

Attempted Suicide Characteristics and Cerebrospinal Fluid Amine Metabolites in Depressed Inpatients

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Background: Serotonin abnormalities have been reported in the brain of suicide victims. Evidence of a serotonin deficiency in suicide attempters is less consistent. We hypothesized that a serotonin deficiency may be present in suicide attempters whose attempt behavior more closely approximates completed suicide. **Method:** Sixty-seven (67) drug-free depressed inpatients (46 suicide attempters, 21 nonattempters) underwent research clinical assessments and a lumbar puncture. Cerebrospinal fluid (CSF) monoamine metabolites were assayed. Degree of medical damage and intent of the most recent suicide attempt were rated. **Results:** CSF amine metabolites did not differentiate suicide attempters as a group from nonattempters. However, reduced serotonergic activity, as indicated by lower levels of CSF 5-hydroxyindoleacetic acid (5-HIAA)

was associated with a history of planned suicide attempts and with suicide attempts that resulted in greater medical damage. Other monoamine metabolites did not correlate with seriousness of suicidal behavior, except for low CSF homovanillic acid and higher medical damage. No correlation was found with violent method. **Conclusions:** Planned and more medically damaging suicide attempts appear to be associated specifically with low serotonergic activity and, therefore, resemble completed suicide both behaviorally and biochemically. It remains to be determined whether low levels of CSF 5-HIAA can predict greater medical damage in future suicide attempts. © 1996 American College of Neuropsychopharmacology [Neuropsychopharmacology 15, 576–586]

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Lower levels of cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) have been found in 11 of 16 studies of patients suffering from an episode of major

depression who have made a suicide attempt compared with patients with depression who have not made a suicide attempt (Mann et al. 1992; Nordin 1988; Secunda et al. 1986; Roy et al. 1986; Roy-Byrne et al. 1983; Vestergaard et al. 1978; Banki and Arató 1983; Jones et al. 1990; Westenberg and Verhoeven 1988; Edman et al. 1986; Ågren and Niklasson 1986; Lopez-Ibor et al. 1985; van Praag 1982; Träskman et al. 1981; Palaniappan et al. 1983; Åsberg et al. 1976a and b). See Table 1 for a summary. Lower levels of CSF 5-HIAA in suicide attempters have also been reported by some, but not all studies of patients with personality disorders (Lidberg et al. 1985; Gardner et al. 1990; Träskman-Bendz et al. 1986; Brown et al. 1982, 1979) and schizophrenia (Cooper et al. 1992; Lemus et al. 1990; Pickar et al. 1986; Roy et al.

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1985; Ninan et al. 1984; van Praag 1983). Therefore, a pattern of low CSF 5-HIAA levels in suicide attempters compared with nonattempters appears present in multiple psychiatric disorders, suggesting that this biochemical difference is independent of psychiatric diagnosis and instead related to the suicidal behavior or a predisposition to suicidal acts. Such observations, taken together with findings in brain of suicide victims, have generated the serotonin deficiency hypothesis of suicidal behavior (Mann and Arango 1992). This hypothesis states that serotonergic activity mediates an inhibitory effect on suicidal behavior and, consequently, low serotonergic activity increases the probability of suicidal behavior.

This hypothesis is important, not only in furthering understanding of suicidal behavior, but also because of its potential diagnostic and treatment implications. It is, therefore, important to determine the basis for the lack of agreement with regards to an association between CSF 5-HIAA and suicidal behavior in depressed patients.

One possible reason why results differ among studies of depressed patients may lie in the composition of the patient populations. For example, negative results have generally been found in bipolar disorder (Vestergaard et al. 1978; Banki and Arató 1983; Secunda et al. 1986a; Roy-Byrne et al. 1983; Ågren 1980). An alternative explanation may be the type of suicidal behavior. Stengel and others (Stengel 1973) have described two broad categories of suicide attempts. The first is called failed suicide. This type of suicide attempt involves planning, a high lethality method, and a low chance of rescue. The second group involves a minimally planned suicide attempt using a low lethality method with a high probability of rescue. This latter type of suicide attempt has been variously termed including pseudocide, parasuicide, or suicide gesture (Lennard-Jones and Asher 1959; Stengel 1973). Few studies have directly examined what types of suicidal acts are related to low levels of CSF 5-HIAA.

