



Platelet Serotonin Concentration Is Associated with Illness Duration in Schizophrenia and Chronological Age in Depression

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Objective Impaired serotonergic neurotransmission has been implicated in the pathogenesis of depression and schizophrenia. Blood platelets have been used for years as a peripheral model of neuronal serotonin dynamics. The objective was to investigate platelet count and serotonin concentration in patients with depression and schizophrenia, in an attempt to ascertain their clinical usefulness.

Methods 953 participants were included in the study, 329 patients with depression, 339 patients with schizophrenia and 285 healthy controls. ELISA was used to assess platelet serotonin concentrations.

Results There were no statistically significant differences among groups regarding age, total platelet count and serotonin concentration. Linear regression analyses revealed inverse correlations between platelet serotonin concentration and age of patients with depression and healthy individuals, as well as between platelet serotonin concentration and illness duration in patients with schizophrenia. In other words, longer illness duration in patients with schizophrenia, and higher age in patients with depression and healthy individuals was associated with lower platelet serotonin concentrations.

Conclusion Platelet count and serotonin concentration did not prove to be of diagnostic value in differentiating patients and healthy individuals. However, illness duration in patients with schizophrenia may be associated with reduced concentrations of platelet serotonin.

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Key Words Blood platelets, Platelet count, Serotonin, Schizophrenia, Depression.

INTRODUCTION

The search for specific diagnostic markers in psychiatry still has not provided that many clinically useful findings and that is especially true in the case of depression and schizophrenia.¹⁻⁶ However, a quantitative test that would be useful in diagnosing and treatment of depression or schizophrenia has yet to be discovered.⁷

Serotonergic system has long been implicated in the pathogenesis of depression, while its proposed effects within the schizophrenic process are closely related to the major impli-

cated pathway of dopamine.⁸⁻¹¹ On these foundations, today's most effective treatments for depression, and to a significant extent also for schizophrenia, affect serotonin system at different levels and targets, all of which have in common alteration of serotonin levels.¹¹ As central serotonergic neurons are still inaccessible, blood platelets have been used for years as a peripheral model of neuronal serotonin dynamics. That is especially the case as in both the process of serotonin release and reuptake seems to be practically the same,^{12,13} although some of the more recent findings argue against such modelling.¹⁴ However, high blood serotonin concentration does not necessarily imply high platelet serotonin concentration, but in physiological conditions could directly relate to it.¹⁴⁻¹⁷

Among other factors that have been shown to influence platelet count and possibly serotonin concentration,^{14,16} we would like to highlight the age. Nowadays there are several lines of evidence that support that platelets from older subjects differ in their function and structure,¹⁸ along with higher sensitivity and an increased responsiveness to serotonin than platelets

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from subjects in their early twenties.¹⁹ Nevertheless, platelet serotonin content seems to decrease with age.²⁰ This leads to the suggestion that platelet hyperactivity can cause an increased release of serotonin in plasma.¹⁸ Most studies in patients with depression did not report significant differences between serotonin concentration and age,^{13,21} nor did studies focusing on schizophrenia.^{13,22,23}

Available findings describe significantly lower platelet serotonin concentrations in depressive patients compared to healthy individuals,^{13,24} although there have been reports of non-significant differences²¹ or no differences at all.²⁵ As far as the psychotic symptoms are concerned, platelet serotonin concentrations were reported to be higher in psychotic depressed patients compared to patients who were not psychotic.²⁶ In suicidal depressive patients, compared to non-suicidal depressive patients and healthy controls, platelet serotonin concentrations have frequently been reported to be significantly lower.²⁶⁻³¹ As far as the treatment is concerned, antidepressants have shown to significantly lower and normalize platelet serotonin concentrations.^{21,26,32-35} Also, a lower platelet serotonin could be a trait of depressive patients with metabolic syndrome.⁶ Based on some of the presented findings, there have been earlier propositions of baseline platelet serotonin concentration being used as a predictor of the antidepressant treatment response.^{33,36,37}

