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Predictive efficiency of phoenixin, spexin and kisspeptin neuropeptides concentration levels in diagnosis of bipolar disorder in paediatric population

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Summary

Aim. The aim of the study was to assess concentrations of the following neuropeptides: phoenixin, spexin and kisspeptin in venous blood serum of children and adolescents suffering from bipolar disorder, and by this their predictive efficiency in this disorder.

Material. The study included 75 individuals with a mean age of 15.26 years (95% CI: 14.86–15.67), of which the study group comprised 57 individuals diagnosed with bipolar affective disorder and the control group – 18 individuals with no psychiatric diagnosis and no pharmacological treatment.

Method. Phoenixin, spexin and kisspeptin levels were determined in the peripheral venous blood serum. Neuropeptide concentrations were measured with the enzyme-linked immunosorbent assay (ELISA).

Results. The mean phoenixin concentration in the studied group equalled 1.57 ng/ml (95% CI: 1.35–1.79), while in the control group – 2.69 ng/ml (95% CI: 2.38–3; U Mann-Whitney test p-value < 0.05). For spexin, these results were 639.65 pg/ml (95% CI: 558.86–720.44) in the studied group, and 354.28 pg/ml (95% CI: 310.33–398.22; U Mann-Whitney test p-value < 0.05) in the control group. The observed differences were statistically significant. The mean concentration of kisspeptin levels in the studied group was 126.02 pg/ml (95% CI: 39.82–212.23; median: 59.85), while in the control group – 54.83 pg/ml (95% CI: 39.23–70.43; median: 51.3; U Mann-Whitney test p-value = 0.29), and the observed difference was not statistically significant.

Conclusions. The occurrence of bipolar disorder symptoms is statistically significantly linked with a decreased phoenixin concentration and to a small degree – with an increased spexin concentration in blood serum of patients. However, it is not linked with the kisspeptin concentration.

Key words: phoenixin, spexin, kisspeptin

Introduction

Bipolar disorder (BD) is a chronic mood disorder, characterised by intermittent episodes of mania/hypomania or depression, or mixed episodes (particularly frequent in paediatric population) with remission periods in between. During periods of exacerbation, apart from mood and activity changes, numerous other symptoms occur, such as: auto-aggression, sleep and appetite changes (with accompanying weight loss or weight gain), changes in sexual drive (e.g. hypersexuality during mania) or – very frequent in this age group – productive symptoms. BD in children and adolescents is often accompanied by other mental disorders, e.g. anxiety, behavioural or eating disorders or attention deficit hyperactivity disorder (ADHD). Furthermore, anxiety symptoms often precede BD occurrence in the paediatric population and are believed to be predictors of disease development [1].

The problem of diagnosis and treatment of BD is a key issue of contemporary psychiatry, particularly children and adolescent psychiatry. Currently applied therapeutic strategies are mainly based on selective pharmacomodulation of relatively well-known monoaminergic pathways of the brain, ion channels and intracellular regulatory mechanisms. As a result of the dynamic development of molecular and cellular neurochemistry in recent years, as well as the implementation of advanced experimental techniques, including *in silico* modelling, we have obtained new information suggesting the participation of neuropeptide signalling in the pathogenesis of mental disorders, including BD [2, 3]. The frequently observed drop of neuropeptide Y (NPY) and somatostatin expression in the brains of BD patients suggests that these classic regulatory neuropeptides may play an important role in the aetiology and course of the disease. A significant drop of NPY expression in the prefrontal cortex of BD patients has been observed [4, 5]. The NPY level in the cerebrospinal fluid (CSF) of BD patients with past suicide attempts was also significantly lower than in the subjects not burdened with this kind of auto-aggressive behaviour. The NPY concentration is particularly decreased in these patients with past suicide attempts in the course of psychiatric observation. Moreover, patients from this group are characterised by a lower NPY level than those who attempted to commit suicide in the past but never repeated these attempts. Therefore, it seems that the NPY signalling pathway is considerably disturbed in the course of BD, and assessing the NPY level in the cerebrospinal fluid may be useful in assessing the risk of future auto-aggressive behaviours of suicidal nature [6].