Table 1. CSF 5-HIAA and Suicidal Behavior

Study	Impulsivity	Diagnosis	Findings in CSF 5-HIAA Attempters vs. Nonattempters	Violent Method
Åsberg et al.	1976	Depression	↓ 40% of attempters had low CSF 5-HIAA vs 15% of nonattempters	Violent method more common in low 5-HIAA group. No data on impulsivity
Vestergaard et al.	1978	Depression	No difference in CSF 5-HIAA	
Ågren	1980	Depression	Seriousness of intent of worst suicide attempt—neg. correlation with CSF 5-HIAA in unipolar but not bipolar depression	
Palaniappan et al.	1983	Depression	CSF 5-HIAA ↓ in attempters	
Träskman et al.	1981	Depression	CSF 5-HIAA ↓ in violent attempters and ↓ in nonviolent attempters	
van Praag	1982	Depression	CSF 5-HIAA ↓ (probenacid) in attempters	No correlation with violence of attempt
Åsberg and Träskman	1981	Depression	Low CSF 5-HIAA predicted 22% suicide rate in 1 year	
Roy-Byrne et al.	1983	Depression	No difference in CSF 5-HIAA	
Lopez-Ibor et al.	1985	Depression	Low CSF 5-HIAA group had more attempters	
Ågren and Niklasson	1986	Depression	CSF 5-HIAA ↓ 12% in attempters ($p = .07$)	
Roy et al.	1986	Depression	CSF 5-HIAA 22% ↓ in attempters vs. nonattempters but nonsignificant	No 5-HIAA differences due to violent attempter method
Secunda et al.	1986	Depression	No diff in 5-HIAA	
Edman et al.	1986	Depression	CSF 5-HIAA ↓ in attempters	Violent lower 5-HIAA and faster skin conductance habituation than nonviolent attempters
Peabody et al.	1987	Depression	CSF 5-HIAA correlated with HAMD	Also correlated with suicide subscale
Westenberg and Verhoeven	1988	Depression	No difference	No differences
Nordin	1988	Depression	No correlation with suicidal thoughts	
Jones et al.	1990	Depressed elderly	CSF 5-HIAA ↓ in attempters	
Banki and Arató	1983	Mixed	↓ in attempters; ↓ 37% in violent vs nonviolent attempters and vs nonattempters	Violent lower 5-HIAA than nonviolent
Mann et al.	1992	Depression	Only high planned suicide attempters had lower CSF 5-HIAA	No differences in violent attempters

Some (Banki and Arató 1983; Edman et al. 1986; Åsberg et al. 1976b) but not most (Westenberg and Verhoeven 1988; van Praag 1982, 1983; Roy et al. 1986; Träskman et al. 1981) studies reported that violent suicide attempts characterize patients with low levels of CSF 5-HIAA. Alternatively, it has been hypothesized that impulsive suicide attempts may be associated with low CSF 5-HIAA. However, there are no data to directly support either of these suggestions (see Table 1). Impulsive, as opposed to premeditated, externally directed violence does appear to be associated with low CSF 5-HIAA in patients with personality disorders as well as in convicted murderers (Virkkunen et al. 1987; Brown et al. 1982, 1979; Linnoila et al. 1983; Lidberg et al. 1985), and CSF 5-HIAA is low in personality disorders characterized by impulsive aggression and suicidal behavior (Träskman-Bendz et al. 1986). Suicide attempters with major depression are more impulsive characterologically than nonattempters (Malone and Mann, unpublished data); this question needs to be studied further.

Impulsivity may be at least partly independent of a second aspect of suicidal behavior, namely the degree of planning or preparation. Completed suicides, as a group, are characterized by more planning of the suicidal act than suicide attempters as a group (Beck and Lester 1976; Beck and Steer 1989). At the same time, completed suicides appear to be associated with brain serotonin system abnormalities that are also independent of associated psychiatric diagnosis (Mann et al. 1996). Most, but not all studies have found serotonergic abnormalities that include reduced brainstem serotonin and/or 5-HIAA levels (Shaw et al. 1967; Pare et al. 1969; Moses and Robins 1975; Lloyd et al. 1974; Korpi et al. 1986; Cochran et al. 1976; Bourne et al. 1968; Beskow et al. 1976), a decreased number of serotonin transporter binding sites in prefrontal cortex in five out of 17 published studies, an increased number of 5-HT_{2A} receptors in prefrontal cortex in eight out of 13 published studies, increased 5-HT_{1A} receptors in entorhinal and prefrontal cortex in two out of three autoradiography studies and none out of three membrane binding studies, and decreased 5-HT_{1D} receptor sites in nondepressed suicides (Arranz et al. 1994); (see Mann et al. 1996 for a summary). Thus, an impressive body of data supports a link between completed suicide and serotonergic abnormalities.

