treatment seeking populations as the Epidemiologic Catchment Area study also reported a 61% lifetime prevalence rate of comorbid substance abuse or dependence in bipolar I disorder in their community-based sample (Regier et al., 1990). Thus, it is well established that substance abuse occurs more commonly in patients with bipolar disorder than expected

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by chance, leading some investigators to propose that there may be shared mechanisms underlying both substance abuse disorders and bipolar illness (Dilsaver, 1987). How substance abuse specifically influences the presentation and course of illness in bipolar disorder remains unclear, however.

One proposed influence of substance abuse is that drugs or alcohol may initiate bipolar disorder in certain vulnerable individuals by precipitating early affective episodes (Goodwin & Jamison, 1990). This hypothesis arises from consideration of reports of psychoactive substance-induced psychosis (e.g. Weller et al., 1988) and from the hypothesized role of kindling and sensitization in the development of affective syndromes (Post, 1993). Specifically, the processes of kindling and sensitization are models for the development of recurrent affective episodes, in that repeated intermittent stressors (such as substance abuse) may initiate progressively more severe affective responses, culminating in manic or depressive episodes, that then become self-perpetuating (Post, 1993). This is postulated to be observable clinically in that the age of onset of bipolar disorder in patients with *antecedent* substance abuse should be earlier than in patients without substance abuse (Goodwin & Jamison, 1990). However, sensitization has not been observed directly in bipolar patients, although recently has been demonstrated in normal volunteers (Strakowski et al., 1996).

Indeed, in contrast to the kindling and sensitization hypothesis, Morrison (1974) observed that alcoholic bipolar patients had an older age of onset of their bipolar disorder (28 years) than did nonalcoholic bipolar patients (23 years), although this difference did not reach statistical significance. Unfortunately, Morrison (1974) did not identify separately those patients whose alcohol abuse predated the onset of the bipolar illness from those whose alcoholism did not. This separation is important, as it is the former patient group in whom a sensitization/kindling-like process would be postulated to be active. In a more recent report, Winokur et al. (1995) observed that bipolar patients with alcoholism beginning prior to the affective illness (primary alcoholism) had a similar age of onset of their bipolar disorder (27 years) than those patients without alcoholism (25 years). Neither of these studies support the sensitization/kindling hypothesis, although both studies are limited by examining primarily multiple-episode patients many years after the onset of the affective illness. Studying such a sample may confound the age of onset data, particularly in differentiating the relative onsets of two disorders (i.e. bipolar disorder, alcoholism) with many similar symptoms. One way to minimize this limitation is by studying *first-episode patients* which helps to define the onset of the affective illness, and, therefore, may permit more valid determination of whether an alcohol abuse syndrome is antecedent, concurrent or subsequent to the bipolar disorder. In contrast to this work in alcoholism, there has been little attention paid to the effects of drug abuse on the age of onset of bipolar illness.

A second possible effect of substance abuse in bipolar disorder involves the self-medication and masking of affective symptoms. Specifically, since the use of psychoactive substances typically alters the user's mood, it may also mask underlying affective disturbances, perhaps making it difficult to identify the bipolar disorder until the patient is sober (Goodwin & Jamison, 1990). For example, Morrison (1974) observed that affective symptoms were present for a longer period in bipolar patients abusing alcohol than those not abusing, perhaps reflecting a moderating or masking effect of the alcohol on the

affective syndrome, thereby delaying hospitalization. In contrast, Reich et al. (1974) found alcoholism to be a significant predictor of hospitalization in bipolar patients, consistent with Berkson's bias, which states that patients with two or more concurrent disorders are more likely to seek treatment than those with a single disorder (Berkson, 1946). Several studies have reported that alcohol use increases during mania suggesting its sedative effects may help modulate the overactivation of the manic episode (Zisook & Schuckit, 1987; Mayfield & Coleman, 1968; Reich et al., 1974). Contrasting this suggestion, Weiss & Mirin (1987) observed increased cocaine abuse during mania to apparently increase the "high" rather than reduce symptoms. This has lead some to propose that substance abuse in bipolar disorder simply reflects the behavioral excesses known to be associated with mania (Liskow et al., 1982; Weiss & Mirin, 1987). Thus, whether some patients use drugs and alcohol to self-medicate or mask symptoms remains unclear. Studying first-episode patients with substance abuse that predates the onset of affective episodes may identify a subgroup of patients who delay their initial treatment by self-medication or who present for treatment only after a period of sobriety, having successfully masked symptoms through substance abuse. Since substance abuse in these patients will have predated the onset of the affective syndrome, it will not be simply in response to an affective episode. Therefore, studying patients with bipolar disorder early in the course of their affective illness may help clarify some of the relationships between substance abuse and symptom modulation that are difficult to elucidate in multiple-episode samples.

