Relationship Between Central and Peripheral Serotonin Indexes in Depressed and Suicidal Psychiatric Inpatients

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- Serious suicidal behavior, affective disorders, and a variety of other psychopathologic behaviors and syndromes have been found to correlate with measures of the serotonin system. Clinical studies have employed a range of serotonin indexes, including the cerebrospinal fluid level of 5-hydroxyindoleacetic acid, the prolactin response to serotonin agonists, such as fenfluramine hydrochloride, and platelet serotonin-related proteins or serotonin content. Many of these indexes are correlated with suicidal behavior, but the interrelationship of these biologic measures has been uncertain. We studied the relationship of a series of serotonin indexes in patients in whom these measures were correlated with suicidal behavior. A positive correlation was found between cerebrospinal fluid 5-hydroxyindoleacetic acid and the maximal prolactin response to fenfluramine but not with platelet serotonin, receptor indexes. The fenfluramine-stimulated maximal prolactin response correlated with platelet serotonin, receptor number, particularly in older patients. We conclude that cerebrospinal fluid 5-hydroxyindoleacetic acid measurements cannot be replaced but can be complemented by less invasive procedures, such as a fenfluramine challenge test or platelet serotonin, measures, in the study of the relationship of the serotonin system to psychiatric disorders.

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Serotoninergic indexes correlate with suicidal behavior and affective disorders. Approaches that have been employed to study the serotonin system include measurement of cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) and neuroendocrine challenge tests using a variety of precursors and direct or indirect serotonin agonists, such as serotonin reuptake inhibitors or serotonin releasing agents. Other serotonin indexes assess peripheral tissue, of which the predominant source is the platelet. Little is known regarding the relationship of central measures, such as CSF 5-HIAA level and the prolactin response to fenfluramine hydrochloride, to peripheral measures, such as platelet monoamine oxidase activity, platelet serotonin content, platelet serotonin uptake, and the platelet serotonin-related receptors, namely the serotonin transporter (typical ligands are tritiated imipramine and tritiated paroxetine) and the serotonin2 receptor. The relationship of central and peripheral serotonin indexes has theoretical and practical importance. The theoretical importance lies in determining what information about brain serotonin systems can be inferred from platelet indexes by studying the relationship of such indexes to brain or central serotonin indexes. For routine clinical purposes, lumbar punctures cannot be performed as readily as blood sampling, and therefore alternative approaches to a lumbar puncture would facilitate the conduct of biologic studies of the serotoninergic system.

We compared CSF 5-HIAA levels and the prolactin response to fenfluramine with platelet 5-HT2 receptor indexes in psychiatric inpatients with and without a history of suicidal behavior to assess the interrelationship of these indexes, because we and others have found all of these biologic probes to be related to suicidal behavior. The relationships between aspects of suicidal behavior and each of the serotonin indexes were the subject of studies that involve larger patient population in the case of each individual serotonin index. The data reported in this article are based on those subjects from these larger patient populations in whom data were available on multiple peripheral and/or central serotonin indexes. The studies of individual serotonin indexes are being reported as separate articles because they involve significantly larger pa...
tient samples and more detailed analyses of general psychopathology and suicidal behavior.

PATIENTS AND METHODS

Patients

Patients were enrolled in the study after giving written informed consent as required by the Institutional Review Board. Eligible inpatients met DSM-III-R criteria for a major or minor depressive episode as independently determined by two research psychiatrists. Apart from chloral hydrate or a benzodiazepine with a short half-life, such as oxazepam, in isolated cases of distressing insomnia, 29 of 34 patients were drug free for at least 2 weeks (6 weeks in the case of flunitrazepam and 3 months in the case of oral neuroleptics) and free of any active physical illness. Of the remaining five patients, four had made a suicide attempt by drug overdose within 2 weeks of study (one patient had taken nonpsychotropic drugs without effect on the brain or significant medical complications 6 days before testing; one patient had taken a benzodiazepine 4 days earlier; the third patient had taken pentobarbital sodium 11 days before testing; and the fourth patient had taken 750 mg of trazodone hydrochloride 7 days before testing). A final patient was found after the study to have received 5 mg of haloperidol 8 days before testing. The baseline prolactin level in this last patient was not above the group mean. None of the biologic measures (CSF 5-HIAA, prolactin response to fenfluramine, or platelet 5-HT2 indexes) in this subgroup differed from those of the rest of the population, and so they were included in the data analysis. The average drug-free interval for all patients was 148 ± 161 days. No patient had taken fenfluramine in the past. Patients were at a point in their clinical illness where they had required admission to a hospital for evaluation and treatment. They were studied immediately before somatic treatment was initiated.

