CME

Factors Associated With Suicide Attempts in 648 Patients With Bipolar Disorder in the Stanley Foundation Bipolar Network

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Background: Clinical factors related to suicide and suicide attempts have been studied much more extensively in unipolar depression compared with bipolar disorder. We investigated demographic and course-of-illness variables to better understand the incidence and potential clinical correlates of serious suicide attempts in 648 outpatients with bipolar disorder.

Method: Patients with bipolar I or II disorder (DSM-IV criteria) diagnosed with structured interviews were evaluated using self-rated and clinician-rated questionnaires to assess incidence and correlates of serious suicide attempts prior to study entry. Clinician prospective ratings of illness severity were compared for patients with and without a history of suicide attempt.

Results: The 34% of patients with a history of suicide attempts, compared with those without such a history, had a greater positive family history of drug abuse and suicide (or attempts); a greater personal history of early traumatic stressors and more stressors both at illness onset and for the most recent episode; more hospitalizations for depression; a course of increasing severity of mania; more Axis I, II, and III comorbidities; and more time ill on prospective follow-up. In a hierarchical logistic regression, a history of sexual abuse, lack of confidant prior to illness onset, more prior hospitalizations for depression, suicidal thoughts when depressed, and cluster B personality disorder remained significantly associated with a serious suicide attempt.

Conclusion: Our retrospective findings, supplemented by prospective follow-up, indicate that a history of suicide attempts is associated with a more difficult course of bipolar disorder and the occurrence of more psychosocial stressors at many different time domains. Greater attention to recognizing those at highest risk for suicide attempts and therapeutic efforts aimed at some of the correlates identified here could have an impact on bipolar illness–related morbidity and mortality.

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Bipolar disorder is associated with a substantial burden of illness-related morbidity and mortality.[1–4] A number of factors have been linked to patients with bipolar disorder who commit suicide, including a history of prior serious attempts,[5,6] as well as genetic and experiential variables. Genetic predisposition to suicide appears to contribute beyond that of affective illness itself.[7–13]

Based on lifetime suicide rates among subjects in the Epidemiologic Catchment Area database, Chen and Dilsaver[14] found that the odds ratio for suicide attempts in patients with bipolar disorder was 6.2, which was a ratio higher than for any other Axis I disorder, including unipolar major depression with an odds ratio of 3.1. Kessler et al.,[15] in the National Comorbidity Survey, also found that the odds ratio for a lifetime history of a suicide attempt was highest in bipolar disorder with an odds ratio of 29.7 (95% CI = 11.7 to 75.1) compared with any other disorder.

Jamison has written extensively on the recent pandemic of suicide, particularly in teenagers and young adults with

affective disorders.[2,16,17] To the extent that bipolar illness puts young individuals at risk for the accumulation of a number of Axis I and Axis II comorbidities (the former including both alcohol and substance abuse disorders), it would appear appropriate to pay special attention to these and other factors potentially associated with suicide attempts so that some of these elements might be prevented or ameliorated. Given the likely presence of a cohort effect for an increased incidence of both unipolar depression and bipolar disorder as a function of each generation since World War II,[18–22] these issues become all the more pressing in relationship to developing early recognition and prevention strategies.

The presence of a comorbid anxiety disorder or extreme psychic agitation and panic during depression[11,23–25] has been linked to suicide attempts or completed suicide. So too have dysphoric mania (i.e., depressive symptoms meeting concomitant criteria for major depression during a manic episode[26,27] as well as subsyndromal symptoms of depression during mania[26]) and a history of alcohol and substance abuse.[9,26] Dilsaver et al.[28] found that patients with bipolar depression were more likely suicidal compared with patients with depressive mania and those with depressive mania much more so compared with patients with pure mania. They also found that the group with depressive mania and bipolar depression had a much higher rate of intra-episode panic disorder than the pure mania group. The occurrence of negative life events[29–31] and the absence of social supports have likewise been closely linked to suicide attempts, as has inadequacy of ongoing psychotherapeutic and pharmacologic therapies. The ready availability of lethal means, such as a handgun or a potentially toxic medication, also seems to be a significant factor for suicidal individuals in general.[16,32]

Although many clinical factors related to suicide have been examined in unipolar major depression, there have been few systematic attempts to identify correlates of suicide attempts in patients with bipolar disorder. We therefore examined potential risk factors in patients with bipolar illness assessed and treated in the Stanley Foundation Bipolar Network (SFBN)[33] who had made a serious suicide attempt in the past compared with those who had not, hoping that a clearer understanding of such factors may lead to better recognition and treatment of those at highest risk. On the basis of previous research in other illnesses, we hypothesized that Axis I and Axis II comorbidity, a family history of psychiatric disorder and/or suicide, early traumatic events and more proximal stressors and lack of social support, earlier illness onset, and a more severe course of bipolar illness would be associated with suicide attempts.[29,34–39]

METHOD

Six hundred forty-eight patients with DSM-IV bipolar I or II disorder gave verbal and written informed consent to participate in the evaluation and treatment of their illness in open naturalistic follow-up and again in open and double-blind, randomized controlled studies, as described in detail elsewhere.[33,40,41] This cohort of patients represents an extension of those previously described regarding demographics,[42] Axis I comorbidity,[43] and the relationship of early physical or sexual abuse to bipolar illness characteristics.[44]

The major focus of this study was to determine the incidence and correlates of serious suicide attempts as reported by patients in a detailed patient questionnaire, which also inquires about a variety of demographic and retrospective course-of-illness factors.[33,42] A serious suicide attempt was defined in the questionnaire as one requiring medical attention, emergency room visit, or hospitalization. We acquired information about the number of suicide attempts each patient had made, but the date of the suicide attempt(s) or treatment status at the time of the attempt(s) was not obtained. Patients received Axis I diagnoses based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-P).[45] Axis II comorbidity was obtained from the self-rated Personality Diagnostic Questionnaire-4+ (PDQ-4+).[46]

