

Original Article

A prospective study of the association of cerebrospinal fluid monoamine metabolite levels with lethality of suicide attempts in patients with bipolar disorder

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Objectives: Bipolar disorder is a severe illness that is associated with suicidal behavior. A biological predictor of highly lethal suicide attempts in patients with bipolar disorder would be valuable. We hypothesized that cerebrospinal fluid (CSF) monoamine metabolite levels are related to lethality of suicide attempts in bipolar patients and examined the relation between CSF 5-hydroxyindolacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) levels and maximum lethality of suicide attempts at baseline and during a 2-year follow up.

Methods: Twenty-seven bipolar depressed patients participated in the study. Demographic and clinical parameters were examined and recorded. Lumbar punctures were performed and CSF 5-HIAA, HVA, and MHPG were assayed by high-performance liquid chromatography with electrochemical detection. Following discharge, patients were evaluated after 3 months, 1 year, and 2 years. Each follow-up interview included an in-depth assessment of suicidal behavior during the intervening time period.

Results: Six subjects made suicide attempts during the 2-year follow-up. Bipolar patients who attempted suicide during the follow-up period had higher aggression and hostility scale scores compared to bipolar subjects who did not make a suicide attempt during the follow-up period. CSF 5-HIAA, HVA, and MHPG levels were negatively correlated with the maximum lethality of suicide attempts during the 2-year follow-up period.

Conclusions: Our finding is the first observation that CSF monoamine metabolite levels may be predictors of lethality of suicide attempts in patients with bipolar disorder. Further studies are necessary to answer the question whether CSF monoamine metabolite levels are clinically useful biochemical predictors of highly lethal suicide attempts or completed suicides.

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Suicide is a major medical problem. About 30,000 Americans commit suicide each year (1). Bipolar disorder is potentially fatal as a result of accidents and increased mortality associated with comorbid

substance use and medical illnesses, but its highest lethality results from suicide (2–5). Lifetime rates of attempted suicide are higher in bipolar disorder than major depressive disorder (ranges of 26–29% versus 14–16%) (6). Rates of completed suicide in bipolar disorder are also high, varying from 10% to 19% (7). A meta-analysis of suicide studies in a range of psychiatric conditions (8) reported that the suicide rate for bipolar disorder was 15 times that of the general population. Suicidal ideation is reported by 79% of those with bipolar depression, occurring much more commonly in that phase of the illness than during mania or mixed episodes (9). Completed and attempted suicide also occurs predominantly during the depressed phase of the illness (10–12). Highly lethal suicide attempters or failed suicides resemble completed suicides both clinically and biochemically (13, 14). Finding a biological predictor of highly lethal suicide attempts in patients with bipolar disorder is, therefore, of potential value in predicting suicide.

Serotonergic, dopaminergic, and noradrenergic dysfunction are involved in the pathophysiology of suicidal behavior (15–18). The concentrations of 5-hydroxyindolacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) in cerebrospinal fluid (CSF) reflect functional activity of the serotonin-, dopamine-, and norepinephrine-containing neurons in the brain (19, 20). We hypothesized that CSF monoamine metabolite levels are related to lethality of suicide attempts in bipolar patients and examined the relation between CSF 5-HIAA, HVA, and MHPG levels and maximum lethality of suicide attempts at baseline and during the 2-year follow-up. To our knowledge, this is the first prospective study of the predictive value of CSF monoamine metabolites for lethality of suicide attempts in bipolar disorder.