We hypothesized that suicide attempters most closely resembling suicide completers are more likely to have a similar abnormality in the serotonin system. We, therefore, studied the relationship between CSF 5-HIAA and the type of suicidal behavior, defined on the basis of the degree of medical damage inflicted and the level of suicidal intent and planning. A group of depressed inpatients who had recently attempted suicide were compared with depressed inpatients who had never attempted suicide. Preliminary results from a subgroup of this

study population ($n = 34$) have been reported elsewhere addressing the relationship of degree of planning of a suicide attempt to CSF 5-HIAA (Mann et al. 1992). We found that highly planned suicide attempts were associated with lower CSF 5-HIAA (Mann et al. 1992). This study needed to be replicated. In the current study, we have extended the previous study by doubling the sample size, examining the relationship of CSF 5-HIAA to degree of medical damage; and studying the noradrenergic and dopaminergic systems to determine the biochemical specificity of the CSF correlates of suicidal behavior.

METHODS

Patients were included in the protocol after admission to a private university psychiatric hospital for evaluation and treatment of depression and subsequently having given written informed consent as required by the Institutional Review Board for Biomedical Research. The group comprised 67 inpatients. The consent rate for patients who were approached for the study was in excess of 70%. Patients who refused the study did not differ from those included in the study on key variables of interest such as number and lethality of suicide attempts (Mann and Malone, unpublished data). The duration of the drug-free period was established by a combination of a drug screen, observation in hospital, and a history obtained from the patient's family and the referring physician. Patients had to be free for at least 14 days from drugs known to affect the serotonin system such as monoamine oxidase inhibitors, tricyclics, selective serotonin reuptake inhibitors, and serotonin agonists. The drug-free interval was longer for drugs with a long half-life such as fluoxetine (6 weeks) or oral antipsychotics (4 weeks). When the drug-free period was recorded, it was arbitrarily limited to 365 days. The group was drug-free for an average of 140 days ($SD = 169$). Suicide attempters who took an overdose included cases who took corrosives and other toxic agents without effect on the brain. The drug-free criteria were also met by the overdose group where the mean period off psychotropics prior to study was 93 days and did not differ from the other patients. Most of the suicide attempters ($n = 46$) had made a suicide attempt within 4 weeks prior to admission, with the interval between suicide attempt and lumbar puncture being 1 to 39 days (9.81 ± 8.3 days). In all cases, patients were medically recovered from the effects of the suicide attempt by the time of the lumbar puncture. The number of lifetime suicide attempts per case was 2.7 ± 2.2 (range 1–10).

Diagnosis was established at a consensus conference according to DSM-III-R criteria (Spitzer et al. 1989) and based on results of a structured clinical interview (SADS)

(Spitzer and Endicott 1978) and on independently carried out supplemental interviews by two research psychiatrists. Of the patients, 55 of 67 had a current major depressive episode (MDE), one was dysthymic with previous major depressive episodes, two had an adjustment reaction with depressed mood, three were schizoaffective or schizophreniform with pronounced depressed mood, and six had a combination of markedly depressed mood currently, borderline personality disorder (BPD) and a past history of major depression. The severity of depression on the 24-item Hamilton Depression Rating Scale (HAMD) (Hamilton 1960) was 31 ± 8.1 (with a range of 10 to 44). Clearly, most subjects were moderately to severely depressed. Of the patients, 16% were psychotic. Seven of the 55 patients with current MDE had bipolar I or II disorder.

Patients had a physical examination and routine laboratory screening tests to exclude neurologic disease and any other active physical disease that could affect their mental status or CSF 5-HIAA. Exclusion criteria included cardiac failure, renal or liver disease, malignancy, obstructive airways disease, endocrinopathies, and neurologic disorders.