With these considerations in mind, we have examined the following questions in a sample of patients hospitalized with a first episode of mania. (1) Do patients with antecedent substance abuse demonstrate an earlier age of onset of their affective illness than those without (i.e. reflecting the sensitization model/kindling)? (2) Do patients with antecedent substance abuse demonstrate a longer time between the onset of the affective syndrome and hospitalization (as evidence of symptom masking or self-medication)? (3) Are patients with antecedent alcohol and drug abuse hospitalized for mania following a period of sobriety, rather than while actively abusing substances (also as evidence of symptom masking)? The subjects used for this analysis were recruited as part of the University of Cincinnati First-Episode Psychosis Project (Strakowski et al., 1995a). This project was designed to examine the temporal stability of principal and comorbid syndromes, as well as the effects of comorbidity on outcome, in patients with first-episode psychosis. Thus, the questions in this paper were tested *post-hoc* after collecting patient data, and, as such, these results should be considered preliminary. However, this patient sample is ideal for examining these hypotheses, because they have had no prior psychiatric hospitalizations and were in the early phases of their illnesses. Indeed, since a history of previous episodes has been identified as a robust predictor of future episodes in affective disorders, other potential factors influencing outcome may be difficult to identify in the setting of established illness chronicity (Winokur et al., 1993). By studying patients early in the course of their illness, the potentially confounding factors of prior treatment and illness chronicity are controlled, and other potentially important factors, such as age of onset, can be more clearly defined.

These results represent a separate analysis with additional patients than included in previous publications from our research group (Strakowski et al., 1995a; McElroy et al., 1995; Keck et al., 1995).

Methods

The details of the University of Cincinnati First-Episode Psychosis Project have been published elsewhere (Strakowski et al., 1995a). Patients experiencing a first psychotic episode were consecutively recruited from admissions to the University of Cincinnati Hospital inpatient psychiatric units. The University of Cincinnati is the primary psychiatric (and substance abuse) emergency evaluation and referral service for the entire Cincinnati tristate area (including southwestern Ohio, southeastern Indiana and northern Kentucky). Further, the University of Cincinnati Psychiatric Emergency Service (PES) serves as the portal of entry into the Hamilton County (Greater Cincinnati) public hospital system. Thus, the University of Cincinnati Hospital serves as both a primary and tertiary referral center for indigent and insured patients (Strakowski et al., 1995b). Patients for this analysis met the following inclusion criteria: (1) aged 16–45 years old; (2) presence of DSM-III-R bipolar disorder, manic or mixed with psychosis; (3) residence within the Cincinnati Metropolitan area; and (4) provision of written informed consent. Patients were excluded: (i) if symptoms resulted entirely from acute intoxication or withdrawal from drugs or alcohol, or acute medical illness (e.g. delirium) as determined by medical evaluation and rapid symptom resolution (within 72 h) after the medical event; or (ii) by a history of previous psychiatric hospitalizations, more than 3 months of prior antipsychotic or mood-stabilizer treatment, or more than 6 months of previous antidepressant treatment. Patients with prior substance abuse hospitalizations were included only if it could be determined that they received no treatment for affective or psychotic syndromes during that hospitalization. Less than 5% of the potential study subjects who were identified were excluded by these criteria.

Axis I psychiatric diagnoses were made using the Structured Clinical Interview for DSM-III-R (SCID-P)(Spitzer et al., 1990). All SCID-P interviews were performed by practicing psychiatrists (SMS, PEK, SLM or SAW) with good inter-rater reliability established for both principal ($\kappa = .94$) and comorbid diagnoses ($\kappa = .90$). In completing the SCID-P, information was obtained from any source available in addition to the patient interview, including medical records, family members and the treating clinicians. A substance abuse syndrome was considered present if the patient met DSM-III-R criteria for psychoactive substance abuse or dependence (heretofore, for simplicity, the term "abuse" will be used to refer to both abuse and dependence). Additionally, from the SCID-P, it was determined whether patients met criteria for a *current* substance abuse syndrome, i.e. symptoms present during the past month. The SCID-P was obtained near the end of the hospitalization (i.e. during the last 1–3 days) when patients were most able to cooperate. Subsequently, the mean length of time after hospital admission that the SCID-P was completed was 12 ($SD = 14$) days. This provided a period of abstinence from psychoactive substances to further assist with identifying patients whose symptoms were entirely secondary to acute psychoactive substance use or withdrawal.