The demographic and clinical characteristics of the study population are shown in Table 1. Severity of depression was assessed by means of the Hamilton Depression Scale,15 and the suicidal behavior was characterized by the level of suicide intent according to the Suicide Intent Scale16 and the degree of medical damage on the Medical Lethality Scale.17 Possible gender and age effects were addressed in the analysis of the results where indicated. Of the women, five (36%) of 14 were menopausal, too few to estimate the effect of menopause on the biologic measures.

CSF 5-HIAA Measurement

Cerebrospinal fluid was drawn from the L4-5 interspace with the patient in the left decubitus position. All patients rested in bed overnight until the procedure and fasted from midnight. The CSF was spun to remove any debris, and the supernatant was stored at −70°C till assay. A 1-ml aliquot of a 15-ml sample was used for assay. The CSF 5-HIAA was assayed by high-performance liquid chromatography with an electrochemical detector as previously described.17 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 per injection. All assays were done by laboratory staff who were unaware of the clinical data.

Platelet 5-HT2 Receptor Indexes

Platelet 5-HT2 receptor binding indexes were assessed in a membrane preparation by iodine 125-lysineacetyl binding with ketanserin to determine specific binding according to our previously published method.9 The maximum number of binding sites per milligram of platelet membrane protein (Bmax) and the dissociation constant (Kd) were calculated from a saturation binding isotherm. Signal transduction was assessed by measurement of serotonin enhancement of adenosine diphosphate–induced platelet aggregation (serotonin augmentation index [SAI]).18 Receptor responsivity or sensitivity was defined as the ratio of signal transduction response and receptor number, or SAI/Bmax. The SAI/Bmax is a measure of the sensitivity of the individual receptor to activation and therefore provides an index of changes in receptor complex responsivity, such as supersensitivity or subsensitivity. Our analyses focused on the total number of receptors (Bmax) and the responsivity of each receptor (SAI/Bmax) because these two measures reflect the effects of receptor regulation.

Fenfluramine Challenge Test

Brain serotonin responsivity was assessed by means of a fenfluramine challenge test.1 Fenfluramine is an indirect serotonin agonist in the sense that it activates serotonin receptors by increasing serotonin levels in the synaptic cleft instead of directly activating the serotonin receptors. Fenfluramine raises levels of serotonin exposed to receptors by a combination of increased release from nerve terminals and inhibition of serotonin reuptake.11,14 The elevated serotonin levels in turn activate serotonin receptors. Fourteen of 34 patients received a single-blind placebo challenge on one day, followed by a 60-mg fenfluramine hydrochloride challenge test generally administered the next day. Twenty of the 34 patients did not receive a placebo challenge.

All patients fasted from midnight and throughout the challenge test. Patients continued to rest in bed after they awoke in the morning until they were tested. They were not permitted to sleep during the procedure. An intravenous line was inserted at approximately 8 AM, and a solution of 5% dextrose and 0.45% saline was administered. Blood samples for assay of prolactin were drawn at approximately 8:45 AM and 9 AM. Either 60 mg of fenfluramine hydrochloride or identical placebo tablets were then administered. Blood samples were drawn 1, 2, 3, 4, and 5 hours after administration of the drug. Blood samples were drawn at 3 and 5 hours to assay levels of fenfluramine and norfenfluramine by high-performance liquid chromatography as we have previously reported.7,8 Prolactin levels were assayed by means of a purchased immunoradiometric assay kit (Hybritech Inc, San Diego, Calif).7,8 The lower level of sensitivity of the assay was 0.3 µg/L, and interassay coefficient of variation was 4%.

