Poor Long-Term Prognosis in Mixed Bipolar Patients: 10-Year Outcomes in the Vitoria Prospective Naturalistic Study in Spain

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Objective: There have been few prospective long-term naturalistic studies of patients with mixed episodes of bipolar disorder. The aim of this study was to examine 10-year outcomes in patients with at least 1 mixed episode.

Method: A naturalistic sample of bipolar I disorder patients (n = 120), representative of bipolar patients treated in a catchment area of Spain, was followed prospectively for up to 10 years. Outcomes including number (primary study outcome) and severity of episodes, hospitalizations, and suicide attempts were recorded at bimonthly visits. Bivariate and logistic regression models identified factors significantly associated with mixed episodes. The study was conducted from 1994 through 2004.

Results: 37% of patients had mixed episodes. Mixed-episode patients had younger mean age at onset compared with the nonmixed group (25.3 vs 30.8 years; $P = .025$). After adjusting for age at onset, mixed-episode patients had an increased risk of hospitalization compared with the nonmixed group (OR = 2.86; 95% CI, 1.09–7.52; $P = .033$) and more episodes (OR = 1.21; 95% CI, 1.10–1.31; $P < .001$). Other differences between mixed and nonmixed patients, such as alcohol abuse, psychotic symptoms, and suicidality, were partially mediated by age at onset and were not significantly different after controlling for this variable. Mixed-episode patients with previous suicide attempts had a significantly shorter time to first suicide attempt during follow-up than those without history of suicide attempts ($P = .014$).

Conclusions: Although some factors associated with mixed episodes are mediated by a younger age at onset, the long-term prognosis of mixed-episode patients is worse than patients with nonmixed episodes.

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Bipolar disorder is characterized by episodes of mania or hypomania, but some patients have coexisting depressive symptoms and this is variably called a mixed episode, mixed mania, or dysphoric mania, as well as several other terms.[1,2] Mixed states have been described since the early 19th century and have a high prevalence, with overall mean rates of 30%–40% depending on the population studied and the definitions or diagnostic criteria used.[2,3] The *DSM-IV* criteria for a mixed episode are the most widely used; they require a patient to meet the criteria for a manic episode and a major depressive episode nearly every day for 1 week, as well as to have a marked impairment in functioning, to have a psychosis, or to be hospitalized.[4] The *International Classification of Diseases, Tenth Revision* (*ICD-10*) criteria for a diagnosis of mixed mania[5] are somewhat different from the *DSM-IV* criteria, and it has been argued that both sets of criteria are too strict for the pattern and severity of patients' symptoms seen in clinical practice.[6] Broader categorical and dimensional approaches for the diagnosis of mixed states have been proposed,[2,7–11] but consensus has not yet been reached. Nevertheless, mixed episodes can be defined by the presence of substantial depressive symptoms.[2]

Mixed episodes are difficult to treat and existing evidence suggests that patients with mixed mania tend to have a more severe and chronic course of illness and a worse prognosis than nonmixed patients[2,7,12] Mixed-episode patients have been reported to have an earlier age of first psychiatric hospitalization and longer duration of illness,[12] longer and more severe episodes,[13] higher rates of relapse/recurrence and hospitalization,[3,14] more frequent substance abuse,[15] more frequent comorbidities,[16–18] and a higher risk of suicide.[19,20] In addition, a study by Sax et al[21] suggested that cognitive functioning may be more impaired in patients with mixed versus pure mania.

However, most research into mixed episodes has been retrospective studies or short- to medium-term clinical trials, and the evidence on prognosis is inconsistent and conflicting. There are little prospective data on the long-term outcomes of patients with mixed episodes in the real-life setting.

The objective of this study in patients diagnosed with bipolar I disorder in 1 health catchment area of Spain (Vitoria) was to compare the long-term outcomes of patients who had at least 1 mixed episode with those who experienced nonmixed episodes. We hypothesized that patients with mixed episodes would have a poorer long-term prognosis in terms of hospitalization, bipolar episodes, and suicidal behavior.