The somatostatin-expressing neuron count was significantly reduced in the parahippocampal region and the amygdala in patients with BD and schizophrenia, which may be the reason for dysfunctions of the mechanisms regulating and controlling anxiety reactions [7, 8]. Also, it cannot be ruled out that anxiety intensification in the morning hours may be related to the circadian changes in somatostatin expression in the amygdala [8]. However, for orexins – hypothalamic neuropeptides with a wide spectrum of activity – assay results are contradictory, since both a drop and increase of orexin A levels have been observed in the serum of BD patients [9, 10]. Nevertheless, the most recent studies have revealed a decreased level of orexin A, ghrelin and

NPY in patients with BD and depression as compared to the control group. On the other hand, major depressive disorder patients showed a higher NPY level than BD patients; there has also been a negative correlation between the concentration of this neuropeptide and episodes of emotional eating in the course of BD [11]. It has also been suggested that oxytocin could be a potential marker of BD; however, as of today there have been no data to fully substantiate this diagnostic stipulation, despite noted changes in the concentration of this neurohormone in the course of the disease [12].

Neuropeptides that are interesting from the perspective of psychiatric diagnostics and characterised by a multi-directional and diversified spectrum of physiological activity include phoenixin (PNX), spexin (SPX) and kisspeptin. PNX is a poorly known neuropeptide, a new regulatory factor present in two molecular forms: a shorter one (PNX-14) and a longer one (PNX-20), which was identified by means of bioinformatics and a bit later its expression was identified in the hypothalamus, amygdala and brainstem of a rat [13, 14]. PNX is a ligand of the G protein-coupled receptor 173 (GPR173) characterised by a wide distribution across various brain structures [15]. From the psychopharmacological point of view, it is worth noting that administration of PNX-14 to the brain and hypothalamus ventricles of adult mice exerts a strong anti-anxiety effect, manifested in behavioural studies [16]. Moreover, the anxiolytic effect of PNX-14 was suppressed by the administration of a selective antagonist of the GnRH receptor. The pioneering clinical studies on PNX carried out in 2017 by the Berlin team of Hofmann et al. [17] showed a correlation between the PNX level and anxiety level in humans.

Another peptide isolated via the *in silico* molecular modelling techniques is SPX, a peptide which is an alternative ligand of the galanin receptors Gal2 and Gal3 [18, 19]. Neurons showing the SPX expression are present in various regions of the brain, with most numerous populations in the hypothalamus, hippocampus, amygdala, cerebellum and brainstem [20]. SPX is a highly anorexigenic peptide [21]. However, it was observed that intraventricular administration of the compound structurally analogous to SPX induces an anxiolytic effect in rats [22].

Kisspeptin, as a ligand of the metabotropic receptor Kiss-1R (GPRS54), plays a key role in the regulation of reproductive functions in mammals by regulating the secretion of gonadotropin (GnRH) by the hypothalamic neurons [23]. Various neuronal populations of the hypothalamus, hippocampus and amygdala are characterised by expression of kisspeptin [24]. This neuropeptide is also a modulator of insulin secretion and a regulator of energy balance of the organism by its effect on the process of food intake [25]. Kisspeptin also participates in mechanisms lying at the base of sexual behaviours and affective processes, and shows anti-depressive and anxiolytic activity [26]. It has been suggested that disturbances in kisspeptin expression in the hippocampus of rodents may trigger behavioural changes characteristic for an animal schizophrenia model [27].

Numerous scientific reports suggest the participation of PNX, SPX and kisspeptin in anxiety mechanisms and pathogenesis of eating disorders; however, there is no data regarding their potential role in neuromolecular changes lying at the base of BD [28].

Material

The study was carried out within the Department of Psychiatry and Psychotherapy of Developmental Age of the Medical University of Silesia in Katowice, Poland, located in the John Paul II Paediatric Centre in Sosnowiec, Sp. z o.o., with participation of the Histology Unit of the Department of Histology and Embryology of the Medical University of Silesia. Participants were recruited among the Silesian population. They were divided into two groups based on a clinically confirmed or excluded BD diagnosis on the basis of DSM-5 diagnostic criteria. Participants with BD were recruited among patients of the Clinical Department of Psychiatry and Psychotherapy of Developmental Age, and the control group – from outpatient clinics, among pupils of Silesian schools and among patients of the John Paul II Paediatric Centre in Sosnowiec, Sp. z o.o.. Informed consent to participate in the study was obtained (once information was provided) both from parents and participants themselves. Data collected in the course of the study were pseudonymisated.

