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# PLATELET SEROTONIN AS BIOMARKER FOR ASSESSING SUICIDAL BEHAVIOUR IN PATIENTS WITH BIPOLAR I DISORDER

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## Abstract

**Context.** Suicide is a global public health issue. Bipolar disorder (BPD) has the highest suicide risk among individuals suffering from mental disorders. Serotoninergic dysfunctions have been linked to suicidal behaviour and platelet serotonin is recognised as a reliable index for the presynaptic serotonin activity.

**Objective.** Our aim was to assess whether alterations occur in platelet serotonin concentrations in BPD type I in respect to suicide attempters compared with non-attempters.

**Design.** This was a cross-sectional, observational study.

**Subjects and Methods.** Plasma platelet serotonin concentrations were measured using ELISA technique in 71 BPD I patients. The participants were assigned into 3 groups (non-attempters, low lethality and high lethality suicide attempters), according to the Columbia-Suicide Severity Rating Scale. Socio-demographical and clinical data was obtained by using MINI 6.0 and a semi-structured questionnaire designed specifically for this research.

**Results.** Our study showed significant lower levels of platelet serotonin in suicide attempters compared with non-attempters ($p = 0.030$) and in high-lethality attempters compared with low-lethality attempters ($p = 0.015$). The study recorded a higher number of total lifetime and lifetime depressive episodes for suicide attempters with BPD I.

**Conclusions.** Our results subscribe to the importance of platelet serotonin as a reliable biomarker in suicide risk assessment.

**Key words:** suicide, suicidal behaviour, suicide attempts, lethality, serotonin, platelet serotonin.

## INTRODUCTION

Suicide is a global public health issue and the 2nd leading cause of death among the 15 to 29 year old group population (1). More than 800,000 people die by suicide, worldwide, each year (1). Suicide thoughts and suicide attempts represent a major risk factor for completed suicide, with lifetime prevalence of, respectively, 9.2% and 2.7% (2).

Psychiatric disorders represent another leading predictor for suicide (3). Approximately 90% of people who complete suicide have a diagnosable psychiatric disorder (4). Sixty per cent of them suffer from mood disorders (5), and the rest from other mental conditions such as schizophrenia (6), substance abuse (7) and personality disorders (8). Bipolar disorder has the highest suicide risk among individuals suffering from mental illness (9). However, only about 15% of bipolar patients die by suicide (10). This implies that the occurrence of a psychiatric disorder is not a sufficient condition for suicidal acts.

The complexity of the suicidal process is underlined by psychosocial, psychopathological, biological and genetic factors. The individual risk for suicide changes across the ideation to behaviour continuum, according to the dynamic interplay between these factors. Thus, several models have been theorized to explain the interactions between individual vulnerabilities and environmental influences (11). The stress-diathesis model proposes genetic susceptibility coupled with childhood adversity, as predisposing risk factors, and psycho-social stressors together with psychiatric disorders, as triggering mechanisms for suicide (12). The theory also supports the existence of a neurobiological backdrop for clinical characteristics of suicidal behaviour. According to this model, impulsivity and aggressiveness are independently associated with

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suicidal behaviour and low serotoninergic functioning (13). Hopelessness, a core feature of suicide (14), correlates with low levels of norepinephrine (15), while a hyperactive hypothalamic-pituitary-adrenal axis (HPA) increases the odds for suicide (16). Therefore, assessing the neurobiological markers of suicide and suicidal behaviour is an important approach for identifying the predisposing risk factors (17).

Serotonin or 5-hydroxytryptamine (5-HT) is particularly important in determining the individual threshold for acting on suicidal impulses due to its link with the impulsive/aggressive traits (18). Serotoninergic pathway dysfunctions have been widely linked to suicidal behaviour and suicide in psychiatric disorders (19, 20). Platelets provide a convenient peripheral tissue for measuring serotonin concentrations (21) and platelet serotonin is recognised as an established and reliable index for presynaptic serotonin activity (22). Research studies report lower levels of platelet serotonin in the plasma of suicidal patients compared to normal controls (20, 23, 24). Likewise, they show significant lower platelet serotonin values for attempters compared with non-attempters (25-27). To our best knowledge, there is no data for assessing suicide risk in bipolar patients by measuring plasma platelet serotonin concentrations.