While participating in the Network, patients were asked to complete daily mood ratings and the degree of mood-related functional impairment on the National Institute of Mental Health Life-Chart Method (LCM).[47,48] A prospective daily version of the LCM was also completed by a clinician together with the patient, whether or not self-ratings were available. This was accomplished at each clinic visit, which ranged from once a week or every 2 weeks during periods of active illness to once a month during illness quiescence. Other ratings included the Inventory of Depressive Symptomatology (IDS-C),[49] the Young Mania Rating Scale (YMRS),[50] and the Global Assessment of Functioning (GAF).[51] Patients were also rated on the Clinical Global Impressions scale, Bipolar Version (CGI-BP)[52] following the completion of each medication evaluation. Interrater reliability across all sites was documented as previously described.[33,53]

The patient questionnaire was also used to assess a positive family history of different psychiatric illnesses and suicide in first-degree relatives. A family history was considered positive if the disorder was rated by the proband as "likely" or "definitely" present in a first-degree relative; however, confirmatory diagnostic interviews were not performed with individual family members. Questions regarding a history of early (childhood or adolescence) physical or sexual abuse were embedded in the patient questionnaire as previously described,[44] and questions about more current stressors (at illness onset and prior to the latest episode) were drawn from DSM-IV, Axis IV:

Table 1. Odds Ratios for Variables Associated With Suicide Attempts: Hierarchical Logistic Regression[a]

Variable	Model 1	Model 2	Model 3	Model 4	Model 5
Family history of suicide or serious attempt	1.46	1.16	1.17	1.01	1.05
Early physical abuse		2.32**	1.99**	1.83*	1.77*
Early sexual abuse		2.33**	2.48**	2.31**	2.27**
Lack of confidant prior to illness onset		1.64*	1.96**	2.00**	2.00**
Suicidal thoughts when manic			1.39	1.18	1.21
> 4 hospitalizations for depression			14.00**	13.37**	12.31**
Suicidal thoughts when depressed			2.07**	1.97**	2.02**
Axis II cluster B comorbidity				2.12**	1.99**
Past history of anxiety disorder				1.28	1.21
Income < $20,000					1.50
No college education					1.44
Inadequate mental health/health care insurance					1.31

[a]Each set of variables was sequentially entered into the logistic regression in rough approximation of occurrence, i.e., family history, early stressors, course of illness, comorbidity, and demographics. Model 5 shows variables that remain independently associated with the occurrence of suicide attempts. Values > 1 suggest an increased likelihood of having a past suicide attempt.
*p < .10.
**p < .05.

Psychosocial and Environmental Problems.

A subset of the total cohort was followed prospectively for at least 1 year, with a mean duration of follow-up of 2.8 years. The duration of time ill was assessed by 2 methods: (1) clinician daily LCM ratings as days depressed at the moderate or higher severity level, and days (hypo)manic at mild or higher severity levels; and (2) IDS ratings equal to or greater than 14 and YMRS ratings equal to or greater than 10. Severity of depressive illness was also assessed with the IDS-C total score at each interview, as well as the degree of suicidal ideation on the IDS-C, item 18, on a 4-point scale.

Statistical analyses were performed using the Statistical Package for the Social Sciences Version 10 (SPSS, Inc., Chicago, Ill., 1999). Severity of illness and other measures were assessed by group t tests in those with and without a reported history of at least 1 serious suicide attempt. Chi-square tests examined the differential percentage of patients without any serious suicide attempt as a function of a given variable. A Hochberg adjustment[54] was applied for multiple comparisons.

In an attempt to understand the magnitude and degree of independent relationships to attempted suicide, a hierarchical logistic regression was performed (Table 1) on the set of variables found significant in the univariate analysis. The variables were organized on a rough time-related continuum with family history and early stressors coming in the first blocks of the regression, and demographics, course-of-illness variables, and comorbidities being added in the later blocks. To deal with the issue of multicollinearity, variables that were highly related to others were removed and those variables with the highest relationship to suicide attempts were retained.

RESULTS

Thirty-four percent of the 648 predominately bipolar I patients in the SFBN reported a history of a serious suicide attempt (Table 2). There were no significant differences in the mean number of suicide attempts by diagnostic subtype and gender. Of those (N = 219) who attempted suicide, 46.2% had made 1 suicide attempt, 25.9% had made 2 attempts, 13.2% had made 3, and 14.1% had made 4 or more attempts. The overall population was highly educated, with 42% having completed 4 or more years of college. Compared to those without, those with a history of a suicide attempt had significantly less college education, less income (below $20,000/year), and an earlier age at onset of bipolar disorder (17.2 vs. 20.6 years). A higher percentage of suicide attempters had an age at illness onset ≤ 14 years than non-attempters (Table 3).

Suicide attempters, when compared with non-attempters, reported a significantly greater family history of substance abuse and suicide attempts; an increased incidence of early physical or sexual abuse (as well as physical abuse in adulthood); a pattern of increasing severity of mania over the course of their illness; more prior hospitalizations for depression; and more reported suicidal thoughts when manic and when depressed. The percentage of patients who reported past suicide attempts increased in a roughly linear fashion, with the reported frequency of physical abuse occurring in either childhood, adolescence, or adulthood (Figure 1). In contrast, any amount of sexual abuse (from rarely to frequently compared with none) as a child was associated with an increased percentage of patients having made suicide attempts. We found an apparent additive effect of the occurrence of both physical and sexual abuse together, as opposed to either alone. Of those patients with no history of abuse, 25.7% attempted suicide. This increased approximately by another 15% with either physical or sexual abuse only and by approximately 30% with the presence