Methods

Subjects

Patients were recruited through advertising and referrals and admitted to a university hospital for participation in mood disorders research. All subjects gave written informed consent as required by the Institutional Review Board for Biomedical Research. Twenty-seven bipolar depressed patients participated in the study. All met DSM-IV (21) criteria for a current major depressive episode. Patients had to be free from prescribed medications known to affect brain serotonin, dopamine, or norepinephrine systems for a minimum of 14 days. The drug-free interval was longer for drugs with a

long half-life (6 weeks for fluoxetine and 4 weeks for oral antipsychotics). Among psychotropics, only low doses of short-acting benzodiazepines were permitted but not 72 h before the lumbar puncture. Patients were free from any substance dependence for at least 6 months and free from any substance abuse for at least 2 months. The duration of the drug-free status of the patients was established by a combination of urine and blood toxicological screenings, observation in hospital, and a history obtained from the patient, the patient's family and the referring physician. Subjects were not allowed to smoke for 12 h before the lumbar puncture. There were no patients with attention deficit hyperactivity disorder in the study group.

Following discharge, patients were evaluated after 3 months, 1 year, and 2 years. Subjects received treatment as usual in the community. Each follow-up interview included an in-depth assessment of suicidal behavior during the intervening time period using the instruments cited below.

Measures

DSM-IV Axis I and Axis II disorders were diagnosed using the Structured Clinical Interview I (SCID-I) and the Structured Clinical Interview II (SCID-II), respectively, for DSM-IV (21). Subjects had a physical examination and routine laboratory screening tests, including urine and blood toxicological screenings to rule out neurological or medical illness that could affect their mental status or CSF monoamine metabolites.

Current severity of depression was assessed by the Hamilton Depression Rating Scale (22) and the Beck Depression Inventory (BDI) (23). Lifetime aggression, impulsivity, and hostility were assessed with the Aggression History Scale (24), the Barratt Impulsivity Scale (25), and Buss–Durkee Hostility Scale (26), respectively. Current hopelessness was measured with the Beck Hopelessness Scale (27). Current suicidal ideation was measured by the Scale for Suicidal Ideation (28). A lifetime history of all suicide attempts, including number of attempts and the method and degree of medical damage for each attempt, was recorded on the Columbia Suicide History Form (29). A lethality scale was used to measure the degree of medical damage caused by each suicide attempt (30). The scale was scored from 0 to 8 (0 = no medical damage, 8 = death), with different anchor points for various suicide attempt methods. A suicide attempt was defined as a self-destructive act that was committed with some intent to end one's life.

The degree of suicide intent was rated with the Suicide Intent Scale (31). Smoking severity was evaluated using the Columbia Baseline Demographic/History Form (29).

The lumbar puncture and CSF monoamine metabolites assay

The lumbar puncture was performed at about 8.00 a.m., after the patient had been kept at bed rest and fasting from midnight. CSF was withdrawn from the L4–L5 inter-space, with the patient in the left decubitus position. After the removal of 1 mL of CSF into the first sample tube, a further 15 mL of CSF was collected in the second and third tubes. These tubes were then immediately transferred on ice water to be centrifuged at 4°C, and the supernatant pooled from the second and third tubes. The 15 mL of supernatant was divided into 1-mL aliquots for storage at –70°C until assay. CSF amine metabolites were assayed in one of the 1-mL aliquots of the 15-mL sample.

Cerebrospinal fluid 5-HIAA, HVA, and MHPG were assayed by high-performance liquid chromatography with electrochemical detection (32). The within- and between-run coefficients of variance of the assay were < 10%. The sensitivity of the assay was 0.5 pmol/injection. All samples were kept frozen until assay. The samples were analyzed within 6 months after collection. Storage effects were not detected.

Statistical analysis

Demographic and clinical characteristics and CSF monoamine metabolites in bipolar depressed patients with or without a history of suicide attempt during 2-year follow-up were compared using *t*-test, Mann–Whitney test, and chi-square test, as appropriate. Spearman correlations were computed to examine the relationship between CSF 5-HIAA, HVA, and MHPG levels and maximum lethality of suicide attempts before the baseline evaluation, maximum lethality of suicide attempts during the 24-month follow-up period, and clinical predictors of suicidal behavior: BDI and Aggression History Scale scores, and smoking severity (4, 33).