Current data suggests that there is a specific biological vulnerability to suicide, regardless of specific psychiatric diagnostic (28). Therefore, biomarker-focused research in suicide is imperative to ascertaining the suicide phenotype. One possibility to further the biomarker research in suicide is by assessing suicide attempters *vs*. non-attempters in high-risk populations. The present research aims to comparatively assess whether alterations occur in platelet serotonin concentrations in respect to suicide attempters *vs.* non-attempters with bipolar I disorder (BPD I).

## MATERIALS AND METHODS

### *Participants*

The sample consisted of 77 participants diagnosed with BPD I aged between 25 and 65. Three participants were removed due to lack of data for platelet serotonin concentrations, and 3 more as outliers after testing for normal distribution (N = 71). The participants were recruited from the "Prof. Dr. Al. Obregia" Clinical Psychiatric Hospital during an eight-month period. The inclusion criteria was the documented diagnosis of BPD I according to the Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV-TR) (29), which was confirmed by administering the Romanian translation version 6.0 of the MINI International Neuropsychiatric Interview (M.I.N.I.)(30) by a trained psychiatrist for each participant. The exclusion criteria were as follows: presence of organic mental disorders, mental retardation, schizophrenia or other psychotic disorders, other affective disorders, uncontrolled or serious medical conditions, pregnancy or postpartum period. The participants were included regardless of their current psychopharmacological treatment, which was comprised of varied combinations between mood stabilisers, antipsychotics, antidepressants and benzodiazepines, prescribed in clinical pharmacological doses.

Informed consent was obtained from each participant after a detailed description of the study. Clinical and biological assessments were performed just once, for each subject, during a three-day interval. The Ethical Committee of "Prof. Dr. Al. Obregia" Clinical Psychiatric Hospital in Bucharest, Romania, approved this study. Biological sample analysis was performed in the Research Department of "C. I. Parhon" National Institute of Endocrinology, Bucharest.

### *Clinical assessments*

Clinical and socio-demographical data were obtained by administering M.I.N.I. and a semi-structured questionnaire, developed and used specifically for this research, thus recording specific characteristics of the sample: type of presentation (in-patient/out-patient), number of voluntary/involuntary past admissions, present clinical state, medical history, substance use, presence of past legal issues, age of onset for BPD I disorder, number and types of past episodes, stressful life events, family history of suicide or psychiatric disorders and current pharmacological treatment.

The clinical assessment of suicide thoughts and behaviour was performed using the Romanian version of Columbia-Suicide Severity Rating Scale (C-SSRS, Baseline Version 1/14/09) (31). This semi-structured questionnaire is divided in two parts. The first, "suicidal ideation", is comprised of a 5-point ordinal subscale, ranging from 1 (wish to be dead) to 5 (active suicidal ideation with specific plan and intent). Additionally, "intensity of ideation" includes five items that rate the frequency, duration, controllability, deterrents and reasons of suicidal thoughts. This subscale uses two different assessment periods (lifetime, past month). The second, "suicidal behaviour" is a nominal subscale that

includes actual, interrupted and aborted attempts, as well as preparatory acts and non-suicidal self-injurious behaviour. Additionally, actual suicide attempts (most recent/most lethal/initial) are assessed by an ordinal Lethality subscale, which categorizes the medical consequences of a suicide attempt as follows: "0 - No physical damage or very minor physical damage", "1 - Minor physical damage", "2 - Moderate physical damage; medical attention needed", "3 - Moderately-severe physical damage; medical hospitalisation and likely intensive care required", "4 - Severe physical damage; medical hospitalisation with intensive care required" and "5 - Death". Furthermore, if actual lethality is 0, Potential lethality will be measured on a separate 3-point ordinal subscale. The scale also contains the number of attempts (actual, interrupted and aborted) and uses different assessment periods (lifetime and past year).

***Biological analysis***

Platelet Serotonin was measured by an ELISA technique (IVD kit – LDN GmbH, Germany, sensitivity 6.2 ng/mL) following manufacturer protocol. Briefly, blood was collected in vacuettes containing EDTA as coagulant. The samples were centrifuged for 10 minutes (200 x g) at room temperature, the supernatant was transferred in another tube, and then platelets were counted. Platelet-rich plasma should contain 350000-500000 platelets/µl. The platelet pellet was obtained by adding 800 µl saline buffer to 200 µl of platelet-rich plasma and centrifugation (4500 x g, 10 minutes, 4˚C). After the supernatant was discarded, 200 µl of deionized water was added, thoroughly mixed and the suspension was stored frozen at below -40˚C.