Table 2. Patient Demographics and History of Suicide Attempt

Variable	Attempters N	Attempters %	Non-Attempters N	Non-Attempters %	χ^2	p Value
Female	136	62	238	56	2.61	.063
Bipolar disorders[a]					0.256	.968
Bipolar I	98	78	207	76		
Bipolar II	20	16	48	18		
Bipolar NOS	5	4	12	4		
Schizoaffective, bipolar type	2	2	5	2		
Income < $20,000	102	47	134	32	13.62	< .001*
No college	143	65	232	54	7.48	.004*
Single	136	62	225	52	5.46	.012*
	N	Mean ± SD	Mean ± SD		F	p Value
Mean age, y	646	40 ± 10	42 ± 12		3.88	.049
Age at onset, y	632	17 ± 10	21 ± 11		15.02	< .001*
Mean years ill[b]	630	24 ± 10	21 ± 10		12.14	.001*
Duration untreated, y	602	9 ± 10	10 ± 11		0.73	.395

[a]Diagnosis obtained using the Structured Clinical Interview for DSM-IV Axis I Disorders on a subset of 397 of 648 patients.
[b]Covaried for age.
*Significant after Hochberg adjustment for multiple comparisons.
Abbreviation: NOS = not otherwise specified.

Table 3. Family History, Environmental Adversities, and Illness Variables in Suicide Attempters and Non-Attempters

Variable[a]	Attempters (N = 219) N	Attempters (N = 219) %	Non-Attempters (N = 429) N	Non-Attempters (N = 429) %	χ^2 (df = 1)	p Value
I. Family history of						
Depression	100	46	274	64	1.36	.141
Bipolar disorder	115	53	228	53	0.04	.453
Alcoholism	122	56	209	49	2.40	.071
Drug abuse	112	51	164	38	9.45	.001*
Schizophrenia	54	25	91	21	1.68	.117
Suicide	96	44	136	32	9.22	.002*
Other psychiatric illnesses[b]	121	55	205	48	3.81	.031
II. Abuse						
Physical[c]						
Early[d]	90	41	94	22	25.54	< .001*
Adult	25	11	18	4	15.53	< .001*
Sexual[e]						
Early	90	41	99	23	21.92	< .000*
Adult	17	8	25	6	2.49	.083
III. Course of illness						
Age at onset ≤ 14 y	92	42	94	22	11.62	< .001*
Hospitalizations for depression	68	31	18	4	82.27	< .001*
More severe episodes over time	97	44	158	37	4.71	.019
Increasing severity of						
Mania	121	55	180	42	10.40	.001*
Depression	137	63	230	54	4.50	.021
Suicidal thoughts						
Manic	52	24	33	8	32.94	< .001*
Depressed	111	51	118	28	33.93	< .001*
Cycling[f]						
Rapid cycling	43	20	76	18	0.67	.238
Ultra rapid cycling	16	7	47	11	1.70	.122
Ultradian cycling	50	23	73	17	4.36	.025

[a]Unless otherwise noted, all data ascertained from patient questionnaire.
[b]Other psychiatric illnesses include anxiety, panic attacks, eating disorders, attention deficit disorder, behavioral problems, and autism.
[c]Physical abuse is defined as occasionally or frequently experiencing physical injury or harm such as beating, punching, kicking, biting, burning, choking, or being assaulted with a weapon.
[d]Early abuse is considered abuse that was experienced during childhood and/or adolescence.
[e]Sexual abuse is defined as rarely, occasionally, or frequently experiencing sexual molestation, sexual attack, or forced sexual activity.
[f]Retrospective cycling frequency is based on clinician assessment.

of both physical and sexual abuse (i.e., a doubling of the rate of suicide attempts to 57.4% compared with 25.7% with no abuse) (Figure 2).

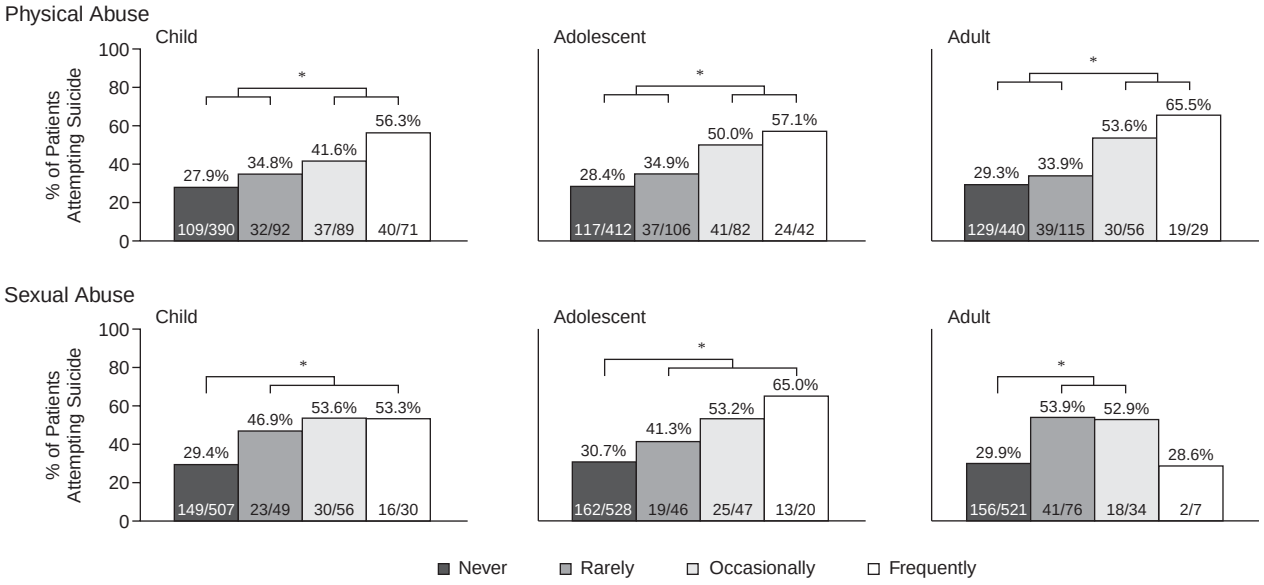
Axis I and II comorbidity (Table 4) was significantly associated with suicide attempts. Suicide attempters had a greater prevalence of a past history of anxiety disorders than non-attempters. Suicide attempters also had a significantly greater prevalence of a past (23% vs. 11%) or current (16% vs. 6%) diagnosis of an eating disorder as well as a greater mean number of Axis I comorbid disorders. Similarly, they showed a greater number of Axis II diagnoses with more diagnoses in each cluster and a higher mean total PDQ score. The most statistically robust relationship held for cluster B disorders (dramatic-emotional), which also remained significant in the hierarchical logistic regression analysis described below.