Results

Demographic and clinical parameters

Twenty-seven patients participated in the study. We compared demographic and clinical features of bipolar subjects who did or did not make a suicide

attempt during the 2-year follow-up (Table 1). There was no difference with regard to demographic parameters. We found no difference in the Hamilton Depression and Beck Depression Scale scores at presentation ($df = 25$, $t = 0.72$, $p = 0.48$, and $df = 24$, $t = 1.95$, $p = 0.63$, respectively). There were 18 suicide attempters at baseline. All six subjects who made a suicide attempt during the follow-up period were suicide attempters at baseline. Bipolar patients who attempted suicide during the follow-up period had higher aggression and hostility scale scores compared with bipolar subjects who did not make a suicide attempt during the follow-up period ($df = 25$, $t = 2.53$, $p = 0.02$; and $df = 24$, $t = 2.73$, $p = 0.01$, respectively). There was also a higher prevalence of the first-degree relatives who attempted or committed suicide among the subjects who made a suicide attempt during the follow-up compared with their counterparts ($df = 1$, $\chi^2 = 11.85$, $p = 0.001$). The lethality scores were not higher during the 2-year prospective period than before baseline ($df = 5$, $t = 0.2$, $p = 0.8$).

Biological data

Data on CSF 5-HIAA, HVA, and MHPG levels are presented in Table 1. As expected, there were positive correlations between CSF 5-HIAA and HVA levels ($r = 0.71$, $p < 0.001$), 5-HIAA and MHPG concentrations ($r = 0.54$, $p = 0.004$), and HVA and MHPG levels ($r = 0.62$, $p = 0.001$). There were no differences in monoamine metabolites between bipolar subjects who did or did not make a suicide attempt during the 2-year follow-up (Table 1). We did not find a correlation between CSF monoamine metabolite levels and maximum lethality of suicide attempts prior to the baseline evaluation (Table 2). However, we found that CSF 5-HIAA, HVA, and MHPG levels were negatively correlated with the maximum lethality of suicide attempts during the 2-year follow-up period (Table 2 and Fig. 1a–c). There was no correlation between CSF monoamine metabolite levels and predictors of suicidal behavior: BDI and Aggression History Scale scores, and severity of smoking (Table 2).

Discussion

Clinical data

Our observation that all subjects who made a suicide attempt during the follow-up period were suicide attempters at baseline is consistent with reports suggesting that suicide attempts in the past

Table 1. Demographic and clinical characteristics and CSF monoamine metabolite levels of bipolar depressed patients with or without a history of suicide attempt during the follow-up period