Studies on platelet serotonin in schizophrenia repeatedly reported significantly higher concentrations, especially in untreated patients,^{13,22,23,38,39} in patients with predominantly positive symptoms^{29,40} or in patients with schizophrenia without significant depressive symptoms.⁴¹ Also, lower platelet serotonin concentrations have been observed in schizophrenic patients treated with neuroleptics²³ and higher platelet serotonin concentration has been linked to a better response to olanzapine therapy in schizophrenic patients.⁴² Regarding patients with first psychoses, Marcinko et al.⁴³ and associates reported significantly lower platelet serotonin concentrations in suicidal than non-suicidal patients and healthy controls. In one direct comparison of depressive and schizophrenic patients, platelet serotonin concentrations were reported to be higher in those suffering from schizophrenia.¹³ Partially confirming and expanding on these findings, in our previous research we observed an association between lower platelet serotonin concentration and more severe depressive symptomatology in schizophrenic patients.⁴¹

These findings indicate that the platelet serotonin concentrations might have a functional significance in pathophysiology and/or treatment of depression and schizophrenia, regardless significant differences between investigations. In this research we focused on two platelet variables, platelet count and platelet serotonin concentration, in an attempt to gain insight into the question if they could be used as a clinically use-

ful diagnostic test in schizophrenia and/or depression.

METHODS

Participants

In total, 953 participants were enrolled in this research. The schizophrenia group consisted of 339 patients, while the depression group consisted of 329 patients. Control group consisted of 285 healthy participants who volunteered to participate in the research. The schizophrenia group included 221 males and 118 females, while the group of patients suffering from depression included 200 males and 129 females. Group of healthy individuals included 160 males and 125 females. Sociodemographic and clinical parameters of all included subjects are presented in Table 1. All subjects with depression and schizophrenia were inpatients. The inclusion criteria for this study were the diagnosis of depression or schizophrenia, using the DSM-5 criteria and the absence of any other psychiatric disorder. Inclusion criteria for the group of healthy volunteers were no personal history of any kind of mental illness and negative hereditary loading for mental illness. Participants with any use of psychoactive compounds including alcohol in their medical history were excluded from the study. Exclusion criteria also included any kind of somatic disorders. None of the patients included in this study had taken any psychotropic medication 30 or more days prior to the study, as it is well known that antidepressants alter platelet serotonin concentrations.³²⁻³⁷ However, it has also previously been shown that antipsychotic treatment is able to alter platelet serotonin concentrations.^{23,39,44} Furthermore, we were able to recruit such a relatively large sample of medication free patients due to the fact they did not adhere to psychopharmacological treatment. This issue is of major concern, as patients with depression and even more so patients with schizophrenia, indeed tend to poorly adhere to their treatment. That is especially an issue with antipsychotic medication, which usually results in increased symptom severity and more frequent hospital admissions.⁴⁵ Although they did not adhere to their treatment, prior to hospital admission majority of patients have been prescribed with an atypical antipsychotic and a minority with a typical antipsychotic medication. Informed consent was obtained from all included patients after a complete and extensive description of the study profile. The study was approved by Ethics Committee of the University Hospital Centre Sestre milosrdnice (EP-6820/13-18).

Medical examination and study design

The study included all patients that had been admitted for inpatient treatment with the diagnosis of schizophrenia or depression in the period from June 2014 to September 2019. All

Table 1. Sociodemographic and clinical characteristics of healthy individuals and patients with depression and schizophrenia