Suicide attempters reported the occurrence of a greater number of negative stressors in the 12 months prior to both illness onset ($F = 12.89$, $df = 326.1$, $p < .001$) and prior to the most recent episode ($F = 11.49$, $df = 365.9$, $p < .001$). In contrast, there were no significant differences in the occurrence of positive life events during the year prior to illness onset ($F = 0.46$, $df = 518$, $p = .499$) or the most recent episode ($F = .06$, $df = 529$, $p = .814$). A greater percentage of patients who had attempted suicide compared with non-attempters had experienced the death of an important other ($\chi^2 = 10.7$, $p < .001$) and a lack of a confidant ($\chi^2 = 9.56$, $p < .001$) in the 12 months preceding the onset of their bipolar illness.

Likewise, single parents showed a higher percentage of suicide attempts compared with those who were married or cohabiting and had children ($\chi^2 = 6.58$, $p < .008$ for mothers; $\chi^2 = 6.77$, $p < .009$ for fathers). In addition to this lack of social (partner) support, patients with a history of suicide attempts reported more medical comorbidity ($\chi^2 = 12.2$, $p < .001$), inadequate health or mental health insurance coverage ($\chi^2 = 8.85$, $p < .002$), and difficulty in getting health/mental health care services ($\chi^2 = 9.89$, $p < .001$) in the 12 months preceding the most recent episode.

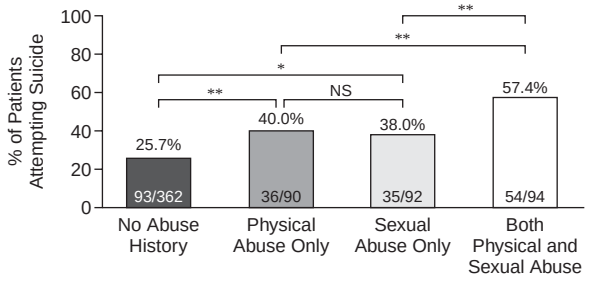
We performed a hierarchical logistic regression (Table 1) using variables that were sig-

Figure 1. Suicidality Increases With Rate of Recurrence of Early Abuse



*p < .001.

Figure 2. Additive Effect of Early Physical[a] and Sexual Abuse[b] on Suicidality[c]



[a]Early physical abuse is defined as occasionally or frequently experiencing physical injury or harm such as beating, punching, kicking, biting, burning, choking, or being assaulted with a weapon during childhood or adolescence.
[b]Early sexual abuse is defined as rarely, occasionally, or frequently experiencing sexual molestation, sexual attack, or forced sexual activity during childhood or adolescence.
[c]Chi-square analysis: *p < .05, **p < .01.

nificant in the univariate analysis. In the last model (model 5) of the hierarchical regression, the distal stressor of early sexual abuse and the lack of a confidant prior to illness onset remained significantly associated with a past history of suicide attempts. The illness variables of greater than 4 hospitalizations for depression and suicidal thoughts when depressed were likewise related to prior attempts. Of the comorbid disorders, only cluster B personality disorders remained significantly associated with having made a suicide attempt.

In the 415 patients who have been followed prospectively with clinician ratings for at least 1 year (mean = 2.8 years; median = 2.4 years; range, 1–5.7 years) (Table 5), those with a prior history of suicide attempts compared with those without such a history experienced a greater overall time ill (by LCM), duration of depression (percent time ill based on the IDS and LCM), severity of depression (by IDS), and amount of current suicidal ideation (item 18 on the IDS).

DISCUSSION

In an examination of factors related to prior serious suicide attempts in patients with bipolar disorder, our data reveal multiple correlates of attempted suicide in a number of different illness, social, and temporal domains. These include genetic or familial variables; distal and proximal environmental adversities; loss of social and medical support; more Axis I, II, and III comorbidities; and a more serious course of bipolar illness reported retrospectively and observed prospectively. Patients who reported the occurrence of the distal stressors of physical or sexual abuse in childhood or adolescence and the more proximal stressors (i.e., the death of an important other or lack of confidant in the 12 months prior to illness onset) were more likely to have a history of a suicide attempt than patients without such stressors. Moreover, there appeared to be a "dosage" effect in the relationship of early adversity and suicide attempts in that both the reported frequency of recurrence of either type of abuse and

Table 4. Lifetime Axis I and II Comorbidities in Suicide Attempters and Non-Attempters

Disorder	Attempters (N = 122)[a]	Non-Attempters (N = 258)[a]	χ^2	F	p Value
Axis I[b]					
Anxiety disorder	64 (52)	100 (39)	6.34		.009*
Eating disorder	28 (23)	29 (11)	8.60		.003*
Drug abuse	37 (30)	59 (23)	1.84		.110
Alcohol abuse	59 (48)	96 (37)	2.58		.068
PTSD	14 (11)	19 (7)	1.83		.125
No. of Axis I comorbidities, mean[b]	1.56	1.11		11.74 (df = 213.82)	.001*
Axis II[c]	(N = 197)	(N = 395)			
Cluster A disorder[c]	100 (51)	156 (39)	6.80		.006*
Cluster B disorder[c]	118 (60)	170 (43)	14.96		< .001*
Cluster C disorder[c]	145 (74)	256 (65)	4.65		.019*
Total PDQ-4+ score, mean[c]	38.5	34.5		6.56	.010*
No. of disorders, mean[c]	3.0	2.4		9.53	.002*