Variable	With a history (n = 6)		Without a history (n = 21)		Analysis		
	Mean (n)	SD (%)	Mean (n)	SD (%)	df	t/z/(χ^2)	p
Demographic							
Age (years)	31.00	5.76	39.10	11	25	-1.67	0.11
Gender (% male)	(3)	(50)	(12)	(57.1)	1	(0.96)	0.76
Race (% white)	(6)	(100)	(16)	(76.2)	1	(1.75)	0.18
Marital status (% married)	(2)	(33.3)	(10)	(47.6)	1	(0.38)	0.53
Education (years)	16.20	3.35	17.10	2.79	24	-0.62	0.54
Clinical Assessment							
Hamilton Depression Rating Scale	18.83	5.04	17.14	5.05	25	0.72	0.48
Beck Depression Inventory	35.80	13.99	25.81	9.37	24	1.95	0.63
Beck Hopelessness Inventory	12.17	4.12	13	5.27	25	-0.36	0.73
Brown–Goodwin Aggression Scale	22.67	4.55	17.76	4.10	25	2.53	0.02
Barratt Impulsivity Scale	61.50	25.59	54.19	21.35	23	0.61	0.54
Buss–Durkee Hostility Inventory	50.20	5.89	35.05	11.95	24	2.73	0.01
Course of illness							
Number of previous hospitalizations	5.33	4.80	2.86	4.36	25	1.20	0.24
Number of previous depressive episodes	3.83	2.64	5.22	4.67	25	-0.69	0.50
Age at first hospitalization	28.33	5.16	33.13	12.19	20	-0.90	0.37
Age at first major depressive episode	18.33	9.31	23.43	13.31	25	-0.87	0.40
Age at first manic episode	24.33	8.12	28.63	10.17	12	-0.85	0.41
Comorbid past alcohol or substance use disorder	(3)	(50)	(13)	(61.9)	1	(0.27)	0.60
Cigarette smoking	(4)	(66.7)	(10)	(47.6)	1	(0.68)	0.41
Suicidal behavior							
Suicide attempt status at baseline	(6)	(100)	(12)	(66.7)	1	(3.86)	0.05
Number of previous suicide attempts	2.50	1.52	2.56	2.23	25	1.02	0.32
Suicide intent at the time of the most lethal attempt	17.67	4.50	16.56	4.69	17	0.89	0.38
Maximum lethality of suicide attempts	3.67	2.50	3.56	2.20	16	0.15	0.89
Prevalence of first-degree relatives who attempted or completed suicide	(4)	(66.7)	(1)	(4.8)	1	(11.85)	0.001
Suicidal ideation scale	23.80	4.92	14.60	10.97	-	-1.74	0.08*
Reasons for Living Scale	127.00	41.71	143.10	39.66	23	-0.74	0.47
CSF monoamines concentrations							
5-HIAA (pmol/mL)	115.41	28.04	99.31	31.76	25	1.12	0.27
HVA (pmol/mL)	202.27	76.12	199.42	69.36	25	0.87	0.93
MHPG (pmol/mL)	32.25	12.75	41.79	17.8	25	-1.22	0.23

CSF = cerebrospinal fluid; 5-HIAA = 5-hydroxyindolacetic acid; HVA = homovanillic acid; MHPG = 3-methoxy-4-hydroxyphenylglycol. *Mann–Whitney test.

predict future suicidal behavior (4, 34–36). For example, in our recent study of unipolar and bipolar subjects, a history of suicide attempt increased the risk for future suicidal behavior more than fourfold (4).

We found that subjects who attempted suicide during the follow-up period had higher aggression and hostility scale scores which is consistent with the literature suggesting that high aggression and hostility are associated with suicidal behavior (4, 37–44). Suicide attempters have been documented to be more aggressive than non-attempters in studies of subjects with bipolar disorder (42), unipolar depression (41), personality disorders (38, 39), alcoholism (44) and in a study of violent offenders (40). A recent study found that aggressive behavior increases the risk of suicide during a 2-year follow-up period (4). Another prospective

study found that army recruits who later died by suicide or accident were more aggressive than comparison subjects (37). Moreover, aggression is associated with suicidal behavior, and both are independently associated with low serotonergic function (15–17, 40, 45, 46).

Biological data

We observed that CSF 5-HIAA, HVA, and MHPG levels were negatively correlated with the maximum lethality of suicide attempts in patients with bipolar disorder during the 2-year follow-up period. We would like to emphasize that this correlation applies only to bipolar patients who attempted suicide during the follow-up period and that monoamine levels did not differ at baseline.

Table 2. Correlations between CSF monoamine metabolites and maximum lethality of suicide attempts and predictors of suicidal behavior

	n	5-HIAA		HVA		MHPG	
		r	p	r	p	r	p
CSF monoamine metabolites and maximum lethality of suicide attempts							
Maximum lethality of suicide attempt before the baseline evaluation	18	-0.11	0.66	-0.23	0.36	-0.06	0.80
Maximum lethality of suicide attempts during 2-year follow-up	6	-0.84	0.04	-0.84	0.04	-0.93	0.008
CSF monoamine metabolites and predictors of suicidal behavior							
Beck Depression Inventory	18	0.13	0.60	-0.20	0.45	-0.22	0.93
Aggression History Scale	18	0.32	0.19	0.34	0.16	0.14	0.58
Smoking severity	18	-0.16	0.53	0.23	0.93	-0.24	0.34

CSF = cerebrospinal fluid; 5-HIAA = 5-hydroxyindolacetic acid; HVA = homovanillic acid; MHPG = 3-methoxy-4-hydroxyphenylglycol.