For the acylation reaction, the frozen samples were thawed, centrifuged at 10,000 x g for 2 min, at room temperature and 25 µl of the supernatant was used.

The content of serotonin in platelets was referred to $10^9$ platelets.

***Statistical analysis***

For statistical analysis we used the IBM SPSS Statistics, Version 22.0. Data was tested for normality using the Shapiro-Wilk test and by assessing Q-Q plots and histogram data distribution. For our analysis, participants were grouped according to C-SSRS criteria for actual, lifetime, suicide attempts into "Non-attempters", patients who scored < 1 on the Suicidal Behaviour subscale, and "Attempters", patients who scored ≥ 1 on the Suicidal Behaviour subscale. Further, we proceeded to divide the "Attempters", according to the most lethal suicide attempt, into two subgroups, based on whether or not they needed medical intervention. Thus, the "Low lethality" subgroup was comprised of suicide attempters who scored ≤ 1 and the "High lethality" subgroup was comprised of participants who scored ≥ 2 on the C-SSRS Lethality subscale.

In order to test for differences of continuous variables across groups, we performed independent samples t-tests. With regard to the reliability of our analytical model and the accuracy of our results, we performed another t-test, bootstrapping for 1000 samples, in addition to the independent samples t-test for the serotonin analysis. For categorical variables, chi-square tests were conducted. Statistical significance was set at $p < .05$ and CI at 95%.

## RESULTS

***Demographical and clinical characteristics***

The mean age of our sample was 44.25 years (SD = 11.254) and there was a slight prevalence of females (N = 39, 54.9%) over males (N = 32, 45.1%). Our study included both in-patients (N = 56; 78.9%) and out-patients (N = 15; 21.1%).

Upon admission in the study, according to M.I.N.I. 6.0 and DSM IV-TR diagnostic criteria, participants were distributed according to current clinical episode as follows: 43.7% mania episode (N = 31), 19.7% depressive episode (N = 14), 7% hypomanic episode (N = 5) and 7% with mixed episode (N = 5). The remaining 22.5% of the participants had a past history of BPD I and were currently in remission (N = 16).

According to C-SSRS criteria, of the 71 BPD I participants included in the analysis, 26.76% (N = 19) had past history of actual suicide attempts ("Attempters"), while 73.24% (N = 52) never attempted suicide ("Non-Attempters"). Only the former group qualified for the lethality scoring and were distributed between the "Low lethality" and the "High lethality" attempt subgroups.

As shown in Table 1, no considerable differences were observed regarding most socio-demographical and clinical factors (age, gender, marital status, occupation, age of onset, illness duration, etc.) between our 3 subgroups. However, the suicide attempters had a significantly higher number of lifetime episodes (19±2.243 *vs* 13.44±1.22; t = 2.303, p = 0.024, r = 0.27) and of lifetime depressive episodes

**Table 1.** Sociodemographic and clinical characteristics of 71 BPD I pacients according to suicide attempts and their respective lethalit

