Suicide Attempts in Major Affective Disorder Patients With Comorbid Substance Use Disorders

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Background: The widely accepted impression that substance abuse and dependence are associated with increased suicidal risk was evaluated by literature review and with new data. ***Method:*** Previous research on this association was reviewed, and clinical data on suicide attempts and substance use in 504 mood disorder patients hospitalized in 4 psychiatric units in Sardinia affiliated with the Italian mental health system were analyzed. ***Results:*** The literature supports associations of alcohol and drug use comorbidity with major affective disorders, and of some substances (polyabuse, alcohol, heroin, cocaine, and even tobacco, but perhaps not marijuana or hallucinogens) with suicidal behavior. Our new findings generally supported these 2-way associations. Suicidal risks were similar in hospitalized men and women but were associated with bipolar II, bipolar I (mainly mixed), and unipolar depressive disorders as well as substance abuse, with little effect of type of agent. Substance abuse was more common in nonmixed bipolar disorders, men, and age below 30. ***Conclusion:*** The tendency for bipolar I, mainly nonmixed patients, to have a relatively high risk of substance abuse and low risk of suicide attempts indicates that mainly depressive or dysphoric (bipolar II, nonbipolar, and bipolar I, mainly mixed) mood disorders may be especially lethal. Differences in risks of substance abuse and suicidal behavior in men and in bipolar I patients further suggest that substance abuse and mood disorders may contribute to suicidal risk with at least partial independence or additivity.

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There is a broad consensus that substance use disorders strongly increase risk of suicidal behavior, particularly in patients with major mood disorders. However, most studies of the topic have not clearly differentiated the contributions of substance abuse and actual substance dependence (addiction), as are now recognized as distinct substance use disorders in DSM-IV. Moreover, studies vary in distinguishing potential contributions of substance use itself from its comorbid association with affective disorders as contributors to suicidal risk, as is considered in other reports from this series.[1–3] Substance use disorders typically start in adolescence, and so may play a particularly ominous role in the 3-fold increase in adolescent suicides in the last 30 years; in that age group, substance abuse may be associated with high rates of depression and bipolar disorders as well as the common tendency toward risk-taking in youth.[4–8]

PREVIOUS FINDINGS

Despite variations in their design and sampling methods, and possibly confounding factors, most studies support the view that abuse of alcohol or psychoactive

substances (including stimulants, sedatives, opiates, cannabis, and perhaps nicotine) is strongly associated with suicidal risk.[9,10] Substance abuse was associated with a 7.5-fold greater risk of attempted suicides in research involving more than 500,000 American military veterans.[11] Such associations have been especially strong in young persons who completed suicide,[6,12–15] including deaths that followed nonfatal suicide attempts.[16,17]

Alcohol. Alcohol abuse has been strongly implicated as a risk factor for suicidal behavior, and ranks second in strength of association only to affective illness.[4] Rates of suicide attempts have ranged from 13% to 50% among alcoholics.[6,18] Completed suicides have been found in 7% to 8% of alcoholics,[19] or at rates that were 7 to 20 times higher than in the general population.[4] An analysis of 32 studies involving some 45,000 subjects found that suicide risk was increased 6-fold in alcohol abusers.[9] Mediating variables between alcohol abuse and suicide are not always clear, but probably include psychosocial and general medical factors, including economic and interpersonal losses, hopelessness, homelessness, and impaired general health. Such factors were found to be associated with suicidal behavior in about a third of alcoholic subjects.[20] Polysubstance abuse, which typically includes alcohol, also accounts for high rates of suicidal behavior.[21,22] The psychological speculation that alcoholism is a self-destructive behavior that may be a substitute or equivalent of suicide remains controversial.[19]

Tobacco. Somewhat surprisingly, a strong correlation has been reported between tobacco smoking and suicidal behavior, including fatalities in middle-aged adults [21] and suicide attempts in women.[22] This association was also supported in a compilation of data involving nearly 450,000 subjects.[9] Similarly, in an epidemiologic study involving more than 100,000 women, the risk of suicide was doubled in association with smoking 1 to 24 cigarettes daily, and increased 4-fold with consumption of more than 25 cigarettes, indicating a dose-risk relationship.[23]