[a]Values shown as N (%) unless otherwise noted.
[b]Axis I comorbidity based on SCID interview.
[c]Axis II comorbidity measured by PDQ-4+. Cluster A includes schizoid, schizotypal, and paranoid personality disorders; cluster B includes narcissistic, borderline, histrionic, and antisocial personality disorders; cluster C includes dependent, avoidant, and obsessive-compulsive personality disorders.
*Significant after Hochberg adjustment for multiple comparisons.
Abbreviations: PDQ-4+ = Personality Diagnostic Questionnaire-4+, PTSD = posttraumatic stress disorder, SCID = Structured Clinical Interview for DSM-IV Axis I Disorders.

Table 5. Bipolar Patients With a History of Prior Suicide Attempts Are More Ill on Prospective Follow-Up[a]

Variable	Attempters (N = 146) Mean ± SD	Non-Attempters (N = 269) Mean ± SD	F	p Value
Severity of depression (IDS score; N = 415)	27.27 ± 6.22	25.23 ± 6.43	9.67	.002*
Current suicidal ideation (IDS item 18)	12.48 ± 17.18	7.17 ± 11.86	9.75	.002*
% of time depressed (IDS score ≥ 14)	56.92 ± 28.23	49.66 ± 29.50	5.90	.016*
% of time depressed (LCM ≥ moderate)	37.76 ± 25.30	30.89 ± 24.38	6.54	.011*
Overall % of time ill/time followed (LCM)	54.42 ± 27.84	44.06 ± 28.83	11.12	.001*

[a]Mean follow-up = 2.8 years.
*Significant after Hochberg adjustment for multiple comparisons.
Abbreviations: IDS = Inventory of Depressive Symptomatology, LCM = National Institute of Mental Health Life-Chart Method.

the concurrence of each type of abuse were roughly linearly or additively associated with increased rates of suicide attempts.

In relationship to suicide attempts, the occurrence of early sexual abuse as well as lack of a confidant prior to illness onset survived the hierarchical logistic regression, while the familial relationships did not. Thus, environmental adversity (i.e., early stressors and more proximal loss of social supports) seems more highly associated with suicide attempts than genetic or familial variables in this population of outpatients with bipolar illness. A substantial preclinical[55–58] and clinical literature[59] supports the notion that early stressful life experiences may act as vulnerability factors and provide an underlying neural substrate for the subsequent provocation of affective episodes by stressors occurring in adulthood. This postulate is better documented in unipolar illness[60–62] than in bipolar illness,[44] although our current data are supportive of such a view.

Bipolar patients with a past history of suicide attempts, in addition to early traumatic experiences and prior interpersonal losses also reported a greater mean number of negative life events prior to their first and most recent affective episode. They also reported an earlier onset of bipolar illness, a pattern of increasing severity of mania over time, and an increased number of prior hospitalizations for depression, as well as a greater incidence of suicidal thoughts when manic and depressed. Furthermore, they reported more medical illnesses and problems with health/mental health insurance and access to health care services in the 12 months preceding their most recent affective episode. A number of these relationships to suicide attempts appear similar to those reported by Brown and Harris[39] for the occurrence of depression itself, namely, that current adversity and loss of social support appear to play a highly significant role.

The Axis I disorders, even though they were significant only in the univariate analysis, are of interest in that anxi-

ety disorders and eating disorders were correlates of suicide attempts, consistent with observations in other illness cohorts. The increased incidence of suicidality in individuals with Axis II comorbidity, particularly comorbidity related to cluster B (histrionic, narcissistic, borderline, antisocial), which survived the hierarchical logistic regression, are of added interest. It appears that this personality disorder comorbidity may have its effect on suicidality above and beyond the effects of additional illness burden, loss of social supports, lack of health care access, and increased negative life events that are often intertwined with personality disorder. Axis II diagnoses based on the PDQ-4+ appear to overestimate the degree of personality disorder comorbidity compared with clinician-derived interviews.[63] Nonetheless, since those in this patient cohort both with and without suicide attempts rated themselves on this same scale, a relative increase in Axis II comorbidity, if not the absolute amount compared with clinician-based interviews, would appear to be pertinent.

The relationship of increased suicidality to comorbid medical illness that we observed again raises many questions about interrelationships and causal associations. An increase in medical comorbidity has been shown to be closely associated with the occurrence of early extreme environmental stressors,[44] as other investigators have suggested.[64–67] This increase of medical comorbidity may indirectly add to illness burden and demoralization in patients with bipolar illness, especially in light of the associated lack of adequate insurance and health care access reported by those who made suicide attempts.