METHOD

Subjects

Following review and approval of the study protocol and consent procedures by the Santiago Apóstol, University Medical Centre International Review Board, all subjects provided written informed consent for participation in a

Table 1. Baseline Sociodemographic Characteristics of Patients With Mixed Episodes Versus Those With Nonmixed Episodes

	Mixed-Episode Patients (n = 44)		Nonmixed-Episode Patients (n = 76)[a]		
Characteristic	n	%	n	%	Statistic
Sex					$\chi^2 = 0.625$, $P = .239$
Men	19	43.2	27	38.6	
Women	25	56.8	43	61.4	
Civil status					Fisher exact test, $P = .718$
Single	18	40.9	25	35.7	
Married	23	52.3	37	52.9	
Other	3	6.8	8	11.4	
Education					Fisher exact test, $P = .866$
Primary	35	79.5	56	80.0	
University	6	13.6	11	15.7	
None	3	6.8	3	4.3	
Socioeconomic status					$\chi^2 = 2.17$, $P = .141$
Low	20	45.4	21	30.0	
Average	24	54.5	49	70.0	
	Mean	SD	Mean	SD	
Age, y	42.16	14.41	47.09	15.98	$U = 1268.5$, $P = .114$
Age at onset, y	25.27	10.10	30.80	13.93	$U = 1156.5$, $P = .025$

[a]Some patients did not have data on all variables.

long-term clinical study that would lead to anonymous and aggregate reporting of clinical findings. The study sample came from the health catchment area of Vitoria, Spain, where the hospital provides comprehensive psychiatric services to a Basque regional population of 300,000 people, independent of economic status. The hospital provides the only psychiatric emergency and hospitalization services in the region. All patients diagnosed with *DSM-III-R* (later updated to meet *DSM-IV* criteria) bipolar I disorder, based on the Structured Clinical Interview for *DSM-III-R*, Patient Version (SCID-P),[22] who were evaluated as outpatients during the 12 months of 1994 and who were receiving long-term prophylactic treatment were invited to take part in the study. Exclusion criteria were bipolar illness or treatment for < 2 years or lack of a family member to participate in the initial and follow-up assessments. Therefore, the study sample is representative of the whole bipolar I population receiving treatment in the area from 1994 to 1995.

Data Collection

Sociodemographic and clinical variables recorded at enrolment (baseline) included gender; age; civil (marital) status; educational background; socioeconomic status; age at onset of bipolar disorder; psychotic symptoms (congruent and incongruent [*DSM-III-R*, SCID-P]); manic, depressive, and mixed episodes (*DSM-III-R*, SCID-P); and history of alcohol and substance abuse (*DSM-III-R*, SCID-P). Baseline characteristics of the sample were published previously.[23]

Follow-up assessments were carried out by trained psychiatrists at least every 8 weeks to review all available information on bipolar disorder morbidity (type, severity, duration), abuse of alcohol or other substances, hospitalizations, suicide attempts, and use and dosage of all psychotropic agents. In addition to these bimonthly visits, major reassessments were carried out with patients and their previously designated family observers at 2 and 10 years' follow-up (ie, in 1996 and 2004). These assessments included detailed and comprehensive reviews of interval morbidity, use of all clinical services, treatments prescribed, and functional status. *Suicidal behavior* (ie, a suicide attempt) was defined as suicide or a self-destructive act sufficient to require medical evaluation and carried out with probable suicidal intent. *Recurrence* was defined as the presence of a bipolar episode (manic, hypomanic, mixed, or depressive). Recurrences and alcohol/drug use were evaluated according to *DSM-III-R* and *DSM-IV* using the SCID-P interview.

Data Analyses

The a priori primary study outcome was recurrence. Severity of recurrence was measured as a secondary outcome and was evaluated by the number of hospitalizations and presence of suicide attempts. In the group of mixed-episode patients, survival analyses were performed to estimate the time to first suicide attempt for patients with and without a history of suicide attempts before study entry.

For the baseline and outcome variables, comparisons between the mixed-episode group and nonmixed group were made using bivariate analyses. Mann-Whitney *U* tests were used for continuous variables and contingency tables for categorical variables (χ^2 or Fisher exact test if n ≤ 5 per cell), all with significance defined as 2-tailed $P < .05$ at stated degrees of freedom. Logistic regression modeling was used to identify factors associated with having mixed episodes versus nonmixed episodes; the variables included in the models were those sociodemographic variables that were significantly different at baseline (ie, age at onset). Data are presented as nonadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) with *P* values.