Cocaine. Cocaine has also been associated with increased rates of completed suicide[24] and suicide attempts,[25] especially in adolescents.[26] Cocaine use was found in 25% of subjects in a postmortem analysis of completed suicides,[27] and evidence of suicidal ideas and planning was found in 17% of a large group of cocaine users.[28] These associations seem to contrast with the increased CNS levels of serotonin that contribute to the pharmacodynamic actions of cocaine[29] since suicidal behavior is believed to be associated with decreased activity of serotonin in the brain.[1,2,30–35] However, changes in regional distribution of CNS serotonin in suicides and in persons abusing cocaine may differ, and cocaine produces complex increases and decreases in serotonergic functioning over time.[35] Suicidal behavior may well be a consequence of the post–cocaine withdrawal state ("crash"), which can either induce or mimic clinical depression, and the poststimulation phase may include a central deficit of serotonergic function.[36]

Opioids. Heroin addiction, too, is associated with suicidal behavior, and both cocaine and heroin abuse are commonly involved in polysubstance abuse along with alcohol and tobacco. The reported rate of suicide among heroin addicts ranged from 7% to 25% in older studies involving a total of 421 subjects.[37,38] Heroin addicts were found to kill themselves approximately 14 times more frequently than drug nonabusers in an analysis of 9 studies involving about 7500 subjects.[9] Important confounding factors in heroin use, particularly by intravenous self-administration, include loss of tolerance to heroin over time between uses and availability of illicit material of unusually high purity unknown to the user; both factors can contribute to fatal overdoses in which explicit suicidal intent may be absent.[39] Intravenous abuse of heroin also increases risk of mortality due to human immunodeficiency virus (HIV) infection, but a relationship of HIV infection to suicidality is not proved.[9]

Miscellaneous psychotropic agents. Associations between suicidal behavior and abuse of other psychoactive substances, including cannabis, amphetamines, and hallucinogens such as lysergic acid diethylamide (LSD) or phencyclidine, are not secure and have not been studied sufficiently as to support even a tentative conclusion. Despite currently widespread use of marijuana and other cannabis products, studies relating suicidal behavior and such abuse are surprisingly few, and inconsistent. Their findings include positive,[40,41] weak,[26] or no [25] associations with suicidal behavior. For amphetamines, suicide attempts were more likely in amphetamine-abusing than other subjects among 270 patients admitted to a general medical center,[42] and deaths by suicide were higher in a small number of amphetamine users than in a control group.[43] High mortality due to suicide has been associated with use of both LSD[44,45] and phencyclidine,[46] and suicide attempts were more common with use of these agents.[47]

Comorbid risk factors. Evaluating specific contributions of mood and substance use disorders to suicidal behavior is a complex task, since substance abuse may add risk either as an independent, although comorbid, condition or as a symptomatic manifestation of a primary mood disorder, such as by self-medication. Assessment of the relationships involved is further compromised technically owing to limited quality of the information available, varied patterns of relationships between specific mood and substance use disorders, lack of appropriate control or comparison groups, and failure to specify whether substance use is present as a symptom, an abuse syndrome, or a true dependency or addictive disorder.[10,48] It is, therefore, not surprising that studies attempting to disentangle associations among mood and substance use disorders and suicidal behavior have yielded conflicting findings.

Depression and substance abuse are widely recognized as the most important identified risk factors for suicides in all age groups, and one or both have been found in a majority of suicides.[49] It has been suggested that they act as both independent and interactive factors in subjects with suicidal ideation or attempts.[5,49–51] Family history studies have not helped to clarify the issue, since familial substance abuse, mood disorder, and suicidal behavior have been associated individually or together among relatives of index suicidal cases.[52–54] Since depression was found at similar rates among alcoholic and nonalcoholic suicides,[55] it may be that alcohol abuse does not exert an additive or synergistic effect on suicide risk. Some observations have suggested that the effect of psychiatric illness may outweigh contributions of substance abuse to suicidal risk.[56] Additional factors that may be associated with substance use disorders include deterioration of social and occupational functioning, general health, and nutrition—all of which may also predispose to suicidal behavior even in absence of major psychopathology.[4]

NEW RESEARCH FINDINGS

One way to examine relationships between substance abuse and suicidal behavior is to consider the association of specific substance use behaviors among persons already identified as having a mood disorder. We are following this strategy in a large population of affectively ill patients in Sardinia, Italy, who are enrolled in studies of an international consortium for mood disorders research.