The study included 75 individuals with a mean age of 15.26 years (95% CI: 14.86-15.67) – the studied group consisted of 57 individuals aged below 18, diagnosed with BD, hospitalised at the Clinical Department of Psychiatry and Psychotherapy of Developmental Age between 2019 and 2022 from the Silesian Province. The mean age in this group was 14.84 years (95% CI: 13.23-15.15), out of whom 75.43% (n = 43) were females. Seven patients (12.2%) had a family history of BD. For 10 children with BD (17.54%), there was a coexisting diagnosis of autism spectrum disorder (ASD). Exclusion criteria in the studied group included mood disorder due to a general medical condition and substance-induced mood disorder. The control group consisted of 18 participants with a mean age of 16.3 years (95% CI: 15.53-17.13), out of whom 22.3% (n = 4) were females. Inclusion criteria included individuals below 18 years of age with no psychiatric diagnosis and not pharmacologically treated. This group does not contain individuals with a positive family history of BD, or any other mental disorder diagnoses.

Method

PNX, SPX and kisspeptin concentrations were determined in the peripheral venous blood serum of participants in the control and studied groups. The venous blood was collected to clot, centrifuged and the obtained serum was stored at – 20°C until assays were made. PNX, SPX and kisspeptin concentrations were measured with the enzyme-linked immunosorbent assay (ELISA) in accordance with the protocols provided by the manufacturers: the sandwich immunoenzymatic assay for quantitative count of kisspeptin in vitro in human serum, plasma and other biological fluids (sensitivity: < 13.1 pg/ml; detection range: 31.2 – 2000 pg/ml); the immunoenzymatic EIA kit to detect human PNX (sensitivity: 0.07 ng/ml; detection range: 0.07 – 2.1 ng/ml); ELISA kit for quantitative count of SPX concentration in vitro in serum (sensitivity: 46.88 pg/ml; detection range: 78.13-5000 pg/ml).

Bioethical Committee approval

The study was carried out with the approval of the Bioethical Committee of the Medical University of Silesia in Katowice, on the basis of resolution no. PCN/0022/KB1/126/19.

Statistical analysis

Statistical analysis was conducted with the StatSoft Statistica software ver. 13. The assumed level of statistical significance is a = 0.05.

Results

Mean PNX concentration in the studied group was 1.57 ng/ml (95% CI: 1.35-1.79), while in the control group – 2.69 ng/ml (95% CI: 2.38-3; Mann-Whitney U test p-value < 0.05). For SPX the results were 639.65 pg/ml (95% CI: 558.86-720.44) in the studied group, and 354.28 pg/ml (95% CI: 310.33-398.22; Mann-Whitney U test p-value < 0.05) in the control group. The observed differences were statistically significant. They are presented in Fig. 1 and 2. For kisspeptin, the mean concentration in the studied group was 126.02 pg/ml (95% CI: 39.82-212.23; median: 59.85), while in the control group – 54.83 pg/ml (95% CI: 39.23-70.43; median: 51.3; Mann-Whitney U test p-value = 0.29). The observed difference was not statistically significant.

In the analysed group the sex of patients, a positive family history of BD or co-existence of ASD had no statistically significant effect on the concentrations of the studied neuropeptides (Mann-Whitney U test p-value > 0.1).

Additionally, the correlation between the age of the studied individuals and concentrations of the selected neuropeptides was analysed. There was a slight, positive correlation between the age and PNX concentration (r = 0.28; p < 0.05). There were also statistically significant correlations between the concentrations of neuropeptides themselves, and the parameters are presented in Table 1 below.

Table 1. **Matrix of correlations of neuropeptide concentrations**

	PNX	SPX	kisspeptin
PNX	-	p-value < 0.05	p-value < 0.05
SPX	-0.52	-	p-value < 0.05
kisspeptin	-0.24	0.35	-

Further in the process, logistic regression was carried out to analyse the odds ratio (OR) of BD occurrence depending on the concentrations of the studied neuropeptides. Due to the observed collinearity within the matrix analysis of correlation of concentrations for each neuropeptide, a separate regression model was created. For PNX and SPX the models obtained statistical significance: OR for PNX was OR = 0.154 (95% CI: 0.059-0.404), while for SPX – OR = 1.009 (95% CI: 1.003-1.015). The model for kisspeptin did not obtain statistical significance.