All statistical analyses were performed with SPSS 16.0 and R 2.5.1 (SPSS Inc., Chicago, Illinois).

RESULTS

Patient Sociodemographic Characteristics at Baseline

Of the 169 patients included in the study, 120 (71%) were followed up over 10 years. Of the remaining 49 patients, 4 died during the follow-up period due to completed suicide (n = 3) and medical problems (n = 1), 16 were living out of Vitoria and could not be interviewed, 11 were not found, and 18 refused to complete the visits. The baseline characteristics did not differ between the patients included in the analysis and those lost to follow-up (sex: $\chi^2 = 1.38$, $P = .24$; age: $t = -0.13$, $P = .89$; age at onset: $t = -0.12$, $P = .91$; drugs: $\chi^2 = 0.96$, $P = .33$).

Of the 120 patients who were prospectively followed up for 10 years, 44 (37%) had mixed episodes and 76 (63%) had nonmixed episodes. There were no differences in sociodemographic characteristics between the mixed-episode patients and the nonmixed group (Table 1). In both

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Table 2. Outcomes Adjusted and Nonadjusted by Age at Onset in Patients With Mixed Episodes Versus Those With Nonmixed Episodes Over the 10-Year Follow-Up[a]

			Nonadjusted Model			Adjusted Model		
Outcome	Mixed-Episode Patients (n = 44)	Nonmixed-Episode Patients (n = 76)[b]	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
At least 1 hospitalization, % (n)	84.1 (37)	63.6 (42)	3.02	1.17–7.82	.023	2.86	1.09–7.52	.033
No. of hospitalizations per patient, mean ± SD	5.43 ± 4.25	1.59 ± 1.86	1.39	1.16–1.66	<.001	1.36	1.14–1.63	<.001
Total no. of episodes per patient, mean ± SD	10 ± 5.75	5.16 ± 3.65	1.23	1.11–1.36	<.001	1.21	1.10–1.31	<.001
At least 1 depressive episode, % (n)	79.6 (35)	70.0 (49)	1.67	0.68–4.07	.262	1.78	0.71–4.45	.217
No. of depressive episodes per patient, mean ± SD	3.66 ± 3.62	2.74 ± 2.93	1.09	0.97–1.22	.150	1.08	0.96–1.22	.197
At least 1 depressive episode requiring hospitalization, % (n)	43.2 (19)	29.9 (20)	1.79	0.81–3.95	.152	1.88	0.83–6.34	.130
No. of severe depressive episodes requiring hospitalization per patient, mean ± SD	1.41 ± 2.74	0.76 ± 1.25	1.17	0.96–1.41	.121	1.17	0.95–1.43	.134
Suicidal behavior, % (n)	29.5 (13)	13.0 (9)	2.84	1.1–7.38	.032	2.38	0.89–6.34	.084

[a]Logistic regression analysis: an odds ratio > 1 indicates a higher risk of the outcome for the mixed-episode group.
[b]Some patients did not have data on all variables.

the mixed and nonmixed groups, there were more women (56.8% and 61.4%) than men, and patients were more frequently married (52.3% and 52.9%). The majority of patients in both groups had received a primary education (79.5% and 80%) and were of medium socioeconomic status (54.5% and 70%). Patients with mixed episodes had a significantly younger mean age at onset of bipolar disorder compared with the nonmixed group: 25.3 years (SD = 10.1) vs 30.8 years (SD = 13.9); *P* = .025.

Retrospective Baseline Clinical Data

Previous mood-incongruent psychotic symptoms were more frequent in the mixed-episode group (43%) compared with the nonmixed group (30%) (OR = 4.26; 95% CI, 1.12–16.24; *P* = .034). However, the difference between groups disappeared after controlling for age at onset (OR = 3.30; 95% CI, 0.84–12.98; *P* = .088). Patients with mixed episodes also had more hospitalizations in the previous year: mean, 1.05 (SD ± 0.16) vs 0.67 (SD ± 0.11) in the nonmixed group (OR = 0.86; 95% CI, 0.18–1.54; *P* = .014). This difference did not remain after controlling for age at onset (OR = 1.48; 95% CI, 0.98–2.23; *P* = .061). At baseline, more patients in the mixed-episode group reported previous abuse of alcohol and drugs than the nonmixed patients, although the differences between groups were not significant: alcohol, 23% vs 16% (OR = 0.46; 95% CI, 0.61–4.10; *P* = .35); drugs, 16% vs 6% (OR = 1.14; 95% CI, 0.86–11.37; *P* = .084).