Methods

The preliminary findings summarized here involve a pooled sample of 504 subjects with bipolar or nonbipolar major affective disorders meeting DSM-IV diagnostic criteria, who were sufficiently ill as to require psychiatric hospitalization at least once. These subjects were identified in 4 collaborating institutions within the Italian mental health system. Included are patients at first admission to a state psychiatric hospital between 1979 and 1996, inpatients from a private psychiatric sanatorium admitted in early 1998, and outpatients evaluated at a university clinic or general hospital emergency room from 1997 to 1998. Analyses of their suicidal behavior considered attempts serious enough to require medical or surgical hospitalization. In addition to considering demographic, diagnostic, and other clinical factors, their substance use disorders were scored for abuse of or dependence on 1 or more specific substances.

All data were gathered from detailed clinical records available within the study's mental health system. Demographic and clinical data were provided from each site, based on consensus operational definitions of all data elements. Study findings were reviewed by a consensus panel of clinical investigators with many years of experience in mood disorder research to verify the apparent accuracy and completeness of data for each subject entered into a pooled database. The database was also passed through a data-cleaning algorithm, including range checks on all variables, and frequency distributions were constructed for each measure. Independent (outcome) variables included a binary measure of suicidality (attempt present or absent) and a continuous rate measure of suicidal intensity (attempts per years-at-risk).

Tables of bivariate associations of suicidality with other variables were first assembled. The strength of associations with suicide attempts was tested with contingency tables (χ^2, for categorical variables) or 1-way ANOVA (F, for continuous variables). For continuous measures, distribution normality and the presence of outliers was checked, with data log-normalized for ANOVA comparisons as necessary.

Multivariate analyses were carried out for the binary outcome measure of suicidality. Independent variables with at least moderate associations ($p < .20$) were selected for entry into multivariate logistic regression models, with suicidality as the outcome measure. For several independent variables with more than 2 values (e.g., affective disorder diagnostic subtype), indicator variables were set up for each category, with one designated as the comparison category (based on its preliminary nonsignificant relationship to suicidality), and omitted from the logistic regression modeling. Final multivariate logistic regression models included independent variables with $p < .05$. Model strength was assessed with an overall model χ^2 statistic and by computing receiver-operator characteristic (ROC) curves.[57,58] Observations having possibly excessive influence on the multivariate models were identified by partial residual plots. Closeness of fit of the multivariate models was assessed by deciles-of-risk methods.[57] Similar multivariate logistic models were developed for men and women subjects separately. Data analyses were carried out with Statview-5® (SAS Corp., Cary, N.C.) and Stata® (Stata Corp., College Station, Tex.) programs.

Results

The reported sample consisted of 504 hospitalized adult (current mean ± SD age = 41 ± 16 years) mood-disorder patients (75% bipolar I or II); 53% were women. At least 1 suicide attempt had occurred in 13% of the subjects, and the rate of suicidal acts averaged 10/100 patient-years (Table 1). These rates are lower than expected, but probably reflect inclusion of patients evaluated at their first-ever psychiatric hospitalization.