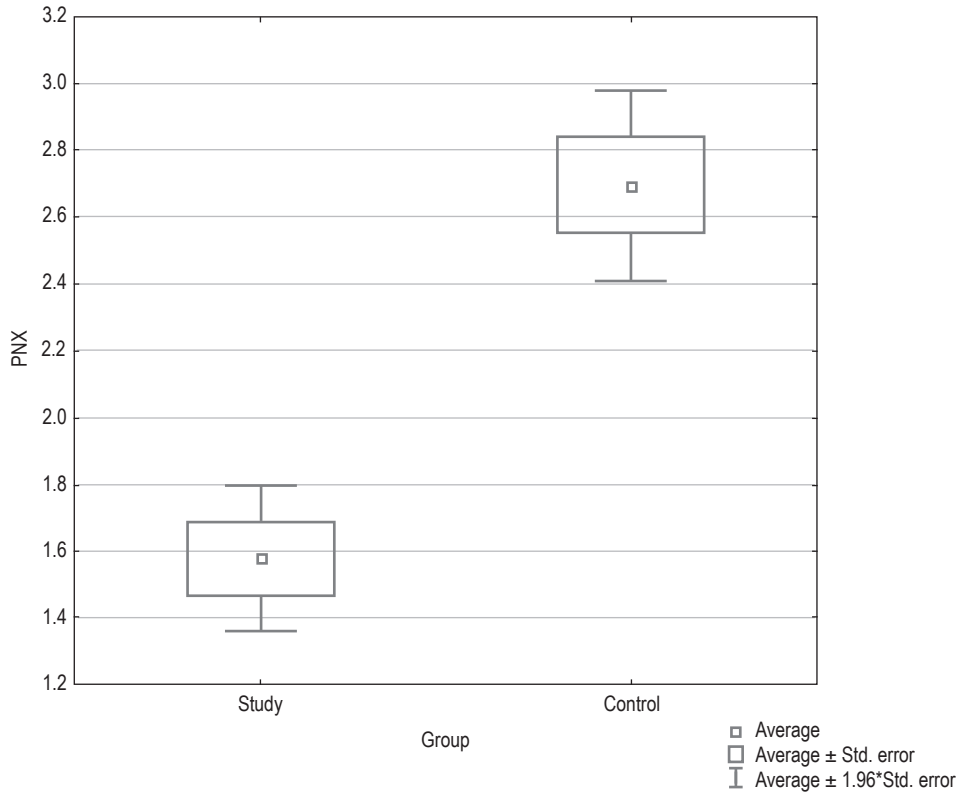

Figure 1. **Difference in the mean PNX concentrations between the control and studied groups (Mann-Whitney U test $p < 0.05$)**

Discussion

In the conducted study the presence of BD was statistically significantly correlated with a decreased concentration in serum of one of the less known neuropeptides, i.e. PNX, which is supposed to be linked with the anxiety level in humans. Also, the logistic regression analysis showed a significant reduction of BD risk together with the increase in PNX concentration. In the study by Hofmann et al. from 2017 [17] (concerning obese males), it was shown that PNX concentration was negatively correlated with anxiety. Anxiety symptoms are believed to be predictors of bipolar affective disorder development, as well as a frequent coexisting disorder in BD patients, particularly in the paediatric population. In retrospective studies up to 75% of bipolar affective disorder patients reported anxiety as a trait in the prodromal phase of the disease, though it should be noted that anxiety is not a specific factor for BD development [29]. On the other hand, up to 54% of young patients with BD simultaneously experience anxiety disorders (in particular panic disorder, agoraphobia, generalised anxiety disorder, posttraumatic stress disorder).