Particular attention was paid to the age of onset of the bipolar and substance abuse syndromes during the SCID-P assessment to establish an estimate of this temporal relationship. Age of onset was determined by reviewing with each patient, as part of the SCID-P interview, the time when affective symptoms first occurred. Then, the age of onset was defined as that age when patients endorsed enough of these symptoms concurrently to meet

DSM-III-R syndrome criteria for a diagnosis. Inter-rater reliability was high for estimating the age of onset of both bipolar and substance abuse diagnoses (intraclass correlation coefficient $>.90$). Psychoactive substance abuse syndromes were defined as *antecedent* if they predated the onset of the bipolar disorder by more than 1 year. This duration was chosen to improve the validity of determining "which came first" by requiring a clear substance abuse history well in advance of the onset of affective syndromes.

Finally, all patients received symptom ratings within 3 days of hospital admission using the Hamilton Depression Scale (HAMD; Hamilton, 1960), the Young Mania Rating Scale (YMRS; Young et al., 1978), and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). For this current analysis, only the total scores were used for comparisons. A SAPS total score was obtained by summing the global rating scores for hallucinations, delusions, thought disorder and bizarre behavior. We have established reliability with these instruments, with total score intraclass correlation coefficients (ICC) determined for each scale as follows: HAMD, ICC = .94; YMRS, ICC = .71; SAPS, ICC = .80.

Statistical analysis

All analyses were performed with the Statistical Analysis System for the Personal Computer, version 6.03 (SAS Institute, Cary, North Carolina, U.S.A.). Nonparametric comparisons were made between patients with no antecedent substance abuse ($n=37$) and those with antecedent alcohol ($n=12$) *and* antecedent drug abuse ($n=19$). (Nine patients had both types of antecedent abuse.) To further the analysis of the association of antecedent substance abuse with age of onset, an additional examination of the age of onset of bipolar disorder as a function of the presence or absence of either *antecedent* drug *or* alcohol abuse was performed using a general linear model (PROC GLM) adjusting for race, sex, employment status, education and age at the time of hospital admission. This model permits the separate determination of the effects of both antecedent alcohol and drug abuse syndromes, while controlling for the potential interactions in patients who meet criteria for both. Given the relatively small size of our sample, the GLM results should be interpreted cautiously, however, and used only as supporting information for the simple statistics.

Results

Fifty-nine patients were included in this analysis, and demographic and clinical data are presented in Table 1. Seven patients (12%) had received prior treatment (five patients without antecedent substance abuse, two with). These included three with brief antidepressant trials, three with brief antipsychotic trials and one with a brief lithium trial for attention-deficit disorder as a child. Of course, all seven of these subjects' treatment was less than that required by our exclusion criteria. Two patients (3%) had prior substance abuse treatment. Fifty-four (92%) of the patients were voluntary admissions; the remaining five patients (three with substance abuse, two without) had been placed on 72-h holds after being brought for evaluation by the local police or family members. None of these five patients were probated for longer-term inpatient treatment.

Fourteen subjects (24%) had prior untreated episodes of nonpsychotic depression, and

Table 1
Demographic and Clinical Variables in 59 Patients with Psychotic Mania at the Time of their First Hospitalization

Variables	Antecedent Abuse[a] None ($n=37$)	Drug ($n=19$)	Alcohol ($n=12$)	Totals ($n=59$)
Age, mean (*SD*), years	24 (5)	25 (5)	28 (4)[b]	25 (5)
Age of onset of bipolar disorder, mean (*SD*), years.	21 (6)	24 (5)	27 (4)[c]	22 (6)
Time to hospitalization, mean (*SD*), months	35 (50)	10 (17)[d]	5 (5)[e]	25 (42)
Sex, *n* (%) women	18 (49)	3 (16)[f]	3 (25)	22 (37)
Race, *n* (%) Caucasian	17 (46)	9 (47)	8 (67)	28 (47)
Education, means (*SD*), years	13 (3)	12 (1)	12 (2)	13 (2)
Unemployed, *n* (%)	14 (38)	11 (58)	7 (58)	27 (46)
Mixed state, *n* (%)	16 (43)	4 (21)	3 (25)	21 (36)
No. prior manic episodes, mean (*SD*)	0.1 (0.4)	0.0 (0)	0.0 (0)	0.1 (0.3)
No. prior depressive episodes, mean (*SD*)	0.8 (2.0)	1.1 (2.6)	1.6 (3.2)	0.9 (2.2)
HAMD total score, mean (*SD*)	14 (9)	11 (6)	13 (7)	14 (8)
YMRS total score, mean (*SD*)	24 (10)	30 (11)[g]	34 (10)[h]	26 (11)
SAPS total score, means (*SD*)	9 (4)	9 (4)	10 (4)	9 (4)