Substance use disorders were diagnosed in 28% of the subjects: substance abuse was found in 26%, and dependence in 2% (Table 2). The most frequent substance abused was alcohol (in 15% of patients), followed by cannabis (4%) and heroin (3%). Polysubstance abuse was found in 6% of patients, and no cases were identified as

Table 1. Characteristics of 504 Subjects With Mood Disorders

Characteristic	Measure
Sex (%)	
Women	53.4
Men	46.6
DSM-IV diagnostic type (%)	
Bipolar disorders (I + II)[a]	75.0
Major depressive disorder	25.0
Onset age, mean ± SD y	36.3 ± 15.1
Current age, mean ± SD y	40.9 ± 16.1
Time at risk, mean ± SD y	4.55 ± 8.03
Suicidal (%)	12.9
Suicidal acts/100 patient-years, mean ± SD	10.2 ± 34.2

[a]Of the 378 patients with bipolar disorder, 6.6% were type II and 93.4% were type I, of whom 28.9% presented mainly (> 50% of episodes) with mixed manic-depressive states.

Table 2. Rate of Substance Use Disorders in Patients With Mood Disorders*

Factor	N	% With Substance Use Disorder
Using any substance	142/504	28.2
Abusing	131/142	26.0
Dependent	11/142	2.2
Substance choice		
Alcohol	74/504	14.7
Polysubstance	32/504	6.4
Cannabis	21/504	4.2
Heroin	15/504	3.0
Sex[a]		
Men	109/235	46.4
Women	33/269	12.3
Age group[b]		
< 30 y	62/149	41.6
≥ 30 y	80/355	22.5
Affective diagnostic type[c]		
Bipolar I (all cases)	115/353	32.6
Bipolar I (mainly mixed)	39/102	38.2
Bipolar I (not mixed)	76/251	30.3
Bipolar II	7/25	28.0
Major depressive	20/126	15.9

*Substance use was diagnosed in 142/504 subjects.
[a]$\chi^2 = 72.1$, df = 1, $p < .0001$.
[b]$\chi^2 = 18.9$, df = 1, $p < .0001$.
[c]$\chi^2 = 15.1$, df = 3, $p < .002$.

involving abuse of cocaine alone. Substance use disorders were significantly more common among men than women (46% vs. 12%), in younger persons under age 30 than in older subjects (42% vs. 23%), and (32%) among bipolar disorder patients (33% of bipolar I and 28% of bipolar II patients) compared with nonbipolar depressives (16%; $\chi^2 = 12.6$, $p = .0004$).

Suicide attempts occurred at similar rates in men (14%) and women (12%), and were somewhat more common in patients under age 30 than in older subjects (18% vs. 11%; Table 3). Suicide attempts also were more common in type II than type I bipolar disorder patients (28% vs. 10%), and nonbipolar depressed patients had an intermediate risk (19%). The great majority of suicidal acts were associated with mixed mood states in bipolar I disorders (29%) or depression in bipolar I or II or nonbipolar patients (20%),

Table 3. Risk of Suicide Attempts and Clinical Features of Patients With Mood Disorders*

Factor	N	% Suicidal
Sex[a]		
Men	33/235	14.0
Women	32/269	11.9
Age group[b]		
< 30 y	26/149	17.5
≥ 30 y	39/355	11.0
Affective diagnostic type[c]		
Bipolar I (all cases)	34/353	9.6
Bipolar I (mainly mixed)	16/102	15.7
Bipolar I (not mixed)	18/251	7.2
Bipolar II	7/25	28.0
Major depressive	24/126	19.1
Mood status at most recent attempt[d]		
Mixed	28/96	29.2
Depressed	32/158	20.3
Manic	5/250	2.0
Substance use disorder[e]		
Present	30/142	21.1
Absent	35/362	9.7
Substance use type[a]		
Abuse	27/131	20.6
Dependence	3/11	27.3
Substance used[f]		
Heroin	5/15	33.3
Polysubstance	9/32	28.1
Alcohol	14/74	18.9
Cannabis	2/21	9.5

*Among suicidal patients (N = 65), current mood ranked: depressed (49.2%) ≥ mixed (43.1%) > manic (7.69%).
[a]$\chi^2 \leq 1.22$, df = 1, NS.
[b]$\chi^2 = 3.90$, df = 1, $p < .05$.
[c]$\chi^2 = 12.7$, df with all bipolar I pooled = 2, $p < .002$.
[d]$\chi^2 = 56.7$, df = 2, $p < .0001$.
[e]$\chi^2 = 11.9$, df = 1, $p < .001$.
[f]$\chi^2 = 4.20$, df = 3, NS.

with few acts associated with mania (2.0%). Substance use disorders increased the risk of suicidal behavior 2.2-fold (21% vs. 10% risk in those with vs. without substance use disorders). However, there was little difference in risk between those with substance abuse (21%) and dependence (27%). The type of agent abused also mattered very little, though polysubstance abuse tended to be associated with a somewhat higher risk (28%) than other forms of drug use (19%).