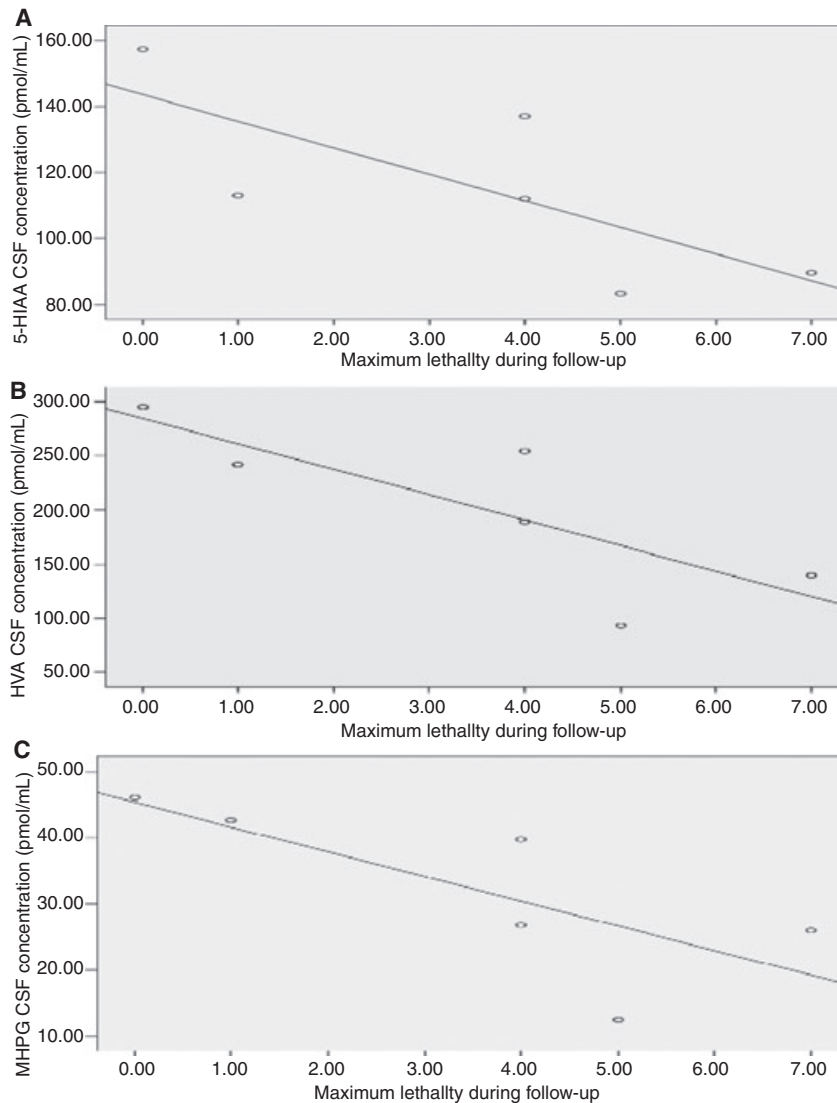


Fig. 1. Correlation between CSF 5-HIAA (A), CSF HVA (B) and CSF MHPG (C) levels (pmol/mL) and maximum lethality of suicide attempts during follow-up. CSF = cerebrospinal fluid; 5-HIAA = 5-hydroxyindolacetic acid; HVA = homovanillic acid; MHPG = 3-methoxy-4-hydroxyphenylglycol.