The severity of depression was assessed by a 24-item version of the HAMD (Hamilton 1960). The most recent suicide attempt was rated by the Suicide Intent Scale (SIS) (Beck et al. 1975) and the degree of medical damage by the Lethality Rating Scale (Beck et al. 1975). Suicide attempts were classified into nonviolent (drug overdose) or violent (gunshot, cutting, stabbing, jumping, or hanging). The suicide attempt method refers to the most recent suicide attempt, for which we had the most detailed data, and included drug overdose ($n = 29$), substance overdose ($n = 1$), shooting ($n = 1$), immolation ($n = 1$), cutting ($n = 9$), jumping ($n = 1$), hanging ($n = 3$) and other ($n = 1$). Thus, approximately two-thirds made a nonviolent attempt compared with one-third who made a violent attempt. The Beck Lethality Scale is scored from 0 to 8, where no medical damage = 0, and death = 8. Thus scores ranged from 0 to 7. Anchor points are provided for 0 to 8 and are individualized for eight different categories of methods of injury covering the major methods of suicide attempt. The scale is constructed to allow comparison of degree of medical damage across each of these eight categories of method of suicide attempt. Lifetime history of aggressive behavior was measured using the aggression history questionnaire developed by Brown and Goodwin (Brown et al. 1982, 1979). A categorical diagnosis of a BPD was based on DSM-III-R criteria, using a checklist (American Psychiatric Association Task Force 1987). Ratings of current psychopathology were based on the patient's clinical status over the 2 weeks prior to the sampling of CSF. Trait-related measures such as the aggression history questionnaire were carried out after stabilization of the patient's acute status. These latter ratings were almost

always done after the CSF sampling and close to the timing of discharge.

Components of suicide intent were further defined based upon the results of our factor analysis (Mieczkowski et al. 1993) of the SIS (Beck et al. 1975). This factor analysis resulted in a two-factor solution. Factor 1, called lethal intent, contained items pertaining to the subjective lethality of the attempt. Factor 2, called planning, contained items pertaining to the objective degree of planning for the attempt (see Table 2). Two subscale scores were generated based upon these results by summing the scores of items included within each factor.

The lumbar puncture was performed at about 0830 hours after the patient had been kept in bed at rest overnight and fasted from midnight. CSF was withdrawn from the L4-5 interspace while the patient was 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 a second, single tube and immediately transferred on ice-water to be centrifuged at 4°C. This 15-ml sample was then aliquoted into 1-ml samples for storage at -70°C until assay. One of the 15 1-ml samples was used for assay of monoamine metabolite levels.

CSF 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) were assayed using our previously published method by high performance liquid chromatography (HPLC) with electrochemical detection (Scheinin et al. 1983). The within-run and between-run coefficients of variation of the assay method were less than 10%. The level of sensitivity of the assay for 5-HIAA was 0.5 pmol/injection. All assays were done by laboratory staff blind to the clinical data. As previously reported, CSF 5-HIAA levels correlated with HVA levels ($r = 0.6$, $p < .0005$) and with MHPG ($r = 0.25$, $p < .024$). CSF HVA correlated with MHPG ($r = 0.23$, $p < .036$).

Cross-classification analyses were performed to test for significant differences in categorical demographic and clinical characteristics. Statistical comparisons between the nonattempters, high planning attempters,

Table 2. The Planning Subscale from a Factor Analysis of the Suicide Intent Scale

Item Number in Original Scale	Description
1	Isolation
2	Timing
3	Precautions against discovery or intervention
4	Acting to gain help during or after attempt
5	Final acts in anticipation of death
6	Active preparation for attempt
7	Suicide note
15	Degree of premeditation

and low planning attempters were made using ANOVA. The Newman-Keuls post-hoc multiple comparison procedure was used to identify which groups were significantly different when a significant group effects was found by ANOVA. Results are reported as mean \pm standard deviation, and all probabilities are two-tailed. Inspection of the scatter plot of the suicide planning factor scores and levels of CSF amine metabolites suggested heterogeneity of variance of the CSF amine metabolites across levels of planning and medical damage. We therefore divided suicide attempters based on median splits into those characterized by high and low levels of suicide attempt planning according to scores on the suicide planning factor (≤ 9 and > 9 , respectively): and, low and high levels of medical damage (< 3 or ≥ 3 score on Lethality Scale). Similarly, patients were divided into those with low and high levels of CSF 5-HIAA (≤ 100 , > 100 pmol/ml), HVA (≤ 190 , > 190 pmol/ml), and MHPG (≤ 43 , > 43 pmol/ml). This approach allowed us to compare our results with some pivotal previously published studies that compared high and low CSF 5-HIAA groups (Träskman et al. 1981; Åsberg et al. 1976b).