Results at each time point were calculated by two methods: (1) as the difference between the prolactin response on the fenfluramine day and the prolactin level on the placebo day at each time point; and (2) as the difference between the mean of the two

Table 1.—Demographic and Clinical Features of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>CSF 5-HIAA and Platelet 5-HT2 Receptors</th>
<th>CSF 5-HIAA and Fenfluramine Hydrochloride</th>
<th>Fenfluramine and Platelet 5-HT2 Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>34</td>
<td>22</td>
</tr>
<tr>
<td>Age, y</td>
<td>43.0 ± 13.1</td>
<td>34.9 ± 11.3</td>
<td>41.6 ± 15.0</td>
</tr>
<tr>
<td>Male-female ratio</td>
<td>11/13</td>
<td>20/14</td>
<td>11/11</td>
</tr>
<tr>
<td>Suicide attempter/nonattempter ratio</td>
<td>17/7</td>
<td>24/10</td>
<td>12/10</td>
</tr>
<tr>
<td>Porportion with current major depressive episode</td>
<td>21/24</td>
<td>30/34</td>
<td>21/22</td>
</tr>
</tbody>
</table>

*CSF indicates cerebrospinal fluid; 5-HIAA, 5-hydroxyindoleacetic acid; and 5-HT2, serotonin.

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Relationships between CSF 5-HIAA, platelet 5-HT2 receptor indexes, and the fenfluramine-stimulated prolactin response, and the relationships of these variables to demographic and clinical variables, were analyzed by means of Pearson correlation coefficients. Spearman rank correlations (rs) were used when the sample size was relatively small. When the relationships among the serotonin indexes were analyzed, multiple regression analyses were used to control for the effects of possible confounding variables, such as age and gender. Group differences were analyzed by one-way analysis of variance. To test whether CSF 5-HIAA or the platelet 5-HT2 receptor indexes were significant predictors of the group status of high-planning attempters vs low-planning attempters and nonattempters, logistic regression analyses were performed. All reported P values are two sided, and results are reported as mean±SD.

RESULTS

Relationship of CSF 5-HIAA to Platelet 5-HT2 Receptor Indexes

The CSF 5-HIAA concentration did not correlate with either platelet 5-HT2 receptor number (Bmax; r = .09, n = 24, P = .7) or platelet 5-HT2 responsivity, defined as SAI/Bmax (r = .09, n = 24, P = .7). Even after exclusion of an outlier, the correlation between CSF 5-HIAA and SAI/Bmax remained nonsignificant (r = .22, n = 23, P = .3). When the effects of age and gender were included with SAI/Bmax in a multiple regression analysis where CSF 5-HIAA level was the dependent variable, the relationship was nonsignificant (r² = .03).

In a larger sample of patients that included all of the patients with CSF data reported in this study, we found lower levels of CSF 5-HIAA in those who had made highly planned suicide attempts (based on a high score on the first part of the Beck Suicide Intent Scale) compared with suicide attempters with a low suicide intent score or nonattempters. In this article, the same result was obtained: high planners (n = 5), 72.8±13.3 nmol/L, vs nonattempter patients (n = 7), 119.0±40.6 nmol/L (F = 5.86, df = 1,10, P = .04), and vs low planners (n = 10), 105.5±30.3 nmol/L (F = 5.18, df = 1,13, P = .04). The low planners did not differ from the nonattempter patients (105.5±30.3 vs 119.0±40.6 nmol/L; F = 0.62, df = 1,15, P = .44).

In a larger series of patients, we found a decrease in platelet 5-HT2 receptor responsivity in suicide attempters (n = 25) compared with nonattempters (n = 18) as assessed by the SAI/Bmax ratio (P<.05, Tukey B). The SAI/Bmax in the high-planning suicide attempters compared with low-planning attempters was not statistically different in the subgroup of patients described in this article (high planners [n = 5], 0.05±0.03, vs low planners [n = 10], 0.05±0.05 [F = 0.00, df = 1,13, P = .997] and vs nonattempters [n = 7], 0.12±0.12 [F = 1.27, df = 1,10, P = .29]). When a logistic regression analysis was performed with high-planning attempters (n = 5) vs nonattempters (n = 7) as the dependent variable and CSF 5-HIAA level, Bmax, and SAI/Bmax as the independent variables, no variable contributed significantly to the prediction of group status after CSF 5-HIAA level was entered into the model. The model with CSF 5-HIAA level as the only independent variable correctly classified 11 (92%) of the 12 subjects as being high-planning attempters or nonattempter patients. Similar results were obtained when high-planning attempters were compared with low-planning attempters, although the percentage correctly classified dropped to 67%.