	Depression N=329	Schizophrenia N=339	Healthy individuals N=285	Statistical details	
				χ^2 -value	p-value
Gender, N (%)				5.337	0.069
Male	200 (60.8)	221 (65.2)	160 (56.1)		
Female	129 (39.2)	118 (34.8)	125 (43.9)		
Education, N (%)				158.124	<0.01
Elementary	44 (13.4)	39 (11.5)	4 (1.3)		
High school	234 (71.1)	240 (70.8)	99 (34.8)		
University	51 (15.5)	60 (17.7)	182 (63.9)		
Marital status, N (%)				95.717	<0.01
Married	236 (71.9)	103 (30.6)	178 (62.4)		
Single	68 (20.6)	213 (62.7)	96 (33.6)		
Divorced	25 (7.5)	23 (6.7)	11 (4)		
Working status, N (%)				181.615	<0.01
Employed	128 (39.0)	105 (30.9)	248 (86.9)		
Unemployed	101 (30.8)	142 (41.8)	28 (10.0)		
Retired	100 (30.2)	92 (27.3)	9 (3.1)		
Place of living, N (%)				4.081	0.130
Urban	223 (67.8)	259 (76.3)	216 (75.7)		
Rural	106 (32.2)	80 (23.7)	69 (23.3)		
				ANOVA	p-value
Ages in years (mean \pm SD)	38.3 \pm 14.5	39.3 \pm 14.0	37.7 \pm 11.8	F 1.026	0.359
Platelets (mean \pm SD)	232.2 \pm 62.2	232.4 \pm 73.5	232.0 \pm 49.5	F 0.005	0.995
Platelet serotonin (mean \pm SD)	475.4 \pm 321.6	532.1 \pm 434.1	507.8 \pm 350.2	F 1.936	0.145
Number of episodes (mean \pm SD)	3.77 \pm 2.65	4.88 \pm 3.64	N/A		
Illness duration (mean \pm SD)	2.40 \pm 1.69	2.04 \pm 1.12	N/A		
PANSS total (mean \pm SD)	N/A	103.74 \pm 20.16	N/A		
PANSS positive (mean \pm SD)	N/A	20.12 \pm 6.23	N/A		
PANSS negative (mean \pm SD)	N/A	27.56 \pm 5.54	N/A		
PANSS general psychopathology (mean \pm SD)	N/A	56.00 \pm 11.24	N/A		
HDRS total (mean \pm SD)	18.13 \pm 6.01	N/A	N/A		

PANSS: Positive and Negative Syndrome Scale, HDRS: Hamilton Depression Rating Scale, N/A: not applicable

patients with depression and schizophrenia presenting the above described exclusion criteria were excluded from the study. Structured clinical interview was performed by a psychiatrist, who made the diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria for schizophrenia. The severity of schizophrenia was assessed by the Positive and negative syndrome scale (PANSS).⁴⁶ With Hamilton depression rating scale (HDRS) we assessed the severity of depression.⁴⁷ Variables of disease features (number of episodes, duration of illness in years) were obtained from the structured clinical interview based on the Mini International Neuropsychiatric Interview (MINI)⁴⁸ and were performed by a trained psychiatrist.

Biochemical measurements and preparation of platelet-rich plasma (PRP)

Blood samples were taken from patients for the analysis to determine platelet serotonin levels. Blood samples were taken from the cubital vein in one vacuumed epruvette with EDTA anticoagulant for the determination of platelet serotonin in the morning, after 12 h of fasting and after a 30 minute pause. The platelet serotonin was determined with the enzyme-linked immunosorbent assay (ELISA) procedure using commercial reagents (DRG Diagnostics, Germany). In our laboratory, the value of the inter-assay CV was 6% for platelet serotonin.

The platelet number was determined on hematology analyzer (Beckman Coulter DxH 800, USA), with prior verifica-

tion of a blank sample. The PRP was prepared a maximum of 2 h after taking the blood sample. The PRP was obtained by centrifuging the sample at 200×g for 10 min at room temperature. The supernatant was separated and the number of platelets within was also determined. Platelets were then lysed by separating 200 µL PRP in 800 µL 0.9% sodium chloride solution and centrifuging the suspended cells at 4,500×g for 10 min at 4°C. After separation of the supernatant, 200 µL of redistilled water was added to the sediment containing platelets and the mixture was mechanically mixed on a vortex mixer to fully lyse the platelets. This prepared platelet lysate was stored at -20°C (for a maximum of three weeks). To determine the concentration of serotonin in the stored platelet lysate, the samples were thawed and centrifuged at 10,000×g for 2 min at room temperature.