There are a number of methodological caveats that suggest caution in the interpretation of these data. This is particularly the case regarding familial or genetic influences because of lack of individual interviews of family members. The lack of verification of the existence of early environmental adversity beyond that of self-report has been previously noted,[44] but in the context of a variety of other demographic and illness-related variables on the patient questionnaire, there would appear to be little reason to suspect their lack of veracity. Moreover, in cases of physical or sexual abuse that have been confirmed in the public record, a link to subsequent affective illness and suicidality has also been observed[68,69] and patient self-report is if anything an underestimate of the actual occurrence of abuse.[65,70,71]

Another shortcoming was that the history of a suicide attempt was also based on retrospective self-report in the patient questionnaire. As such, detailed information about the date of the attempt, precipitating factors, timing of attempt, and the degree of lethality cannot be accurately ascertained. However, a serious suicide attempt was defined operationally for the patient as one requiring medical attention, emergency room visit, or hospitalization, and this would likely lessen the reporting of superficial harm to oneself. In addition, we evaluated variables in relationship only to the presence or absence of a suicide attempt and not to number of suicide attempts or the potential impact of treatment. We also could not be certain whether a given life event preceded or followed a suicide attempt, since details surrounding attempts and the dates of the event or suicide attempt were not gathered. However, it is highly likely that the occurrence of physical or sexual abuse (in childhood or adolescence) and interpersonal loss and lack of social support at illness onset preceded the suicide attempts, especially since the mean age at onset of bipolar illness was 17 years and most attempts would presumptively occur after illness onset.

In this analysis, we have not taken into account the adequacy or type of past treatment. Patients were in naturalistic treatment in the vast majority of instances prior to their entry into the SFBN, and accurate data about treatment at the time of the attempt were not available. How lithium[72–74] and other treatments might have interacted with the presence or absence of prior suicide attempts remains to be delineated. Finally, it is unknown how these findings pertaining to the occurrence of suicide attempts may or may not pertain to the occurrence of completed suicide.

Despite these limitations, this study provides data on a substantial cohort of patients with well-diagnosed and characterized bipolar illness. Patients were all highly motivated outpatients willing to take on the added burden of research participation and its associated questionnaires and rating forms on a regular basis. How our findings apply to other, more severely ill inpatient cohorts or to perhaps less severely ill bipolar outpatients in the private sector remains to be determined. However, the identification of genetic or familial factors, distal and more proximal psychosocial adversities, as well as the accumulation of comorbid disorders, negative life events, and the occurrence of a more severe course of illness, are each consistent with the multiplicity of factors related to the occurrence of suicide attempts in the general literature. To the extent that these findings are applicable to at least some cohorts of outpatients with bipolar illness, their apparent multi-factorial nature takes on added interest. The data suggest that multiple domains, and within each domain the total number or burden of problems, are important correlates of suicide attempts in outpatients with bipolar illness.

The current data thus highlight a number of public health and public policy issues and suggest multiple avenues for potential intervention. The early recognition of those at highest risk may be of great importance in instituting appropriate and early treatment. Early severe stressors, more than 4 prior hospitalizations for depression, suicidal thoughts when depressed, and cluster B personality disorders were strongly associated with suicide

attempts. Having made a suicide attempt in the past was predictive of current increased amount of time depressed and more severe depression and suicidal ideation in prospective follow-up. While family history and some comorbid psychiatric disorders, demographic, and course-of-illness variables lost significance in the hierarchical model, they nevertheless may prove to be important contributors to suicidality clinically, and additional therapeutic efforts targeted to these variables would appear in order if they are present. More vigorous treatment of the depressive phases of bipolar disorder, which are 3 times more prevalent than manic periods in general[75] and are especially prominent in those patients with a history of suicide attempts in particular, would also appear to be an important avenue of pursuit. When lithium treatment is maintained in a continuous fashion over the long term, its amelioration of the high rate of suicide in the primary affective disorders also appears worthy of refocus and reconsideration.[72–74]

The literature is not conclusive as to the effectiveness of antidepressants in lowering suicide rates even in unipolar depressed patients,[76] and the best approaches to the treatment and prevention of depressive episodes in bipolar disorder remain controversial and to be established in controlled clinical trials. How specific medications or combinations thereof may additionally aid in the prevention of suicidality, suicide attempts, and completed suicides in bipolar patients is much further from being established. However, Angst et al.[77] found that in unipolar and bipolar patients the risk for completed suicide was markedly reduced if one was in treatment (6.4% suicide rate) compared with not being in treatment (29.2% suicide rate). Better detection and proper diagnosis[78,79] as well as intensive and long-term treatment have been found to reduce suicidal behavior in both unipolar and bipolar patients.[80–82]

Further intensive study and perhaps the eventual development of more specific guidelines for addressing and treating the depressive components of bipolar illness and its associated suicidality would be helpful in mandating better and more intensive care in this era of limited health care access. Such guidelines might include explicit statements about the necessary frequency of visits to physicians and other members of a multidisciplinary team required to adequately address the large segment of patients with bipolar disorder who are at high risk for suicide and who are treatment resistant.[75] Without the necessary health care supports that are required to adequately deal with bipolar illness, which is the most complex, highly comorbid, and potentially lethal illness among the major psychiatric disorders, its associated morbidity and suicidality will continue to have devastating effects on large numbers of individuals and their families.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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REFERENCES

1. Guze SB, Robins E. Suicide and primary affective disorders. Br J Psychiatry 1970;117:437–438
2. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY: Oxford University Press; 1990
3. Goodwin FK. Anticonvulsant therapy and suicide risk in affective disorders. J Clin Psychiatry 1999;60(suppl 2):89–93
4. Oquendo MA, Waternaux C, Brodsky B, et al. Suicidal behavior in bipolar mood disorder: clinical characteristics of attempters and nonattempters: J Affect Disord 2000;59:107–117
5. Goldstein RB, Black DW, Nasrallah A, et al. The prediction of suicide. Arch Gen Psychiatry 1991;48:418–422
6. Nordström P, Asberg M, Aberg-Wistedt A, et al. Attempted suicide predicts suicide risk in mood disorders. Acta Psychiatr Scand 1995;92:345–350
7. Giovanni PA, Placidi MA, Oquendo MA, et al. Aggressivity, suicide attempts and depression: relationship to cerebrospinal fluid monoamine metabolite levels. Biol Psychiatry 2001;50:783–791
8. Mann JJ, Brent DA, Arango V. The neurobiology and genetics of suicide and attempted suicide: a focus on the serotonergic system. Neurospychopharmacology 2001;24:467–477
9. Mann JJ, Waternaux C, Haas GL, et al. Toward a clinical model of suicidal behavior in psychiatric patients. Am J Psychiatry 1999;156: 181–189
10. Klimes-Dougan B, Free K, Ronsaville D, et al. Suicidal ideation and attempts: a longitudinal investigation of children of depressed and well mothers. J Am Acad Child Adolesc Psychiatry 1999;38:651–659
11. Fawcett J, Busch KA, Jacobs D, et al. Suicide: a four-pathway clinical-biochemical model. Ann N Y Acad Sci 1997a;836:288–301
12. Brent DA, Bridge J, Johnson BA, et al. Suicidal behavior runs in families. Arch Gen Psychiatry 1996;53:1145–1152
13. Stallone F, Dunner DL, Ahearn J, et al. Statistical predication of suicide in depressives. Compr Psychiatry 1980;21:381–387
14. Chen YW, Dilsaver SC. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. Biol Psychiatry 1996;39:896–899
15. Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. Arch Gen Psychiatry 1999;56:617–626
16. Jamison KR. Suicide and bipolar disorder. J Clin Psychiatry