Statistical Analyses

Severity of the medical damage caused by the suicide attempt did not correlate significantly with CSF 5-HIAA level (r = .08, n = 16, not significant) or SAI/Bmax ratio (r = .08, n = 16, not significant), but it did correlate positively with Bmax for platelet 5-HT2 receptors (r = .6, n = 16, P = .01). The presence of a major depressive episode or the severity of depression did not correlate with CSF 5-HIAA or platelet 5-HT2 receptor indexes.

Relationship of CSF 5-HIAA to Fenfluramine-Stimulated Prolactin Release

The CSF 5-HIAA level correlated significantly with the maximum increase in prolactin level after administration of fenfluramine (rₚ = .46, n = 34, P = .006; Figure). When patients were divided into suicide attempters and nonattempters, the CSF 5-HIAA level and the prolactin response correlated in the group of suicide attempters (rₛ = .50, n = 24, P = .01), and although the correlation was also positive in the nonattempters, it was not statistically significant (rₛ = .36, n = 10, P = .30). This result may be due to there being less variance in CSF 5-HIAA levels in the nonattempter group. When an outlier was removed from the nonattempter group, the correlation with prolactin response became even less significant (rₛ = .28, n = 9, P = .46), and the variance in CSF 5-HIAA level was significantly less than in the attempter group (F = 4.87, P = .03).

To determine whether age or suicide attempter status influenced the correlation between fenfluramine-stimulated prolactin response and CSF 5-HIAA level, a multiple linear regression analysis was conducted with CSF 5-HIAA as the dependent variable; the independent variables were age less than 30 years or greater than or equal to 30 years (B = 14.7, t = 0.97, P = .36), maximum prolactin response (B = 3.9, t = 3.14, P = .004), and attempter status (B = 3.3, t = 0.23, P = .082). Only the maximum change in prolactin response was statistically significant.

Relationship of Platelet 5-HT2 Indexes to Fenfluramine-Induced Prolactin Release

Because of the age-related decline in fenfluramine-induced prolactin response before the age of 30 years, we compared patients under 30 years old and 30 years of age and older separately (Table 2). In patients under the age of 30 years, there was no correlation between any platelet 5-HT2 index and prolactin levels. When prolactin responses were corrected for fenfluramine and norfenfluramine levels, the results remained nonsignificant. In patients 30 years old and older, the maximum change in prolactin response to fenfluramine was positively correlated with Bₘₐₓ (rₛ = .59, n = 16, P = .02), and there were trends toward re-
Table 2.—Correlation of Platelet 5-HT₂ Indexes With Maximum Fenfluramine Hydrochloride-Stimulated Prolactin Release in Patients Under 30 Years of Age and 30 Years and Older*

<table>
<thead>
<tr>
<th>Index</th>
<th>Spearman Rank Correlation Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;30 y (n=6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B&lt;sub&gt;max&lt;/sub&gt;</td>
<td>-0.20</td>
<td>.70</td>
</tr>
<tr>
<td>K&lt;sub&gt;0&lt;/sub&gt;</td>
<td>-0.37</td>
<td>.47</td>
</tr>
<tr>
<td>SAI</td>
<td>-0.09</td>
<td>.87</td>
</tr>
<tr>
<td>SAI/B&lt;sub&gt;max&lt;/sub&gt;</td>
<td>0.20</td>
<td>.70</td>
</tr>
<tr>
<td>Age ≥30 y (n=16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B&lt;sub&gt;max&lt;/sub&gt;</td>
<td>0.59</td>
<td>.02</td>
</tr>
<tr>
<td>K&lt;sub&gt;0&lt;/sub&gt;</td>
<td>0.44</td>
<td>.09</td>
</tr>
<tr>
<td>SAI</td>
<td>0.05</td>
<td>.85</td>
</tr>
<tr>
<td>SAI/B&lt;sub&gt;max&lt;/sub&gt;</td>
<td>-0.49</td>
<td>.06</td>
</tr>
</tbody>
</table>