Statistical analyses

Kolmogorov-Smirnov test was used to assess normal distribution for all measures and for each group. Sociodemographic and clinical characteristics of patients and healthy control subjects were compared in frequencies using the chi-square test and for continuous sociodemographic variables and platelet count and serotonin concentration using the independent samples t-test (comparison between two groups) or ANOVA (comparison between three groups). We performed linear regression analysis in order to test the predictions of symptom severity of schizophrenia and depression (PANSS and HDRS), number of episodes and overall illness duration for both disorders on platelet count and serotonin concentration. We also used linear regression analysis to test the predictions of patient's age on total platelet count and serotonin concentration. Optimal sensitivity and specificity of the platelet serotonin concentration for the diagnosis of depression and schizophrenia were determined with the receiver operating characteristic (ROC) curve analysis and utilizing a nonparametric approach. The Youden index was calculated for each cut-off value as corresponding [(sensitivity+specificity)-1] to find the cut-off values that maximize discriminating power of the test. Alpha values were conservatively considered significant at less than 0.01. Statistical analyses were conducted using SPSS software (SPSS for Windows 20.0, IBM Corp., Armonk, NY, USA).

RESULTS

We established statistically significant differences between patients with depression and patients with schizophrenia and healthy individuals regarding several sociodemographic and clinical characteristics. However, there were no statistically significant differences among groups regarding age, total platelet count and serotonin concentration. Two groups consisting

of patients with depression and schizophrenia did not statistically differ in terms of number of illness episodes and illness duration (Table 1).

In order to establish if age influences total platelet count, we performed linear regression analysis in which platelet count was a dependent variable and age (separately for all three groups) was a predictor variable. Linear regression analysis established that the variance of the dependent variable is explained by 0.1% ($r^2=0.001$) in depression, 0.2% ($r^2=0.002$) in schizophrenia and 0.3% ($r^2=0.003$) in healthy individuals. Analysis of variance was performed as the next phase of linear regression. It did not reveal statistical significance of the model ($F=0.278$; $p=0.598$ in depression; $F=0.514$; $p=0.474$ in schizophrenia and $F=0.786$; $p=0.376$ in healthy individuals), which means that platelet count does not depend on age (Table 2).

Next step was to test if number of episodes and illness duration have an influence on the total platelet count. Therefore, we performed linear regression analysis in which platelet count was a dependent variable and number of episodes and illness duration (separately for groups with depression and schizophrenia) were predictor variables. Linear regression analysis established that the variance of the dependent variable is explained by 1.9% ($r^2=0.019$) in depression and 1.6% ($r^2=0.016$) in schizophrenia. Analysis of variance was performed as the next phase of linear regression. It did not reveal statistical significance ($F=1.217$; $p=0.300$ in depression; $F=2.249$; $p=0.107$ in schizophrenia), which means that platelet count does not depend on the two included predictor variables (Table 2).

And finally, we tested if clinical severity scores (HDRS and PANSS) have an influence on the total platelet count. Linear regression analysis was performed with platelet count as a dependent variable and clinical severity scores as predictor variables. In the end, variance of the dependent variable is explained by 2.6% ($r^2=0.026$) of the HDRS score in depression and 1.7% ($r^2=0.017$) of the PANSS score in schizophrenia. Analysis of variance was performed as the next phase of linear regression. It did reveal statistical significance ($F=5.382$; $p=0.021$ for HDRS and $F=1.095$; $p=0.360$ for PANSS), which means that platelet count does not depend on PANSS scores in schizophrenia, but it does on HDRS score in depression (Table 2).