| | Non attempters (A) N= 52 Mean (SD) / N (%) | Attempters N = 19 High lethalithy (B) N= 10 Mean (SD) / N (%) | Low lethalithy (C) N=9 Mean (SD) / N (%) | A *vs*. B+C | | B *vs*. C | |
|---|---|---|---|---|---|---|---|
| | | | | t or $X^2$ | p | t or $X^2$ | p |
| Age | 44.22 (12.148) | 43.11 (3.690) | 44.80 (2.264) | .296 | .768 | -.380 | .709 |
| Gender | | | | | | | |
| Male | 27 (51.9%) | 1 (10%) | 4 (44.4%) | 3.686 | .055 | 2.898 | .089 |
| Female | 25 (48.1%) | 9 (90%) | 5 (55.5%) | | | | |
| Marital status | | | | | | | |
| Not married | 32 (61.5%) | 6 (60%) | 6 (66.6%) | .004 | .948 | .090 | .764 |
| Married | 20 (38.5%) | 4 (40%) | 3 (33.3%) | | | | |
| Ocuppation | | | | | | | |
| Employed | 16 (32.3%) | 2 (20%) | 3 (33.3%) | .111 | .740 | .277 | .599 |
| Unemployed | 34 (65.3%) | 7 (70%) | 6 (66.6%) | | | | |
| Age of onset | 30.18 (8.964) | 30.50 (10.058) | 25.44 (7.892) | .884 | .397 | -1.209 | .243 |
| Illness duration | 14.04 (10.29) | 14.3 (10.488) | 17.666 (6.442) | .695 | .489 | .831 | .418 |
| No. of life time episodes | 13.44 (8.638) | 16.6 (10.211) | 21.67 (9.083) | **2.303** | **.024** | 1.137 | .271 |
| No. of life time depressive episodes | 4.62 (3.979) | 8 (7.688) | 8.89 (7.59) | **2.115** | **.046*** | .253 | .803 |
| No. of life time mania episodes | 5.08 (4.035) | 4.8 (4.417) | 7.22 (5.974) | 655 | .518 | 1.012 | .326 |
| No. of life time mixed episodes | 1.50 (2.526) | 1.9 (1.524) | 3.44 (2.404) | 1.730 | .088 | 1.692 | .109 |
| On Mood stabilizers | | | | | | | |
| Yes | 45 (86.5%) | 8 (80%) | 8 (88.8%) | .450 | .502 | .281 | .596 |
| No | 5 (9.6%) | 2 (20%) | 1 (11.1%) | | | | |
| On Antipsychotics | | | | | | | |
| Yes | 47 (90.4%) | 7 (70%) | 8 (88.8%) | 3.422 | .064 | 1.017 | .313 |
| No | 3 (5.7%) | 3 (30%) | 1 (11.1%) | | | | |
| On Antidipressants | | | | | | | |
| Yes | 8 (15.4%) | 5 (50%) | 2 (22.2%) | 3.515 | .061 | 1.571 | .210 |
| No | 42 (80.7%) | 5 (50%) | 7 (77.7%) | | | | |
| Smoking | | | | | | | |
| Yes | 27 (51.9%%) | 8 (80%) | 5 (55.5%) | 1.175 | .278 | 1.310 | .252 |
| No | 23 (44.23%) | 2 (20%) | 4 (44.4%) | | | | |

*Equal variances not assumed. Levene's test < .05.

(8.42±1.707 *vs* 4.62±0.563; t = 2.115, p = 0.046, r = 0.41) compared with non-attempters.

We proceeded to test the distribution of current psychiatric treatment and smoking habits across our subgroups and found no significant differences in distribution.

***Platelet-rich plasma serotonin levels in respect to suicidal behaviour***

Patients with past history of suicide attempts had significant lower platelet-rich plasma serotonin levels compared with patients who never attempted suicide (331.092 ± 49.733 *vs*. 489.046 ± 38.951 ng/$10^9$ platelets; t = 2.218, p = 0.030, r = 0.27). Likewise, when analyzing the plasma concentrations between the high and low suicide lethality subgroups, we found that platelet serotonin was significantly lower in high lethality suicide attempters (209.898 ± 23.654 *vs*. 465.753 ± 82.113 ng/$10^9$ platelets; t = 3.137, p = 0.015, r = 0.605).

Bootstrapping for 1000 samples rendered similar results, showing significant lower levels of serotonin in suicide attempters compared with non-attempters (331.092±52.207 *vs*. 489.046±39.288 ng/$10^9$ platelets; t = 2.218, p = 0.017, r = 0.27), and in high-lethality attempters compared with low-lethality attempters (209.898±23.752 *vs*. 465.753±82.468 ng/$10^9$ platelets; t = 3.137, p = 0.021, r = 0.716) (Table 2).

## DISCUSSION

To the best of our knowledge, there is no data for assessing suicide risk in bipolar patients by measuring plasma platelet serotonin concentrations.

**Table 2.** Platelet rich plasma serotonin concentrations of 71 BPD I pacients according to suicide attempts and their respective lethality, with and without Bootstrapping

| | | Attempters N = 19 | | | |
|---|---|---|---|---|---|
| | Non attempters (A) N= 52 Mean (SD) | High lethalithy (B) N= 10 Mean (SD) | Low lethalithy (C) N=9 Mean (SD) | A *vs*. B+C | B *vs*. C |
| Platelet Serotonin | 489,046 (280,879) | 209,898 (74,801) | 465,753 (246,340) | **t = 2.218 p = .030** 95% CI [15.885, 300.022] **t = 2.218 p = .017** BCa 95% CI [30.586, 273.882]* | **t = 3.137 p = .015**** 95% CI [63.572, 448.138] **t = 3.137 p = .021**** BCa 95% CI [78.829, 423.392]* |