[a] Nine subjects had both antecedent drug and antecedent alcohol abuse.
[b] Significant difference vs none: $z=2.1$, $df=1$, $p=.04$.
[c] Significant difference vs none: $z=3.2$, $df=1$, $p=.001$.
[d] Significant difference vs none: $z=2.2$, $df=1$, $p=.02$.
[e] Significant difference vs none: $z=2.8$, $df=1$, $p=.006$.
[f] Significant difference vs none: two-tailed Fisher's exact test, $p=.02$.
[g] Significant difference vs none: $z=2.2$, $df=1$, $p=.03$.
[h] Significant difference vs none: $z=2.8$, $df=1$, $p=.004$.

two subjects (3%) had prior episodes of untreated, nonpsychotic mania (see Table 1). Six patients (10%) had prior affective episodes that were too indistinct and enumerate to determine whether they were several previous episodes or one continuous affective disturbance. Five of these six patients had no antecedent substance abuse.

Seventeen (29%) patients had a history of alcohol abuse ($n=5$) or dependence ($n=12$) which was antecedent in 12 (71%). The mean age of onset of antecedent alcohol abuse was 17 ($SD=3$) years. Patients with antecedent alcohol abuse differed from those without antecedent substance abuse in current age ($z=2.1$, $df=1$, $p=.04$), total YMRS score ($z=2.8$, $df=1$, $p=.004$) and age of onset of bipolar disorder ($z=3.2$, $df=1$, $p=.001$). Twenty-two (37%) patients had a history of drug abuse ($n=4$) or dependence ($n=18$) which was antecedent in 19 (86%). The drugs of abuse included cannabis ($n=19$; 32%), cocaine ($n=4$; 7%), sedatives ($n=4$, 7%), hallucinogens ($n=3$, 5%), opiates ($n=3$, 5%) and amphetamine ($n=1$, 2%). Three patients (5%) met criteria for polysubstance dependence. Nine patients (15%) met criteria for both antecedent drug and alcohol abuse. The mean age of onset of antecedent drug abuse was also 17 ($SD=3$) years. Men were significantly more likely than women to have a history of an antecedent drug abuse syndrome (two-tailed Fisher Exact Test, $p=.02$), and patients with antecedent drug abuse had higher total YMRS scores ($z=2.2$, $df=1$, $p=.03$).

The results of testing the three questions are as follows. First, as noted using simple statistics, antecedent alcohol abuse was associated with a later age of onset of bipolar

disorder, but there was no association of age of onset with antecedent drug abuse. Using the previously described GLM statistical model to adjust for race, sex, employment status, education and current age, antecedent alcohol abuse remained significantly associated with age of onset of the bipolar disorder ($F=8.5$, $df=1$, $p=.005$), and antecedent drug abuse did not ($F=.1$, $df=1$, $p>.7$). Second, the time between the onset of the first affective syndrome and hospitalization was shorter in patients with antecedent alcohol abuse than those without (see Table 1; $z=2.8$, $df=1$, $p=.006$), and, similarly, in patients with antecedent drug abuse than those without (see Table 1; $z=2.2$, $df=1$, $p=.02$). Finally, 13 (68%) antecedent drug abusers and 10 (83%) antecedent alcohol abusers met full substance abuse or dependence criteria during the month prior to hospitalization.

Discussion

Rather than observing antecedent substance abuse to be associated with an earlier age of bipolar disorder onset, as predicted by the sensitization and kindling model, we found that antecedent alcohol abuse was associated with an older age of onset. This finding is consistent with that of Morrison (1974) who also observed that patients with concurrent alcohol abuse had a later age of onset than those without, and the ages of onset of his sample were similar to the ages of onset of our sample. One interpretation of these data is that since older patients have passed through a longer period of risk for developing alcohol abuse, an older age of onset of bipolar disorder in patients with antecedent alcohol abuse may simply reflect this cumulative effect as patients age. Another interpretation is that these patients may have masked or self-medicated their symptoms, preventing them from meeting full criteria for an affective episode. However, as suggested by Winokur et al. (1995), antecedent alcohol abuse may represent a risk factor for some patients who otherwise have a relatively lower risk of developing bipolar illness, therefore resulting in a delay in onset of the bipolar disorder until after several years of alcohol abuse. In our sample, these same patients also appeared more symptomatic, in that they had higher total mania rating scores. Thus, this may be a subgroup of patients who require an additional stressor (alcohol abuse) before an affective episode is precipitated, consistent with the sensitization/kindling model. As these patients are followed prospectively, the relationships between affective episodes and alcohol abuse may be further clarified. In contrast, antecedent drug abuse was not associated with age of onset of the bipolar disorder in our sample.