RESULTS

The demographic and clinical characteristics of the patients (subdivided by lifetime history of no suicide attempt, and high versus low degree of medical damage) are shown in Table 3. The overall group of patients was moderately to severely depressed as indicated by the mean 24-item HAMD score of 31.1 ± 8.1 . There were no significant group differences in age, sex ratio, severity of depression, lifetime aggressivity, or rates of comorbid BPD. The interval between the index suicide attempt

and the lumbar puncture was 9.5 ± 8.4 days (range 1 to 39), and all were medically well at the time of the spinal tap. Of the suicide attempters, 65% took an overdose and the remainder used violent means. We assessed the relationship of CSF monoamine metabolite levels to the time since the last suicide attempt and found no correlation (CSF 5-HIAA: $r = 0.07$, $n = 42$, $p < .7$; CSF HVA: $r = 0.09$, $n = 41$, $p < .60$; CSF MHPG: $r = -0.07$, $n = 39$, $p < .7$).

Males tended to have lower levels than females of CSF 5-HIAA (98.1 ± 33.9 versus 113.3 ± 33.1 pmol/ml, $t = 1.86$, $df = 65$, $p < .07$), and CSF HVA (170.7 ± 82.6 versus 211.2 ± 85.7 pmol/ml, $t = 1.95$, $df = 64$, $p < .06$). There was no sex difference in CSF MHPG levels.

We initially compared mean levels of CSF 5-HIAA, HVA, and MHPG in all patients who had made a suicide attempt to patients who had never made a suicide attempt. No significant differences were found between attempters and nonattempters for CSF 5-HIAA (103.3 ± 33.3 vs 112.0 ± 35.7 ; $p > .05$), CSF HVA (183.1 ± 83.1 vs 209.6 ± 91.4 , $p > .05$) or CSF MHPG (44.1 ± 12.4 vs 44.1 ± 8.4 , $p > .05$). A two-way ANOVA, including sex as an independent variable, identified no group or sex effect.

We then evaluated the type of suicide attempt. The degree of medical damage, the degree of planning for a suicide attempt, and whether or not violent method was used, were all considered. There was a significant positive correlation between planning and degree of medical damage ($r = 0.47$, $n = 46$, $p < .009$). Based on a median split of the planning factor scores, planned suicide attempts resulted in greater medical damage than suicide attempts involving little planning (4.1 ± 0.9 vs 2.5 ± 2.3 , $t = 3.44$, $df = 40$, $p < .001$). High and low medical damage attempters did not differ in terms of severity of depression (Table 3). No significant linear correlations were observed between the CSF amine metabolites and the degree of medical damage. How-

Table 3. Demographics and Clinical Features of Populations

Variables	Suicide Attempters		
	Nonattempters	Lethality of Attempted Suicide	
		Low Medical Damage	High Medical Damage
Number of patients ^a	21	28	21
Age (years)	49.3 ± 14.7	42.1 ± 16.3	39.0 ± 16.6
Male/Female ratio	11/10	12/13	9/12
Hamilton depression scale score (24 item)	30.0 ± 6.9	28.7 ± 8.0	32.0 ± 9.1
Life-time aggression history score	15.4 ± 3.5	16.5 ± 4.7	15.9 ± 4.6
Percentage violent attempters	---	28%	43%
Percentage comorbid borderline P.D.	55%	40%	45%

^a Note that for technical reasons, all patients did not have all three amine metabolites assayed, and so numbers may vary in analyses of individual metabolite results.

ever, when patients were divided into those with high and low levels of CSF amine metabolites, and high and low medical damage (based on a median split of the Medical Damage Scale Score, ≥ 3 and < 3 , respectively), it was observed that lower levels of CSF 5-HIAA were associated with more medical damage and higher levels of CSF 5-HIAA were associated with less medical damage (see Table 4). Lower CSF HVA also appeared associated with greater medical damage.