*B<sub>max</sub> indicates maximal number of binding sites per milligram of platelet membrane protein; K<sub>0</sub>, dissociation constant; and SAI, serotonin augmentation index.

relationships with K<sub>0</sub> (r<sub>p</sub> = .44, n = 16, P = .09) and SAI/B<sub>max</sub> (r<sub>p</sub> = -.49, n = 16, P = .06). Fenfluramine and norfenfluramine levels did not differ between subjects 30 years old and older and those under 30 years of age.

When patients were also divided into attempters and nonattempters in a multiple linear regression analysis, including the effect of being under 30 years old or greater than or equal to 30 years old, there was a trend for SAI/B<sub>max</sub> (receptor responsiveness) to predict fenfluramine-induced prolactin release (B = -190.3, t = -1.8, P = .08). When prolactin response was adjusted for fenfluramine and norfenfluramine levels, this result became statistically significant (B = -3.2, t = -2.46, P = .02). When B<sub>max</sub> was entered into a similar analyses, the results were not statistically significant. When the maximum increase in prolactin level was the dependent variable in a similar analysis, SAI/B<sub>max</sub> was a significant predictor (B = -86.4, t = -2.16, P = .04), whereas B<sub>max</sub> was not.

COMMENT

We have confirmed the previously reported association between serious or high-intent suicidal acts and low levels of CSF 5-HIAA in this study population. Moreover, we also found a relationship between platelet 5-HT<sub>2</sub> receptor number and medical damage as well as between 5-HT<sub>2</sub> receptor sensitivity and a history of suicide attempts. However, these two serotonin indexes (CSF 5-HIAA and platelet 5-HT<sub>2</sub> receptor binding or responsivity) did not correlate and therefore appear to explain different components of the variance in suicidal behavior. We have found that CSF 5-HIAA level correlates with degree of objective suicide intent or planning, whereas platelet serotonin indexes reflect medical damage. Although suicide intent and degree of medical damage are also correlated, only CSF 5-HIAA level proved a significant discriminator of patients who had carried out highly planned suicide attempts compared with patients who had made impulsive suicide attempts or never attempted suicide. In contrast, platelet 5-HT<sub>2</sub> indexes correlated with the degree of medical damage but not with the degree of planning or suicide intent.

There are few studies of the relationship of CSF 5-HIAA to platelet serotonin indexes, and they generally have found no correlation. Oreland and colleagues reported no difference in platelet monoamine oxidase activity in a group of patients who had histories of attempted suicide and had low CSF 5-HIAA levels compared with nonattempter psychiatric controls. Platelet imipramine binding was found not to correlate with CSF 5-HIAA level in a study of surgical patients. Sarrias and colleagues reported a correlation only between the ratio of platelet to plasma serotonin levels and CSF 5-HIAA levels and suggested that this correlation may be explained by the action of monoamine oxidase, which is partly under genetic control. However, human brain MAO and platelet MAO activity have been reported not to correlate, so that some alternative explanation is warranted, such as a common effect on a biosynthetic enzyme. The levels of CSF 5-HIAA, brain 5-HIAA, and platelet serotonin content and uptake all appear to undergo seasonal and/or diurnal variation, which suggests a common systemic effect. The mechanism of this effect is unclear. One suggestion has been that external cues, such as the light-dark cycle, drive the circadian rhythm of serotonin in brain regions, such as the hypothalamus.

The absence of a correlation between CSF 5-HIAA levels and platelet serotonin indexes may be due to phase differences in their rhythms, although other explanations clearly are also possible.