Outcomes

All patients received mood stabilizers during follow-up. The most commonly prescribed treatment was lithium salts (65%), followed by valproate (26%) and carbamazepine (9%). There were no differences between the mixed-episode and nonmixed groups in the percentages of patients prescribed mood stabilizers.

Table 2 summarizes the outcomes over the 10-year follow-up for patients in the mixed-episode and nonmixed groups adjusted and nonadjusted by age at onset. Logistic regression analysis showed that the mean (± SD) total number of episodes (recurrences) was significantly higher in the mixed-episode group compared with the nonmixed group: 10.00 (± 5.75) vs 5.16 (± 3.65) episodes per patient in the nonadjusted model (OR = 1.23; 95% CI, 1.11–1.36; *P* < .001) and after adjusting by age at onset (adjusted OR = 1.21; 95% CI, 1.10–1.31; *P* < .001). In addition, more patients with mixed episodes had at least 1 hospitalization during follow-up: 84.1% vs 63.6% in nonmixed group (nonadjusted OR = 3.02; 95% CI, 1.17–7.82; *P* = .023). This difference remained significant after adjusting by age at onset (adjusted OR = 2.86; 95% CI, 1.09–7.52; *P* = .033). The mean (± SD) number of hospitalizations per patient was also significantly higher in the mixed-episode group: 5.43 (± 4.25) vs 1.59 (± 1.86) in the nonmixed group (nonadjusted OR = 1.39; 95% CI, 1.16–1.66; *P* < .001). After adjusting by age at onset, the difference between groups remained significant (adjusted OR = 1.36; 95% CI, 1.14–1.63; *P* < .001).

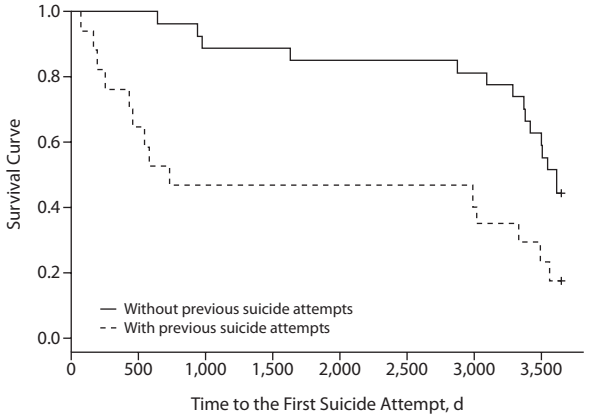
There were no significant gender differences for the total number of mixed episodes and total number of hospitalizations due to mixed episodes over the 10-year follow-up, although women represented a higher (but nonsignificant) percentage of all mixed episodes: 59.7% of mixed episodes and 60.7% of hospitalizations due to mixed episodes.

Table 2 shows there were no significant differences between the mixed-episode and nonmixed groups for any of the outcomes relating to depressive episodes (ie, at least 1 depressive episode, number of depressive episodes per patient, at least 1 depressive episode requiring hospitalization, and number of severe depressive episodes requiring hospitalization per patient).

There was a significant difference in alcohol use between the mixed group (25%) and the nonmixed group (10%) in the nonadjusted analysis (OR = 3.00; 95% CI, 1.06–8.46; *P* = .038). However, the difference between groups disappeared after adjusting for age at onset in the logistic regression model (OR = 2.64; 95% CI, 0.92–7.59; *P* = .071). There were no significant differences in drug abuse between groups, either in the nonadjusted model (OR = 0.95; 95% CI, 0.22–4.19; *P* = .630) or in the model adjusting for age at onset (OR = 0.75; 95% CI, 0.16–3.40; *P* = .706).