The relationship of high versus low planning suicide attempts to high versus low levels of CSF 5-HIAA, HVA, and MHPG was analyzed (Table 5). A significant difference was observed between low and high planned suicide attempter status for CSF 5-HIAA, but not HVA or MHPG (Table 5). Of patients with a history of highly planned suicide attempts, 73% had low CSF 5-HIAA compared with 37% of low planners ($X^2 = 4.27$, $df = 1$, $p < .04$). The relationship of CSF 5-HIAA to level of planning was not linear. The rank order of mean levels of CSF 5-HIAA was high planners $<$ low planner attempters $<$ nonattempters (90.9 ± 24.8 vs 107.3 ± 35.0 and 112.0 ± 35.7 pmol/ml, respectively, $F(2,64) = 1.45$, $p < .24$) and HVA (153.8 ± 57.4 vs 191.5 ± 87.9 and 209.6 ± 91.4 pmol/ml, respectively; $F(2,63) = 1.44$, $p < .24$); however the differences were not statistically significant. Low planning attempters had a mean level of CSF 5-HIAA closer to nonattempters than high planners. There was a trend for a greater proportion of high planners to have low CSF 5-HIAA compared with nonattempters ($p = .1$), but no difference between low planning attempters and nonattempters ($p = .67$). Mean CSF MHPG levels were 44 pmol/ml in all three groups. Considering gender in a two-way ANOVA did not alter the results. Factor 1 or subjective suicide intent did not correlate with any biochemical measures. In contrast to objective planning, the degree of subjective intent also did not correlate with degree of medical damage.

We compared violent and nonviolent suicide at-

Table 5. Relationship of Objective Indices of Planning of Suicide Attempts to Cerebrospinal Fluid Monoamine Metabolite Levels

	High Planners	Low Planners
High CSF 5-HIAA	3	22
Low CSF 5-HIAA	8	13
$X^2 = 4.27$, $p = .04$		
High CSF HVA	2	14
Low CSF HVA	8	21
$X^2 = 1.36$, $p = .24$		
High CSF MHPG	5	14
Low CSF MHPG	5	20
$X^2 = 0.25$, $p = .62$		

tempters in terms of higher or lower levels of CSF metabolites (see Table 6). No differences were found. Of the 16 subjects who carried out violent suicide attempts, 3 (19%) fell into the high medical damage group, compared with 15 (50%) of the 30 nonviolent attempts ($X^2 = 4.28$, $p < .04$). In this series of patients, the most lethal attempters involved drug overdoses.

DISCUSSION

This study examined systematically the relationship between dimensions of suicidal behavior in depressed patients and reduced levels of CSF 5-HIAA. We found that lower levels of CSF 5-HIAA were associated with first, suicide attempts resulting in more medical damage, and second, a greater degree of objective planning. No relationship was found with violent suicide method, subjective suicide intent, or the recency of the suicide attempt.

It was originally reported that CSF levels of 5-HIAA are distributed bimodally in depressed patients (Träskman et al. 1981; Åsberg et al. 1976a), and that the group with lower levels of CSF 5-HIAA are distinguished by a higher rate of past serious suicide attempts and a higher rate of future suicide (Åsberg and Träskman 1981).

Table 4. Relationship of Degree of Medical Damage Resulting from the Most Recent Suicide Attempt to Cerebrospinal Fluid Amine Metabolite Levels

	High ^a Medical Damage	Low ^a Medical Damage
High CSF 5-HIAA	9	16
Low CSF 5-HIAA	16	5
$X^2 = 7.43$, $p = .0006$		
High CSF HVA	5	11
Low CSF HVA	19	10
$X^2 = 4.86$, $p = .027$		
High CSF MHPG	10	9
Low CSF MHPG	14	11
$X^2 = 0.05$, $p = .82$		

^aBased on scores of ≥ 3 and < 3 on the Lethality or Medical Damage Scale (Beck et al. 1975).

Table 6. Relationship of Violent and Nonviolent Suicide Attempts to Cerebrospinal Fluid Amine Metabolite Levels

	Violent Attempt	Nonviolent Attempt
High CSF 5-HIAA	11	14
Low CSF 5-HIAA	5	16
$X^2 = 2.05$, $p = .15$		
High CSF HVA	5	11
Low CSF HVA	11	18
$X^2 = 0.20$, $p = .65$		
High CSF MHPG	9	10
Low CSF MHPG	6	19
$X^2 = 2.61$, $p = .11$		

Since that report, many other studies have been published (Table 1) examining the relationship of CSF 5-HIAA to suicidal behavior in depressed patients and other psychiatric populations. Eleven previous studies (see Table 1) found lower levels of CSF 5-HIAA in patients with a major depressive disorder who had also carried out a suicide attempt compared to depressed patients who had not attempted suicide. Five studies did not find lower CSF 5-HIAA in suicide attempters.