We found a positive correlation between CSF 5-HIAA levels and the maximum prolactin response to fenfluramine. The prolactin response to fenfluramine is partly dependent on the level of serotonin available for release and partly on the responsivity of the postsynaptic serotonin receptor populations. Levels of CSF 5-HIAA have been reported in at least two human postmortem studies to correlate with levels of 5-HIAA in frontal cortex. Whether levels of available serotonin in the hypothalamic neurons involved in prolactin release correlate with CSF 5-HIAA levels remains to be determined. Brewerton and colleagues found that CSF 5-HIAA level was negatively correlated with the peak increase in prolactin levels after challenge with m-chlorophenylpiperazine (a serotonin agonist) in 12 low-weight anorexic patients (r = -.69) but not in weight-recovered patients. Further study of the relationship of CSF 5-HIAA level to neuroendocrine indexes of brain serotoninergic function in different patient populations is warranted. Our findings suggest that fenfluramine-stimulated prolactin release may be an indicator of brain serotoninergic activity in areas other than the hypothalamus, because CSF 5-HIAA is derived from multiple brain regions, including prefrontal cortex.

A blunted prolactin response to fenfluramine has been found to be associated with suicidal behavior in patients with depression as well in patients with personality disorders. Since the prolactin response to fenfluramine and the level of CSF 5-HIAA correlate, these measures may explain similar parts of the variance in suicidal behavior. For example, CSF 5-HIAA level correlated with objective suicidal intent or planning. Insufficient data were available to determine what aspect of suicidal behavior correlated with a blunted prolactin response to fenfluramine. If it appears that fenfluramine-stimulated prolactin responses correlate with the same dimension of suicidal behavior, then the fenfluramine challenge may be an alternative to CSF 5-HIAA measurement as an investigative tool in the study of suicide attempters. Another possibility is that the two measures may be complementary.

A positive correlation was found between platelet 5-HT<sub>2</sub> receptor number and the prolactin response to fenfluramine. The relationship was apparent only in patients...
aged 30 years and older, perhaps because patients under the age of 30 years had a much greater variance in prolactin responses. We previously reported the finding of a positive correlation between the prolactin response to fenfluramine and platelet 5-HT\textsubscript{2} receptor responsivity as measured by serotonin saturation of adenosine diphosphate–induced platelet aggregation (SAI) in young adults with autistic disorder,\textsuperscript{7}\textsuperscript{26} indicating that this relationship extends to other patient populations. This correlation was not statistically significant in this study or in the sample of seven young normal male controls in the study of autistic patients.\textsuperscript{8} Because the variance in SAI is less than \(B_{\text{new}}\), larger samples will be required to determine whether age is an important factor in determining the presence of a correlation between prolactin responses to fenfluramine and platelet 5-HT\textsubscript{2} receptor responsivity.

We also found that another part of variance in suicide behavior, namely the degree of medical damage resulting from the suicide attempt, may be explained by platelet 5-HT\textsubscript{2} receptor number. Therefore, if this measure were combined with a fenfluramine challenge test, it may enhance a research approach that uses CSF 5-HIAA measurement.

It is not clear why platelet 5-HT\textsubscript{2} receptor number correlates with the prolactin response to fenfluramine. Studies\textsuperscript{1,26} have attempted to determine which serotonin receptor populations mediate the prolactin response to serotonin, and the results are not entirely consistent. A role has been suggested for 5-HT\textsubscript{3} receptors, but some studies suggest that 5-HT\textsubscript{2} receptors may also be involved.\textsuperscript{7}\textsuperscript{26} If 5-HT\textsubscript{2} receptors are not involved, then it is difficult to propose a common receptor regulatory effect that involves 5-HT receptors mediating prolactin release and platelet 5-HT\textsubscript{2} receptors.

In conclusion, the concentration of CSF 5-HIAA has been found to correlate with serious suicidal behavior. The observation that suicidal behavior correlates with other indexes of serotonin activity, namely platelet 5-HT\textsubscript{2} receptor binding kinetics and responsivity and the prolactin response to fenfluramine, offers the possibility of employing such alternative measures for studying the serotonin system in suicidal patients. Prolactin response to fenfluramine but not platelet 5-HT\textsubscript{2} indexes correlates with CSF 5-HIAA level. It remains to be determined whether these measures explain the same or different components of the variance in suicidal behavior and perhaps different aspects of suicidal behavior. These studies will determine whether CSF 5-HIAA continues to be an important measure in the study of suicidal behavior.

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