Linear regression analyses were also performed in order to establish the influence of the same set of variables on platelet serotonin concentration. In the first step platelet serotonin concentration was the dependent variable and age (separately for all three groups) was a predictor variable. Linear regression analysis established that the variance of the dependent variable is explained by 1.5% ($r^2=0.015$) in depression, 0.3% ($r^2=0.003$) in schizophrenia and 1.8% ($r^2=0.018$) in healthy individuals. Analysis of variance was performed as the next phase

of linear regression. It did reveal statistical significance in patients with depression ($F=5.038$; $p=0.025$) and healthy individuals ($F=4.464$; $p=0.036$), but not in patients with schizophrenia ($F=1.080$; $p=0.300$), which means that platelet serotonin concentration does depend on age in patients with depression and healthy individuals (Table 3).

Next step was to test if number of episodes and illness duration have an influence on platelet serotonin concentration. In this linear regression analysis number of episodes and illness duration (separately for groups with depression and schizophrenia) were predictor variables. Linear regression analysis established that the variance of the dependent variable is ex-

Table 2. Predictive values of age, illness duration, episode number and clinical severity scores (HDRS and PANSS) on total platelet count

Platelet count	Unstandardized coefficients		Standardized coefficients	t	p	95.0% confidence interval for B	
	B	Std. error	β			Lower bound	Upper bound
Age							
Depression	0.165	0.314	0.037	0.528	0.598	-0.453	0.784
Schizophrenia	0.221	0.309	0.043	0.717	0.474	-0.387	0.830
Healthy	-0.244	0.276	-0.059	-0.886	0.376	-0.788	0.299
Depression							
Episode number	0.307	2.127	0.013	0.144	0.885	-3.902	4.516
Illness duration	-5.225	3.349	-0.138	-1.560	0.121	-11.853	1.404
HDRS	1.675	0.722	0.161	2.320	0.021	0.251	3.098
Schizophrenia							
Episode number	-2.006	1.168	-0.104	-1.718	0.087	-4.306	0.293
Illness duration	-5.659	4.827	-0.071	-1.172	0.242	-15.162	3.844
PANSS total	2.635	1.961	0.722	1.344	0.180	-1.226	6.497
PANSS positive	-2.001	2.090	-0.170	-0.957	0.339	-6.117	2.116
PANSS negative	-1.809	2.313	-0.138	-0.782	0.435	-6.364	2.747
PANSS general	-3.585	2.065	-0.545	-1.736	0.084	-7.652	0.481

HDRS: Hamilton Depression Rating Scale, PANSS: Positive and Negative Syndrome Scale

Table 3. Predictive values of age, illness duration, episode number and clinical severity scores (HDRS and PANSS) on platelet serotonin concentration

Platelet serotonin concentration	Unstandardized coefficients		Standardized coefficients	t	p	95.0% confidence interval for B	
	B	Std. error	β			Lower bound	Upper bound
Age							
Depression	-2.912	1.297	-0.123	-2.244	0.025	-5.465	-0.360
Schizophrenia	-1.755	1.690	-0.057	-1.039	0.300	-5.079	1.568
Healthy	-4.178	1.977	-0.136	-2.113	0.036	-8.074	-0.283
Depression							
Episode number	0.228	10.388	0.002	0.022	0.982	-20.306	20.763
Illness duration	9.613	16.360	0.049	0.588	0.558	-22.728	41.954
HDRS	3.333	3.481	0.064	0.957	0.339	-3.527	10.193
Schizophrenia							
Episode number	-0.357	6.882	-0.003	-0.052	0.959	-13.900	13.186
Illness duration	-62.869	22.306	-0.160	-2.819	0.005	-106.763	-18.975
PANSS total	-3.718	11.638	-0.168	-0.320	0.750	-26.626	19.189
PANSS positive	-2.148	12.354	-0.030	-0.174	0.862	-26.465	22.169
PANSS negative	6.377	13.642	0.079	0.467	0.641	-20.474	33.229
PANSS general	-3.837	12.223	-0.097	-0.314	0.754	-27.897	20.222

HDRS: Hamilton Depression Rating Scale, PANSS: Positive and Negative Syndrome Scale

plained by 0.2% ($r^2=0.002$) in depression and 2.6% ($r^2=0.026$) in schizophrenia. Analysis of variance revealed statistical significance for the sample of patients with schizophrenia ($F=3.972$; $p=0.020$), but not for the sample of patients with depression ($F=0.174$; $p=0.840$), which means that platelet serotonin concentration does depend on the illness duration variable in patients with schizophrenia (Table 3).