We found that a history of a recent suicide attempt resulting in a greater degree of medical damage is associated with lower levels of CSF 5-HIAA, relative to a suicide attempt involving less medical damage or no history of a suicide attempt. The degree of medical damage was defined a priori on the basis of a median split of the scores on the Lethality Scale, and that split turned out to separate those requiring hospitalization for medical treatment from those not requiring admission to hospital. Because medical damage is a dimension that distinguishes completed suicide from failed suicide, and failed suicide from parasuicide, its relationship to low CSF 5-HIAA is of great interest. Previous studies of CSF 5-HIAA have not quantified the degree of medical damage, so direct comparison with our results is difficult. However, we recently found that the prolactin response to serotonin release by fenfluramine was blunted in a totally new group of patients with a current major depression and a past history of a high suicide attempt resulting in high medical damage (using the same cut-off score on the Medical Damage Scale as in this study) compared with a group of depressed patients who had made only low medical damage suicide attempts (Malone et al. 1995). That study offers powerful evidence in support of the current study's results, because it used a different method for assessing the serotonin system and involved a different group of patients.

The question exists as to whether the CSF 5-HIAA levels were affected by the degree of medical damage. The lack of correlation between CSF 5-HIAA levels and the time interval separating the attempt and the lumbar puncture, together with the drug-free interval, and the fact that all patients were medically well at the time of the lumbar puncture, suggests that the CSF 5-HIAA level was not a consequence of the suicide attempt or residual drug effects. A prospective study will be better able to address this question.

Another possible reason for lack of agreement in the literature may be the type of affective disorder included in the study population. Three of the five studies that did not find reduced CSF 5-HIAA levels in depressed patients who attempted suicide had included a significant number with bipolar disorder (Secunda et al. 1986; Vestergaard et al. 1978; Roy-Byrne et al. 1983). One study found lower CSF 5-HIAA levels in association with suicidal behavior in unipolar but not in bipo-

lar depressed patients (Ågren 1980b). However, a second study where the depressed population comprised about 50% bipolar cases did find reduced CSF 5-HIAA in the attempters (Banki and Arató 1983). In our study, only 12% had a bipolar disorder, and yet we did not find lower levels of CSF 5-HIAA when all types of suicide attempts were considered. Moreover, disagreement is not limited to studies of depression, because it also occurs in studies of schizophrenia. Thus, it appears that diagnostic group or subgroup may not be a significant factor.

Another aspect of the type of suicidal act that may relate to low CSF 5-HIAA is the degree of planning. We found that more planning was associated with lower CSF 5-HIAA. It should be noted that planning and impulsivity are not opposites. The decision to act on a careful plan may be impulsive. Previous studies have not quantified either planning or impulsivity (see Table 1), so their relationship to CSF 5-HIAA has been hitherto unclear. Based on extrapolations from studies of externally directed aggression, suggesting that it is impulsive aggression that correlates with low CSF 5-HIAA (Linnoila et al. 1983; Lidberg et al. 1985; Virkkunen et al. 1987, 1989a,b), it may be presumed that impulsivity is greater in suicide attempters and, if so, impulsivity would be hypothesized to be negatively correlated with CSF 5-HIAA. Future studies of suicide attempters should quantitate impulsivity to determine whether this relationship is present in depressed suicide attempters.

In a pilot study involving half the subjects in this study, we found the same results as in this study, namely that only depressed patients with a history of a well-planned suicide attempt had lower CSF 5-HIAA than nonattempters (Mann et al. 1992). It has been reported (Beck et al. 1974a) that Beck SIS scores are higher in patients who complete suicide compared with patients who have attempted suicide, and this scale assigns higher scores to planning. Moreover, SIS scores are higher in patients who reattempt suicide in the future (Beck et al. 1974a, b) and in those who ultimately complete suicide (Beck and Steer 1989). Because degree of planning and premeditation are associated with greater medical damage (Pallis and Sainsbury 1976), from a behavioral standpoint, suicide attempters who plan suicide attempts resemble completed suicides. Moreover, it is the lethality of a suicide attempt that ultimately distinguishes a completed suicide from a failed suicide attempt or gesture. Thus, our findings and other studies indicate that highly planned, high lethality suicide attempters resemble suicide completers behaviorally.