A measure of suicidal intensity was taken as the number of suicide attempts per years at risk. The overall rate for all 504 subjects, at risk for a mean ± SD of 4.55 ± 8.03 years (a relatively short time due to inclusion of some first-admission subjects), was 0.10 ± 0.34 attempts/year, but among the 65 persons with any suicide attempts, the rate was 7.8-times greater, at 0.79 ± 0.60 acts/year over 4.22 ± 7.26 years at risk. The rate was nonsignificantly higher in men than women, but was more than twice as high in persons under age 30 years than in older patients (Table 4). The rate also differed as much as 3.6-fold between diagnostic types, ranking: bipolar II (0.29) > major depression (0.15) > bipolar I (0.08 attempts/year). In addition, patients with a current mixed bipolar mood state or acute depression, respectively, had 74- and 62-times

Table 4. Suicidal Intensity for 504 Subjects

Factor	Attempts/Year Mean	SD
Sex[a]		
Men	0.125	0.372
Women	0.083	0.312
Age group[b]		
< 30 y	0.165	0.431
≥ 30 y	0.076	0.293
Affective diagnostic type[c]		
Bipolar I (all cases)	0.084	0.301
Bipolar I (mainly mixed)	0.091	0.264
Bipolar I (not mixed)	0.063	0.284
Bipolar II	0.290	0.734
Major depressive	0.153	0.370
Current mood status[d]		
Mixed	0.219	0.398
Depressed	0.185	0.494
Manic	0.003	0.024
Substance use disorder[e]		
Present	0.166	0.414
Absent	0.077	0.306
Substance use type[f]		
Abuse	0.170	0.423
Dependence	0.120	0.299
Substance used[g]		
Alcohol	0.113	0.300
Polysubstance	0.148	0.349
Other (heroin, cannabis)	0.148	0.349

[a]$F \leq 1.91$, df = 1,502, NS.
[b]$F = 7.25$, df = 1,502; $p = .007$.
[c]$F = 4.80$, df with all bipolar I pooled = 2,446; $p < .009$.
[d]$F = 22.5$, df = 2,501; $p < .0001$.
[e]$F = 6.93$, df = 1,502; $p < .009$.
[f]$F = 0.143$, df = 1,140; NS.
[g]$F = 2.59$, df = 2,139; NS.

greater attempts/year than those who were manic at their index assessment.

A multivariate logistic regression analysis[57] of associations of substance use disorders and other factors with suicidal behavior was also carried out, based on preliminary univariate associations identified in the preceding analyses (Tables 1–4). This analysis resulted in an explanatory model that was highly significant overall ($\chi^2 = 40.1$, $p < .0001$), and it indicated associations of being suicidal with the following factors, in rank-order of their overall significance: bipolar II disorder > major depressive disorder > bipolar I disorder with mainly (> 50%) mixed episodes > substance abuse ≥ age below 30 years (Table 5). This model also yielded a significant area under a Bayesian ROC function (sensitivity vs. [1–specificity]) of 0.735.[58] As the number of factors included in the model was increased from 0 to 3 (pooling for depressive or mixed mood state), the predicted likelihood of a suicide attempt rose from 4.4% (0 factors) to 11.9% (1 factor), 22.5% (2 factors), and 47.8% (with any 3 factors, pooling diagnostic groups into a single factor; Figure 1).