Suicidal behavior was higher in the group of mixed-episode patients (29.5% patients/10 years) compared with the group of nonmixed patients (13% patients/10 years)

Figure 1. Time to First Suicide Attempt During Follow-Up in Patients With Mixed Bipolar Episodes With and Without a History of Suicide Attempts



in the simple logistic regression analyses (OR = 2.84; 95% CI, 1.10–7.38; $P = .028$). However, the difference between groups was not significant after including age at onset in the model (OR = 2.38; 95% CI, 0.89–6.34; $P = .084$). Similarly, the number of suicide attempts over the 10-year follow-up was higher in the mixed-episode group (59 suicide attempts/100 patients) than in the nonmixed group (23 suicide attempts/100 patients) in the nonadjusted analysis (OR = 2.77; 95% CI, 0.07–1.97; $P = .035$), but this difference disappeared after adjusting by age at onset (OR = 1.35; 95% CI, 0.87–2.07; $P = .177$).

Survival Analysis of Suicide Attempts in Patients With Mixed Episodes

Of the 44 patients with mixed episodes, 17 (39%) had attempted suicide before entering the study. Figure 1 shows that mixed bipolar patients with previous suicide attempts prior to study entry had a shorter time to first suicide attempt during follow-up compared with mixed bipolar patients without a history of attempted suicide (likelihood ratio test = 6.07; $df = 1$; $P = .014$). Patients with mixed episodes and a history of previous suicide attempts had more than twice the risk of attempting suicide during the 10-year follow-up than patients without such a history (hazard ratio = 2.26; 95% CI, 1.21–4.21).

DISCUSSION

There are few data in the literature about the long-term follow-up of mixed bipolar patients. The majority of studies have been retrospective assessments or data obtained from short- to medium-term clinical trials.[2] In the Vitoria prospective, naturalistic, longitudinal study, we showed that mixed-episode patients had more episodes and more hospitalizations during the 10-year follow-up than nonmixed patients, indicating that mixed-episode patients have a worse long-term prognosis. This is the second study reporting long-term prospective follow-up data, and the results are in line with the first study, which demonstrated that a mixed episode at baseline was associated with greater chronicity during long-term follow-up over 13 years.[24] The results are also consistent with our baseline data and with the results of other retrospective studies[16] or short-term prospective studies.[25,26] Nevertheless, some studies have found no differences in outcome between patients hospitalized for a mixed or nonmixed episode during 12 months' follow-up.[27]

Mixed-episode patients represent more than one-third of the bipolar I disorder population in the Basque region of Spain. The percentage of mixed-episode patients is similar to that reported in other studies using the *DSM-III-R* criteria: 21% in the study by Cassidy and Carroll[12] and 45% in the studies by Dell´Osso et al.[13,17] Likewise, in a representative French national sample of mania, 30% of patients had mixed mania defined by the presence of at least 2 depressive symptoms.[3] The European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study, a large epidemiologic survey across several European countries, including Spain, found 24% mixed episodes among patients with acute mania.[28]

Age at onset differed significantly between the mixed-episode and nonmixed groups, with mixed-episode patients having a younger mean age at onset. This finding is in agreement with Cassidy and Carroll,[12] who used age at first psychiatric hospitalization as an indicator of age at onset, but it conflicts with the classical view that mixed episodes are associated with a later age at onset and first hospitalization.[2] Age at onset may be an important prognostic factor in bipolar disorder, with early age at onset being associated with a more severe disease course and greater comorbidity,[28] and with mixed symptoms.[29,30]

Age at onset has been related to mood-incongruent psychotic symptoms and to suicide in bipolar I disorder patients.[25,31,32] It has been defined as a genetic marker[23] and as the most important variable related to misdiagnosis in bipolar disorder.[31] Recently, age at onset has also been proposed as a definition marker for mood disorders[33] and as a potential course specifier for *DSM-V*.[34] This is interesting, as one of the main findings of our study is that age at onset mediates some of the classical factors related to outcome in mixed-episode patients: alcohol abuse, suicide attempts, and depressive relapses.[2] Although we cannot exclude completely that the lack of significance between groups for mixed episodes, suicide attempts, mood-incongruent psychotic symptoms, and depressive relapses is due to the sample size (note that they were all close to reaching statistical significance, with P values between .05 and .1), the important finding is that age at onset at least partially mediates the results. The importance of this mediation cannot be ignored, as it may have important implications both for new treatment targets and in genetic studies.