Several studies (see Mann et al. 1996 for a review) have reported lower levels of serotonin and/or 5-HIAA in the brainstem of suicide victims compared with controls (Shaw et al. 1967; Pare et al. 1969; Moses and Robins 1975; Lloyd et al. 1974; Korpi et al. 1986; Cochran et

al. 1976; Bourne et al. 1968; Beskow et al. 1976). Levels of 5-HIAA in frontal cortex correlate with CSF levels at postmortem (Stanley et al. 1985), indicating that CSF levels may reflect neuronal activity in relevant brain areas. Changes involving multiple serotonin receptors (serotonin transporter, 5-HT_{2A} and 5-HT_{1A}) have also been found by some, but not all, studies in the brain of suicide victims (Arango et al. 1990; Stanley and Mann 1983; Arango and Mann 1992; Mann et al. 1989; Paul et al. 1984; Stanley et al. 1982) (see Mann et al. 1996 for a review). These findings in suicide completers appear to be independent of diagnosis. Therefore, although our study was largely confined to depressed patients, the findings suggest that a relationship exists between suicide completers and a subgroup of suicide attempters based on the behavioral dimension of suicide planning and the biological dimension of altered serotonergic activity. A category of failed suicide has been proposed (Beck et al. 1975; Stengel 1973) on the basis of similarities in the pattern of the suicidal behavior, namely use of a highly lethal method, minimization of the chances of rescue, and planning the attempt. On the basis of our CSF results, and our observation that greater planning is associated with more severe medical damage, failed suicides appear to be related to completed suicide not only in terms of behavioral aspects but also in biological measures of serotonin function.

It has also been hypothesized that the dimension of the suicidal behavior related to low CSF 5-HIAA is the degree of violence of the attempt as opposed to some other aspect of suicidal behavior such as suicidal intent. We did not find such a relationship. Our results are supported by the literature. Only three out of eight studies with available data reported that violent suicide attempts are associated with lower levels of CSF 5-HIAA (see Table 1). In agreement with our findings in suicide attempters, no relationship has been found between serotonin indices in the brain of suicide victims using violent as opposed to nonviolent suicide methods (Arango and Mann 1992). Therefore, the weight of the evidence is against this hypothesis. We have previously reported (Marzuk et al. 1992) that availability of method is a major factor determining choice of suicide method. Thus, selection of a violent method for suicide does not appear to be biologically determined, but instead may be dependent on the availability of specific methods, for example guns compared with pills.

With regard to suicidal behavior and CSF levels of HVA or MHPG, no consistent pattern has emerged in the literature. We found low CSF HVA was more frequent in association with high medical damage suicide attempts. We did not find an association between low CSF HVA and degree of planning. Some, but not all, studies report lower levels of CSF HVA in attempters (Ågren 1980a; Träskman-Bendz et al. 1986; Roy et al. 1986; Secunda et al. 1986a; Träskman et al. 1981; Ågren

1980a). There is also disagreement as to whether this relationship holds true only for major depressive disorder (Träskman et al. 1981) or whether it is also present in other diagnostic groups (Roy et al. 1986; Ågren 1980b). Thus, both our findings, and those in the literature, are less persuasive of a relationship between CSF HVA and suicidal behavior compared with the evidence for CSF 5-HIAA. CSF MHPG appears to have a unimodal distribution in affective disorders with levels tending to be elevated relative to controls (Koslow et al. 1983). One study found a complex relationship between CSF MHPG and suicidal behavior (Ågren 1980a,b). However, our study found no correlation. Unlike CSF 5-HIAA, we found that CSF MHPG did not have statistically significant relationships with either degree of medical damage or planning of the suicide acts, indicating a biochemical specificity for this biobehavioral correlation. This conclusion is supported by a recent report (Nordström et al. 1995) that CSF MHPG and HVA did not predict future suicide in a sample where low CSF 5-HIAA was associated with an increased suicide rate, 1 year after study.

In conclusion, we found that lower CSF 5-HIAA was associated with recent suicide attempt behavior characterized by greater planning and resulting in more medical damage. Given the genetic regulation of levels of CSF 5-HIAA (Higley et al. 1993; Oxenstierna et al. 1986), its stability over time (Hildebrand et al. 1990; Menachem et al. 1989), this test may have potential for not only predicting future suicide (Nordström et al. 1994; Träskman et al. 1981) and suicide attempts (Cooper et al. 1992; Roy et al. 1989), but also the seriousness of the attempt. Studies should be carried out to determine whether CSF 5-HIAA correlates with seriousness of suicidal behavior at a point remote in time from testing. If so, it may represent a measure of vulnerability for more lethal suicide attempts. Identification of such high risk patients is an essential step in order that treatment intervention can be targeted at the most appropriate population for the purpose of efficacy studies that are almost totally lacking in suicidal patients.

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