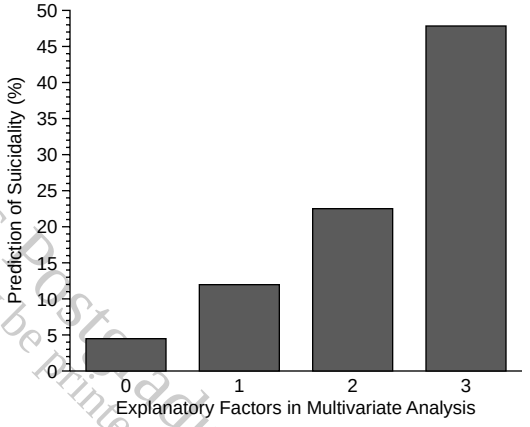
When similar models were considered for women and men separately, the diagnosis of bipolar II disorder again exerted the strongest influence (odds ratio [OR] = 9.19, 95% confidence interval [CI] = 1.70 to 49.7 in men; OR = 6.69, CI = 1.57 to 28.5 in women). Younger age was a more powerful factor in women (OR = 4.67, CI = 1.95 to 11.2) than in men (OR = 1.54, CI = 0.59 to 4.06). In contrast, the diagnosis of bipolar I disorder with mainly mixed episodes was more strongly associated with suicidal behavior in men (OR = 4.71, CI = 1.44 to 15.4) than in women (OR = 1.83, CI = 0.60 to 5.60). Finally, substance abuse made a similar contribution to suicidal risk for each sex as with the pooled data.

Table 5. Multivariate Analysis of Factors Associated With Suicide Attempts*

Factor	Odds Ratio	95% CI	z Statistic	p Value
Bipolar II disorder	8.33	(2.79 to 24.8)	3.80	< .0001
Major depressive disorder	5.31	(2.53 to 11.1)	4.43	< .0001
Bipolar I/mainly mixed episodes	3.34	(1.51 to 7.37)	2.98	.003
Substance use disorder	2.68	(1.50 to 4.80)	3.32	.001
Age < 30 y	2.60	(1.38 to 4.90)	2.97	.003

*In the logistic regression model (df = 4) for all 504 subjects, $\chi^2 = 40.1$, $p < .0001$, with a significant area under a Bayesian receiver-operator characteristic (ROC) function (sensitivity vs. [1–specificity]) of 0.735. As the number of factors included in the model was increased from 0 to 3, prediction of likelihood of a suicide attempt rose from 4.4% (0 factors), to 11.9% (1 factor), 22.5% (2 factors), to 47.8% (with any 3 factors, pooling the diagnostic variables as a single factor), as is illustrated in Figure 1.

Figure 1. Ability of Factors Developed by Multivariate Logistic Regression Modeling to Account for (or Predict) Suicide-Attempting Behavior in 504 Patients With Mood Disorders*



*This figure considers any of 3 factors shown in Table 5 (substance abuse history, current age below 30 years, and diagnostic subtype with diagnostic groups pooled into a single diagnostic factor).

COMMENTS AND CONCLUSIONS

In the present Sardinian sample of 504 hospitalized mood disorder patients, there was a significant association of substance use disorders with suicide attempts, even when corrected for other covariates. The findings support

and extend impressions gained from the preceding review of substance abuse and suicidal behavior. In the new clinical sample, substance abuse was most commonly found in bipolar I disorder patients, whereas the presence and annual rate of suicide attempts were much higher in bipolar II and nonbipolar depressive patients. Moreover, as expected, the mood state associated with suicide attempts was much more commonly dysphoric-mixed or depressive than manic. The annual rate of suicidal acts was increased among affectively ill patients who also abused drugs or alcohol, as well as in young patients under 30 years of age. These findings support the widely accepted conclusion that both depressed mood and substance abuse are strongly associated with suicidality. However, the 2-fold greater suicidal risk in mood disorder patients with comorbid substance use disorders suggests additional risk related to the presence of a substance use disorder. Finally, it seems likely that substance abuse may limit or counteract expected decreases in suicidal rates related to modern treatments, for which evidence is emerging.[15,33,34,59,60]

Drug name: phencyclidine (Sernylan).

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