Serotonergic function and suicide. A number of post-mortem studies of suicide have examined the serotonergic system and identified abnormalities of the serotonin system in prefrontal cortex in suicide

victims (47–49). Postsynaptic serotonin 5-HT_{1A} and 5-HT_{2A} receptors are reported by some studies to be upregulated in the prefrontal cortex of suicide victims (50, 51). Postsynaptic serotonin receptor

upregulation might be a compensatory response to the low activity of serotonin neurons. Hypofunction of the serotonin system in suicide is indicated in most studies of brainstem levels of serotonin or its main metabolite, 5-HIAA (15–18, 46, 52). Brainstem results are consistent with the cortical receptor findings and with reports of low CSF 5-HIAA with a history of serious suicide attempts (53). Low CSF 5-HIAA has been reported in suicide attempters with major depression, schizophrenia and personality disorders when compared with people who did not attempt suicide but have the same psychiatric diagnosis (15, 54). A biochemical trait, low CSF 5-HIAA, predicts future suicide attempts and suicide completions and is consistent with low post-mortem brainstem levels of serotonin or 5-HIAA in suicide victims, independent of psychiatric diagnosis (55, 56). The relationship between low serotonergic function and suicidal behavior is also indicated by a blunted prolactin response to serotonin that is released by fenfluramine in suicide attempters with major depression or personality disorders compared to controls (38, 57). It has been reported that the more lethal the suicide attempt, the lower the CSF 5-HIAA and the prolactin response to fenfluramine (57, 58). A positron emission tomographic study has demonstrated that prefrontal localized hypofunction and impaired serotonergic responsivity are proportional to the lethality of the suicide attempt (59). This is consistent with our observation that CSF 5-HIAA levels negatively correlated with the maximum lethality of suicide attempts during follow-up.

Dopaminergic function and suicide. Depressed suicide attempters have lower CSF HVA levels compared with depressed non-attempters (60–63). Lower levels of CSF HVA have been found in depressed patients with a history of either violent or nonviolent suicide attempts than in controls (64). Two other studies also showed a highly significant relationship between low CSF HVA levels and suicidal behavior (65, 66). In a 5-year longitudinal study, Roy et al. (67) observed that patients who reattempted suicide during the follow-up had lower CSF HVA levels compared to controls. This predictive value of low CSF HVA concentrations has been confirmed in another longitudinal study over a period of 2 years (68). The results of our study also suggest that CSF HVA levels may have a predictive value with regard to suicidality.

Noradrenergic function and suicide. Changes in the noradrenergic system have been the subject of fewer studies in comparison with serotonergic and

dopaminergic systems. There are fewer noradrenergic neurons in the locus coeruleus in suicide victims with major depression (69). Noradrenaline levels are lower in the brainstem of suicide victims, whereas α_2 -adrenergic receptor numbers are higher, upregulated perhaps secondary to lower noradrenaline levels (70). In 1980, Agren (71) reported that seriousness of intent at the time of the most lethal past suicide attempt correlated negatively with CSF MHPG levels which is consistent with our observation.

The serotonergic, dopaminergic, and noradrenergic systems are involved in the neurobiology of bipolar disorder (71–73). Therefore, CSF 5-HIAA, HVA, and MHPG levels may reflect pathophysiological processes in bipolar disorder.

The finding that the levels of CSF monoamine metabolites are lower in patients with suicidal behavior is in agreement with our observation that there is a negative correlation between the maximum lethality of suicide attempts in bipolar patients during the follow-up period and CSF monoamine metabolite levels. The small sample size is a limitation of this study and therefore, our results should be treated with caution until replicated. We hope that our study may revitalize the field of finding biological predictors for dangerous behaviors. Further studies are necessary to answer the question whether CSF monoamine metabolite levels can be used clinically as biochemical predictors of highly lethal suicide attempts or completed suicides.

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