We also found that patients with antecedent alcohol and drug abuse, compared with those without antecedent substance abuse, demonstrated a shorter period between the onset of the first affective syndrome and hospitalization. This observation is consistent with Berkson's bias (Berkson, 1946) and the previously discussed publication by Reich et al. (1974). Thus, in these patients, antecedent substance abuse hastened the time to hospitalization, once criteria for an affective syndrome were met, suggesting that if patients were self-medicating, it was not particularly effective. As an additional qualitative evaluation of the masking hypothesis, we examined the rate of patients with antecedent drug and alcohol abuse who had been sober more than 1 month prior to admission. Most patients were actively abusing psychoactive substances during that time; therefore, a period of sobriety was not necessary for identification of manic symptoms, again suggesting that any symptom

masking, if occurring, was not particularly marked. None the less, 17% of alcohol abusers and 32% of drug abusers had decreased their substance use during the month prior to admission, so may represent a subgroup of patients in whom substance abuse did provide some symptom modulation. Just as likely, however, is that these patients had not yet passed through the age of risk for bipolar illness when they stopped abusing drugs and alcohol, so that the subsequent affective episodes were independent occurrences from the discontinuation of substance abuse.

There are several important limitations to this study which should be considered in its interpretation. First, these hypotheses were tested in a data set not specifically designed for them, so, as with any *post-hoc* analysis, the results should be considered preliminary. On the other hand, *post-hoc* analyses such as these minimize the potential risks of rater bias. Second, the assessment of substance abuse was limited to the SCID-P evaluation. A more complete evaluation, including a structured substance abuse questionnaire, would provide more substantial data. Therefore, we were not able to determine other important factors related to psychoactive substance abuse, such as a dimensional measure of the severity of the use. Third, substance abusers are notoriously poor historians, which raises questions about the validity of the assessments of the age of onset of various syndromes. However, the high reliability of our assessments of age of onset suggest these measurements provide a good first estimate to address the stated hypotheses. Fourth, since SCID-P interviews were completed during the period of hospitalization, it is possible that some patients with antecedent substance abuse had affective symptoms from protracted withdrawal syndromes, rather than "true" bipolar disorder. Currently, there is no consensus regarding how long an interval must pass after abusing psychoactive substances to be confident that affective symptoms represent an underlying mood disorder. Suggestions for this interval range from the duration of acute intoxication and withdrawal to several weeks or months (Weiss et al., 1992; Strakowski et al., 1994). Others have noted that even though psychoactive substance abuse can produce some affective symptoms, primary substance abusers often fail to meet syndrome criteria for specific psychiatric disorders when structured diagnostic interviews are employed (Schuckit, 1986; Miller & Fine, 1993). Thus, our methodology of excluding patients whose symptoms occur in the context of acute psychoactive substance intoxication or withdrawal while utilizing a structured diagnostic interview (the SCID-P) near hospital discharge (after a mean of 12 days of abstinence) should minimize the effects of this limitation. Fifth, these results are most applicable to patients with psychotic mania requiring hospitalization, which may not be representative of other bipolar patients who are less ill and can be managed as outpatients, or patients who seek treatment for their substance abuse rather than affective syndrome. Thus, our findings are generalizable only to similar patient samples. Finally, the relatively small sample size limits the strength of statistical findings, in particular the analysis of covariance.

In summary, in a sample of patients hospitalized for a first manic or mixed episode of bipolar disorder, we found antecedent alcohol abuse, but not drug abuse, was associated with a later age of onset of the bipolar illness. Antecedent alcohol and drug abuse were associated with a shorter delay between the onset of the affective syndrome and hospitalization. Our results should be considered preliminary, given the small sample size and the *post-hoc* design of the study. Additional prospective studies of patients with new onset

bipolar disorder and antecedent substance abuse syndromes are needed to further clarify the complex relationships between substance abuse and bipolar disorder.

Acknowledgements—Supported in part by grants from the Scottish Rite Research Foundation, the Ohio Department of Mental Health, and the Theodore and Vada Stanley Foundation.

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