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2000;61(suppl 9):47–51
17. Jamison KR. Night Falls Fast: Understanding Suicide. Knopf A, ed. New York, NY: Knopf; 1999
18. Gershon ES, Hamovit JH, Guroff J, et al. Birth-cohort changes in manic and depressive disorders in relatives of bipolar and schizoaffective patients. Arch Gen Psychiatry 1987;44:314–319
19. Klerman GL, Weissman MM. Increasing rates of depression. JAMA 1989;261:2229–2235
20. Weissman MM, Bland R, Joyce PR, et al. Sex differences in rates of depression: cross-national perspectives. J Affect Disord 1993;29:77–84
21. Visscher P, Yazdi MH, Jackson AD, et al. Genetic survival analysis of age-at-onset of bipolar disorder: evidence for anticipation or cohort effect in families. Psychiatr Genet 2001;11:129–137
22. McInnis MG, McMahon FJ, Chase GA, et al. Anticipation in bipolar affective disorder. Am J Hum Genet 1993;53:385–390
23. Bakish D. The patient with comorbid depression and anxiety: the unmet need. J Clin Psychiatry 1999;60:20–24
24. Fawcett J. Treating impulsivity and anxiety in the suicidal patient. Ann N Y Acad Sci 2001;932:94–102; discussion 102–105
25. Fawcett J. The detection and consequences of anxiety and depression. J Clin Psychiatry 1997;58:35–40
26. Goldberg JF, Garno JL, Portera L, et al. Correlates of suicidal ideation in dysphoric mania. J Affect Disord 1999;56:75–81
27. Strakowski SM, McElroy SL, Keck PE Jr, et al. Suicidality among patients with mixed and manic bipolar disorder. Am J Psychiatry 1994;153:674–676
28. Dilsaver SC, Chen YW, Swann AC, et al. Suicidality, panic disorder and psychosis in bipolar depression, depressive-mania and pure mania. Psychiatry Res 1997;73:47–56
29. Brown J, Cohen P, Johnson JG, et al. Childhood abuse and neglect: specificity of effects on adolescent and young adult depression and suicidality. J Am Acad Child Adolesc Psychiatry 1999;38:1490–1496
30. Tsai SY, Lee JC, Chen CC. Characteristics and psychosocial problems of patients with bipolar disorder at high risk for suicide. J Affect Disord 1999;52:145–152
31. Isometsä E, Heikkinen M, Henriksson M, et al. Recent life events and completed suicide in affective disorder: a comparison with major depressive suicides. J Affect Disord 1995;33:99–106
32. Hirschfeld RM, Russell JM. Assessment and treatment of suicidal patients. N Engl J Med 1997;337:910–915
33. Leverich GS, Nolen WA, Rush AJ, et al. The Stanley Foundation Bipolar Treatment Outcome Network, 1: longitudinal methodology. J Affect Disord 2001;67:33–44
34. Molnar BE, Berkman LF, Buka SL. Psychopathology, childhood sexual abuse and other childhood adversities: relative link to subsequent suicidal behaviour in the US. Psychol Med 2001;31:965–977
35. Roy A. Relation of family history of suicide to suicide attempts in alcoholics. Am J Psychiatry 2000;157:2050–2051
36. Roy A. Family history of suicide. Arch Gen Psychiatry 1983;40:971–974
37. Vocisano C, Klein DN, Keefe RS. Lifetime comorbidity, lifetime history of psychosis and suicide attempts, and current symptoms of patients with deteriorated affective disorder. Psychiatry Res 1997;73:33–45
38. Edmonds LK, Moseley BJ, Admiraal AJ, et al. Familial bipolar disorder: preliminary results from the Otago bipolar genetic study. Aust N Z J Psychiatry 1998;32:823–829
39. Brown GW, Harris T. Social Origins of Depression. New York, NY: The Free Press, a division of McMillan Publishing Co; 1978
40. Post RM, Nolen WA, Kupka RW, et al. The Stanley Foundation Bipolar Network, 1: rationale and methods. Br J Psychiatry 2001;178:S169–176
41. Kupka RW, Nolen WA, Altshuler LL, et al. The Stanley Foundation Bipolar Network, 2: preliminary summary of demographics, course of illness and response to novel treatments. Br J Psychiatry 2001;178: S177–S183
42. Suppes T, Leverich GS, Keck PE Jr, et al. The Stanley Foundation Bipolar Treatment Outcome Network, 2: demographics and illness characteristics of the first 261 patients. J Affect Disord 2001;67:45–69
43. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry 2001;158:420–426
44. Leverich GS, McElroy SL, Suppes T, et al. Early physical and sexual abuse associated with an adverse course of bipolar illness. Biol Psychiatry 2002;51:288–297
45. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders (Research Version, 2/96 Final). New York, NY: Biometric Research, New York State Psychiatric Institute; 1996
46. Hyler S. Personality Questionnaire With Two Additional Research Categories of Personality Disorders: The PDQ 4+. New York, NY: New York State Psychiatric Institute; 1994
47. Leverich GS, Post RM. Life charting the course of bipolar disorder. Curr Rev Mood Disord 1996;1:48–61
48. Leverich GS, Post RM. Charting of affective illness. CNS Spectrums 1998;5:21–37
49. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996;26:477–486
50. Young RC, Biggs JT, Ziegler VE. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429–435
51. Global Assessment of Functioning (GAF). In: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994:30–31
52. Spearing MK, Post RM, Leverich GS, et al. Modifications of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997;73:159–171
53. Denicoff KD, Leverich GS, Nolen WA, et al. Validation of the prospective NIMH-Life-Chart Method (NIMH-LCMp) for longitudinal assessment of bipolar illness. Psychol Med 2000;30:1391–1397
54. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75:800–802
55. Levine S, Huchton DM, Wiener SG, et al. Time course of the effect of maternal deprivation on the hypothalamic-pituitary-adrenal axis in the infant rat. Dev Psychobiol 1991;24:547–558
56. Zhang LX, Xing GQ, Levine S, et al. Effects of maternal deprivation on neurotrophic factors and apoptosis-related genes in rat pups. Soc Neurosci Abstracts 1998;24:451
57. Caldji C, Francis D, Sharma S, et al. The effects of early rearing environment on the development of $GABA_A$ and central benzodiazepine receptor levels and novelty-induced fearfulness in the rat. Neuropsychopharmacology 2000;22:219–229
58. Meaney MJ, Bhatnagar S, Larocque S, et al. Individual differences in the hypothalamic-pituitary-adrenal stress response and the hypothalamic CRF system. Ann N Y Acad Sci 1993;697:70–85
59. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 1992;49:999–1010
60. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. Am J Psychiatry 1999;156:837–841
61. Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. Am J Psychiatry 2000;157:1243–1251
62. Kendler KS, Thornton LM, Gardner CO. Genetic risk, number of previous depressives episodes, and stressful life events in predicting onset of major depression. Am J Psychiatry 2001;158:582–586
63. Kay JH, Altshuler LL, Ventura J, et al. Prevalence of Axis II comorbidity with and without alcohol use disorders. Ann Clin Psychiatry 1999;11:187–195
64. Lechner ME, Vogel ME, Garcia-Shelton, et al. Self-reported medical problems of adult female survivors of childhood sexual abuse. J Fam Pract 1993;36:633–638
65. Moeller TP, Bachmann GA, Moeller JR. The combined effects of physical, sexual, and emotional abuse during childhood: long-term health consequences for women. Child Abuse Negl 1993;17:623–640
66. Wurtele SK, Kaplan GM, Keairnes M. Childhood sexual abuse among chronic pain patients. Clin J Pain 1990;6:110–113
67. Putnam FW, Trickett PK. Psychobiological effects of sexual abuse: a longitudinal study. Ann N Y Acad Sci 1997;821:150–159
68. Kaplan SJ, Pelcovitz D, Labruna V. Child and adolescent abuse and neglect research. A review of the past 10 years, pt 1: physical and emotional abuse and neglect. J Am Acad Child Adolesc Psychiatry 1999;38:1214–1222
69. Kaplan SJ, Pelcovitz D, Salzinger S, et al. Adolescent physical abuse: risk for adolescent psychiatric disorders. Am J Psychiatry 1998;155: 954–959
70. Brown J, Cohen P, Johnson JG, et al. A longitudinal analysis of risk