As the last step we tested if clinical severity scores (HDRS and PANSS) have an influence on the platelet serotonin concentration. Clinical severity scores were predictor variables. Variance of the dependent variable is explained by 0.4% ($r^2=0.004$) of HDRS score in depression and 5.2% ($r^2=0.052$) of PANSS score in schizophrenia. Analysis of variance revealed statistical significance of the model with platelet serotonin concentration as a dependent variable and PANSS score as a predictor variable ($F=3.878$; $p=0.004$), but not when HDRS was a predictor variable ($F=0.917$; $p=0.339$), which means that platelet serotonin concentration does not depend on HDRS score in depression, but it does on PANSS score in schizophrenia. However, when analysing PANSS subscale scores and even total PANSS score independently, that significance was not present (Table 3).

ROC analysis did not establish significant diagnostic value of platelet serotonin concentration when comparing patients with depression and healthy individuals. The area under the curve (AUC) was 0.517 with a 95% confidence interval (0.472–0.563; $p=0.455$). ROC analysis also failed to demonstrate the diagnostic value of platelet serotonin concentration when comparing patients with depression and schizophrenia. The area under the curve (AUC) was 0.515 with a 95% confidence interval (0.471–0.558; $p=0.514$). Finally, ROC analysis did not establish significant diagnostic value of platelet serotonin concentration when comparing patients with schizophrenia and healthy individuals. The area under the curve (AUC) was 0.510 with a 95% confidence interval (0.465–0.556; $p=0.655$). We did not include graphical presentations due to non-significant findings of the ROC analysis.

DISCUSSION

This study included 953 participants, which is to the best of our knowledge largest investigation of platelet serotonin count and concentration in depression and schizophrenia. There were no differences in ratio of males to females when comparing three groups of participants, and majority of patients (compared to healthy individuals) were of lower educational status, unemployed or retired. All of these findings reflect our understanding of the burden that psychiatric disorders impose on patients, especially those suffering from schizophrenia.⁵¹ When it comes to their marital status, patients with

depression did not statistically differ from healthy individuals, but both of those groups were significantly more often married than patients with schizophrenia.⁴⁹

The groups did not differ in age, platelet count and platelet serotonin concentration. When it comes to comparing patients with depression and healthy individuals, previously there have been similar findings,^{21,25} but also of lower platelet serotonin concentrations in depressive patients.^{13,23} On the other hand, majority of research on platelet serotonin in schizophrenia repeatedly reported significantly higher concentrations,^{13,22,23,38,39} except in a subgroup of patients with schizophrenia and significant depressive symptoms⁴¹ and suicidal first episode psychoses.⁴³ Although our results did not replicate it, in one previous comparison of depressive and schizophrenic patients, platelet serotonin concentrations were higher in patients with schizophrenia.¹³ In order to test for associations between clinical severity score (HDRS and PANSS) and platelet count and serotonin concentration we also performed regression analyses which revealed the association between HDRS score and platelet count in depression (but not platelet serotonin concentration). Therefore, we had to conclude that symptomatology of schizophrenia (quantified by four PANSS scores) was not correlated with platelet count nor platelet serotonin concentration, which is a replication of our previous findings.⁴¹

Previous reports in healthy individuals established that age was inversely associated with platelet count and platelet serotonin content.²⁰ Although we did not find a significant association regarding platelet count (in all three groups) we did replicate the association between platelet serotonin concentration and age in healthy individuals. Somewhat surprisingly, the same positive association was also present in patients with depression, which is contrast with previously reported non-significant findings, although on smaller samples.^{13,21} One thing to keep in mind when interpreting those findings is the possibility of false positive results due to antidepressant treatment, which is known to alter platelet serotonin concentrations.³²⁻³⁷ In this sample, patients were off their antidepressant and other medications for at least a month prior to study enrolment, which is sufficient to rule them out as a confounding variable. Similarly to previous reports, in our sample platelet serotonin concentration in schizophrenia was not associated with age.^{13,22,23}