There were no gender differences between the mixed-episode and nonmixed groups in our study, in which subjects were enrolled as outpatients; both groups comprised about 60% women. In contrast, many inpatient samples have shown that more women than men have depressive symptoms during manic episodes.[16] Cassidy and Carroll[12] found no gender differences between mixed and manic groups when

they used the *DSM-III-R* criteria, but the gender difference was significant when alternative criteria for defining mixed mania were used; almost two-thirds of the mixed group were women, whereas approximately half of the nonmixed group were women.[12] Likewise, Hantouche and colleagues[3] reported that women were overrepresented in a mixed mania group defined using fewer depressive symptoms. In a previous study of inpatients from the same catchment area as the present study, we found that women were overrepresented in the mixed group when using the broader criteria of the Cincinnati's group.[35] Also, women were overrepresented in samples of mixed hypomania.[11,36] Taken together, these findings highlight the impact that study population/setting and diagnostic criteria can have on gender ratios.

Depressive episodes did not differ significantly between the mixed and nonmixed groups, although mixed patients had numerically more depressive episodes. Our findings are consistent with an 11-year study of bipolar patients who had at least 3 entries in a management information system, in which the number of depressive episodes was similar between mixed and nonmixed patients.[37] Some cross-sectional studies[16] and short-term follow-up studies[13] also had similar findings.

Bipolar disorder patients have a greater risk of suicide than patients with any other psychiatric disorder.[38] Up to 50% of bipolar patients will attempt suicide at least once during their lifetime, and the death rate from suicide may be as high as 20%.[23,39] In this study, mixed-episode patients had more suicide attempts during follow-up than nonmixed patients, although the difference was not significant after adjusting for age at onset. These findings are consistent with reports of higher suicidality among patients with mixed versus nonmixed episodes[19,20] and with a 2-year naturalistic study that identified that mixed episodes were independently associated with an increased risk of suicide in patients with bipolar I disorder.[39] It has been suggested that the depressive symptoms of a mixed episode are responsible for the higher suicidality.[39] In a previous study of suicide attempts in bipolar I patients, we found that suicide attempts were associated with severe depressive episodes, drug abuse, and a family history of affective disorders.[23] Recently, the Jorvi Bipolar Study in Finland, a prospective, naturalistic study of inpatients and outpatients with a new episode of bipolar disorder, found that suicidal behavior was associated with depressive aspects of the illness and that severity of depression and younger age predicted suicide attempts during mixed episodes.[40] The Barcelona Bipolar Disorder Program also found an association between suicidality, comorbidity, and the burden of depressive symptoms during depressive as well as nonmixed episodes.[41] Further research on the associations between a diagnosis of mixed mania, severity of depressive symptoms and suicidality is needed.

Mixed-episode patients with a history of suicide attempts were at increased risk of repeated suicide attempts and had a shorter time to their next suicide attempt compared with patients without a history of suicidal behavior. Our findings are consistent with earlier studies showing that previous suicide attempts are one of the main risk factors for suicide in bipolar patients.[42,43] Patients with previous suicide attempts may benefit from treatment aimed specifically at reducing the risk for suicide.

Several limitations of this study must be considered. First, the diagnosis of a mixed episode was based on *DSM-III*/*DSM-IV* criteria and, therefore, only includes patients with severe symptoms and impairment. Thus, acute mania patients experiencing concurrent depressive symptoms but not a full major depressive syndrome will not have been diagnosed with a mixed episode according to the *DSM* criteria and will be in the nonmixed group. Second, our definition of suicidal behavior (suicide or a self-destructive act sufficient to require medical evaluation and carried out with probable suicidal intent) may differ from that used in other studies, making comparisons difficult. Third, information was provided by patient self-reporting at the bimonthly visits, which may give rise to recall bias, although family member reports and clinical records may have reduced this bias. Another possible limitation of our study is that other variables not included in the analysis may have influenced outcomes. Moreover, patients received psychopharmacologic treatment as usual during the study but, as treatment was not randomized or controlled, it may have influenced outcomes.

Despite the limitations of the present study, the findings of a worse long-term prognosis in patients with bipolar mixed episodes imply that greater attention should be paid to such patients. In particular, efforts to reduce depressive morbidity and suicidal risk may be beneficial.

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