factors for child maltreatment: findings of a 17-year prospective study of officially recorded and self-reported child abuse and neglect. Child Abuse Negl 1998;22:1065–1078
71. Finkelhor D, Dziubia-Leatherman J. Children as victims of violence: a national survey. Pediatrics 1994;94:413–420
72. Baldessarini RJ, Tondo L, Hennen J. Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. J Clin Psychiatry 1999;60(suppl 2):77–84
73. Schou M. The effect of prophylactic lithium treatment on mortality and suicidal behavior: a review for clinicians. J Affect Disord 1998;50: 253–259
74. Tondo L, Ghiani C, Albert M. Pharmacologic interventions in suicide prevention. J Clin Psychiatry 2001;62(suppl 25):51–55
75. Post RM, Leverich GS, Nolen WA, et al. A reevaluation of the role of antidepressants in the treatment of bipolar episodes. Bipolar Disord. In press
76. Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials. Arch Gen Psychiatry 2000;57:311–317
77. Angst J, Sellaro R, Angst F. Long-term outcome and mortality of treated versus untreated bipolar and depressed patients: a preliminary report. Int J Psychiatry Clin Pract 1998;2:115–119
78. Rihmer Z. Strategies of suicide prevention: focus on health care. J Affect Disord 1996;39:83–91
79. Rihmer Z. Can better recognition and treatment of depression reduce suicide rates? a brief review. Eur Psychiatry 2001;16:406–409
80. Angst F, Stassen HH, Clayton PJ, et al. Mortality of patients with mood disorders: follow-up over 34–38 years. J Affect Disord 2002;68:167–181
81. Andersen UA, Andersen M, Rosholm JU, et al. Psychopharmacological treatment and psychiatric morbidity in 390 cases of suicide with special focus on affective disorders. Acta Psychiatr Scand 2001;104:458–465
82. Rucci P, Frank E, Kostelnik B, et al. Suicide attempts in patients with bipolar I disorder during acute and maintenance phases of intensive treatment with pharmacotherapy and adjunctive psychotherapy. Am J Psychiatry 2002;159:1160–1164

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