Two groups of patients did not differ regarding number of episodes and overall illness duration. However, when examining for a possible correlation between number of episodes and overall illness duration on platelet count and serotonin concentration, we established a single positive correlation, the one between overall illness duration and platelet serotonin concentration in schizophrenia. Therefore, in patients with schizophrenia there is a significant decline of platelet serotonin concentration (in an otherwise not significantly declining platelet

count) with longer duration of illness. This finding is to the best of our knowledge the first report of such an association. It also adds some weight to the hypothesized serotonergic dysfunction in schizophrenia⁵⁰ and chronic widespread stress-induced serotonergic changes in ongoing schizophrenia,⁵¹ quite possibly associated with inadequate treatment. Previously, schizophrenia has been associated with elevated concentrations of platelet serotonin,^{13,22,23,38,39} but correlations with age and illness duration were lacking or deemed non-significant. Depression on the other hand was often associated with reduced platelet serotonin concentrations,^{13,24} which we did not establish, nor did platelet count and serotonin concentrations seem to be affected by number of episodes and overall illness duration.

There are several limitations to this study; one of those is the fact that it was cross-sectional without a prospective design. Therefore, it was not possible to study the dynamics of the influence of the clinical course and/or the influence of psychopharmacological treatment on the investigated parameters, which is important, as studies have shown that antidepressants and antipsychotics can influence platelet serotonin and scores of scales used in this study.^{23,36-39,44,52} Another limitation is that serotonin system homeostasis in platelets depends on the function of several factors, such as the activity of the serotonin transporter, extracellular serotonin concentrations and enzyme monoamine oxidase B.^{14,16} Although that is the case, we evaluated serotonin concentration solely by measuring its platelet concentration and further research should include all of these parameters for a more comprehensive insight into serotonin dynamics.

In conclusion, this study provides first evidence of differing platelet serotonin concentrations in schizophrenia regarding the duration of the illness in a manner that duration seems to be inversely correlated to platelet serotonin concentration. Interestingly, age was not correlated with platelet serotonin concentration in schizophrenia, suggesting that illness duration solely influences platelet serotonin homeostasis and is quite possibly a trait of schizophrenia duration. Combined with age wise significant findings in patients with depression and healthy individuals, this finding could be specific to schizophrenia. In terms of distinguishing patients with schizophrenia and healthy individuals (or patients with depression for that matter) platelet serotonin concentration did not prove to be of diagnostic value. However, this finding does not allow us to make generalizations about the concentration of intracellular serotonin. In a platelet model such as this, intracellular serotonin depends also on several other factors, which were not investigated at this point. Future studies should therefore include all relevant elements of serotonin homeostasis across the human life span in an attempt to clarify serotonin dynamics in ageing of psychiatric patients, which might provide an answer to relatively

ambiguous findings regarding platelet serotonin concentrations in researches performed so far.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Dalibor Karlović. Data curation: Vjekoslav Peitl, Biserka Getaldić-Švarc. Formal analysis: Vjekoslav Peitl. Investigation: Vjekoslav Peitl, Biserka Getaldić-Švarc, Dalibor Karlović. Methodology: Biserka Getaldić-Švarc, Dalibor Karlović. Resources: Dalibor Karlović. Software: Dalibor Karlović. Supervision: Vjekoslav Peitl, Biserka Getaldić-Švarc, Dalibor Karlović. Validation: Vjekoslav Peitl, Dalibor Karlović. Writing—original draft: Vjekoslav Peitl, Biserka Getaldić-Švarc, Dalibor Karlović. Writing—review & editing: Vjekoslav Peitl, Dalibor Karlović.

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