*Bootstrapped for 1000 samples using BCa = Bias-corrected and accelerated Confidence Interval
** Equal variances not assumed, Levene's test p = 0.02

The present comparative study showed that BPD I patients with past history of suicide attempts had significantly lower levels of platelet 5-HT compared with non-attempters. Other research studies have also reported similar findings in depression (25, 27, 32), schizophrenia (33, 34), schizoaffective disorder (35) or post-traumatic stress disorder (PTSD) (26). However, there are also reports of low platelet 5-HT levels in correlation with depressive symptoms and measures of suicidality, but no significant differences were found regarding the rate of attempted suicide in patients suffering from schizophrenia (36).

Additional to the difference in platelet 5-HT concentrations between attempters and non-attempters, our study found even lower levels of platelet serotonin in high lethality attempters compared with low lethality attempters. This is broadly in agreement with other studies that reflect an altered serotoninergic activity in platelets of the high-lethality suicide attempters (37).

Contrary to our findings, some previous studies dispute the high diagnostic and prognostic value of platelet serotonin levels in respect to suicide risk (38). These authors express concern regarding the insufficient matching criteria between study participants. The present research study found no influence of age, gender, smoking habits or current psychiatric treatment across our subgroups distribution, as shown in Table 1. Moreover, even if these authors question the usefulness of platelet 5-HT, monoamine oxidase B (MAO-B), 5-HT2A receptor binding and tryptophan availability as potential biological markers for suicidal behavior, the same research group has subsequently reported a significantly lower platelet 5-HT concentration in suicidal vs. non-suicidal depressed patients (25). Medication, such as SSRI, is known to reduce platelet 5-HT concentration (39-41). However, the influence of psychotropic treatment and especially SSRI on platelet 5HT concentration across our groups, through a layered regressive model, could not be assessed in our sample due to size limitation. Moreover, due to the same size sample limitations, particularly in the suicide attempter's subgroup, we were unable to weigh the low platelet 5-HT results in respect to multiple drugs interactions and distinct clinical entities of the bipolar disorder spectrum. Our data needs to be further replicated in order to properly test for these research assumptions and support recent views which regard suicide behaviour as a trait-like feature, irrespective of psychiatric diagnosis (28).

The lack of difference concerning the socio-demographical characteristics (age, gender, marital status, occupation) between the high-lethality, low-lethality and non-suicide attempter's subgroups highlights the relevance of our results in regard to sample matching criteria. However, in a recent meta-analysis, conflicting data is reported concerning gender differences in regard to suicide attempts. Some studies show no gender-based variance, while, others, report that women were significantly more likely to attempt suicide (42). Our study shows no significant differences between these two groups based on gender criteria. Moreover, the same meta-analysis reports a 2.99 younger age of illness onset among patients with a history of suicide attempt compared with non-attempters (42). Our results did not show a significant difference between the high-lethality, low-lethality and non-suicide attempter's subgroups relating to the illness age of onset. However, clinically wise, our results report a significant difference between the suicide BPD I attempters compared with the non-attempters. The patients with past history of suicide attempts had a significantly higher number of total lifetime episodes and of lifetime depressive episodes, compared with non-attempters. The increased suicide risk could be related to a higher frequency of psychopathological episodes (43) and to the positive correlation between suicide and depression (44).

Nonetheless, several limitations of the current study need to be considered. First, clinical and biological assessments were performed just once, thus,

longitudinal data for completed suicide attempts is not available. Second, our suicide attempter's sample size was too small in order to properly test for specific BPD I psychopathological episodes and different medication effects on platelet 5-HT levels.

**In conclusion,** the results of the present study have shown lower platelet 5-HT levels in suicide attempters compared with non-attempters, and that platelet 5-HT concentrations are lower in high lethality attempters compared with low lethality attempters in BPD I. Moreover, a higher number of total lifetime and lifetime depressive episodes were recorded for suicide attempters with BPD I. Our results are in line with the current research findings that support a low serotoninergic function in relation to suicidal behaviour (23, 25-27, 32-35) and subscribe to the importance of platelet serotonin as a reliable biomarker in suicide assessment. Thus, plasma platelet serotonin may be of great clinical value for assessing and preventing suicide behavior in BPD I patients.

**Conflict of interest**

The authors declare that they have no conflict of interest concerning this article.

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