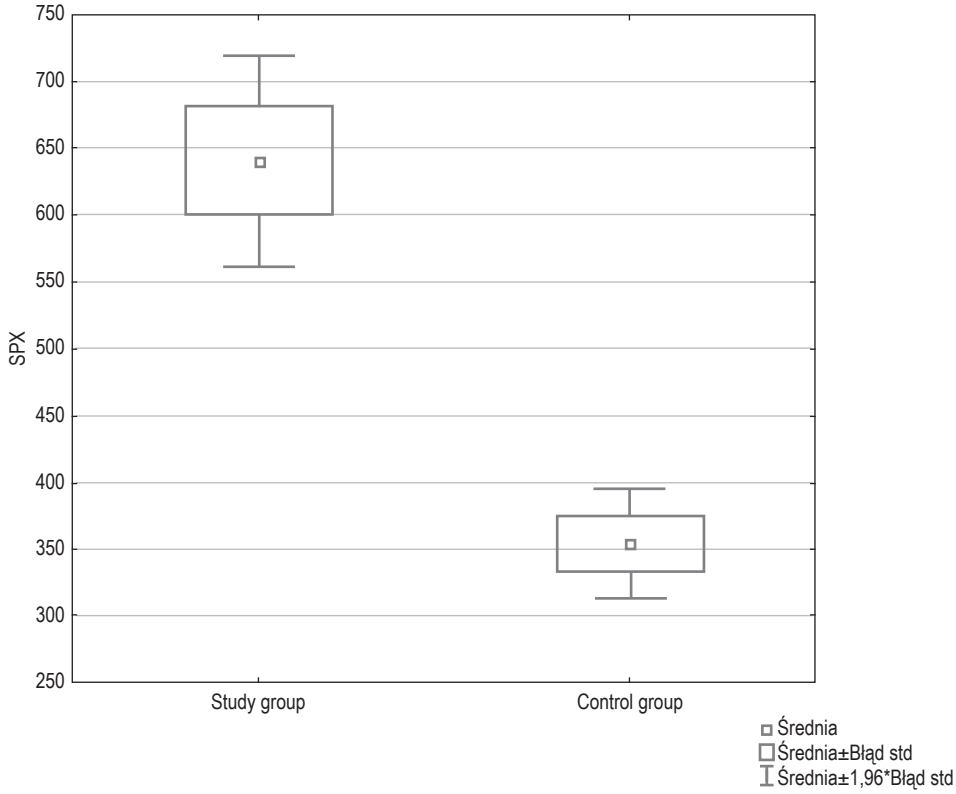

Figure 2. **Difference in the mean SPX concentrations between the control and studied groups (Mann-Whitney U test p < 0.05)**

Coexistence of BD and anxiety disorders in the paediatric population seems to be linked with a worse functioning of the child [30]. Therefore, it should be assumed that anxiety symptoms may be frequent in the group of hospitalised subjects due to BD. Further studies should be therefore directed towards the assessment of the correlation between serum PNX concentration and the severity of anxiety symptoms in the studied individuals.

Similarly, a reduced PNX concentration was observed in the study on young anorexia nervosa (AN) patients [31]. This type of correlation seems to be extremely interesting, especially in the context of reappearing reports on correlations between eating disorders and other mental disorders [32]. For instance, in the study by Kask et al. from 2016 [33], other mental disorders were observed in 41% of the AN patients, while in 23.4% – episodes of depression and/or BD. Similar results can also be observed in reverse analyses, where a higher prevalence of AN was noted in the course of BD than in the general population. What is more, the occurrence of AN in these studies is linked with an earlier onset and more severe course of BD. Authors of studies devoted

to this subject suggest that there is an aetiopathological correlation between these two nosological units [34, 35]. These reports as well as the hypotheses presented therein seem especially interesting in the context of results obtained in the presented study, as well as in the study by Pałasz et al. [31]. However, the subject of AN and BD interrelation in the paediatric population in the context of the role of neuropeptides and their physiology needs a deepened future analysis with an attempt to isolate differences in the course of both these disorders and specific clinical symptoms which could be linked with PNX concentration.

The study on mice also revealed that PNX prevents the development of non-alcoholic fatty liver disease induced by a high-fat diet [36]. Literary sources also pay attention to a possible effect of PNX on food intake, which requires further studies [37]. In our study, BD patients, despite lower PNX concentrations than in the control group, manifested normal, increased or reduced appetite; they also used pharmacotherapy which could possibly affect appetite and future development of metabolic syndrome. Therefore, it seems necessary to continue the study on correlations between PNX concentrations and body mass/BMI of the studied individuals.

It is also believed that PNX plays a significant role in the female reproductive system, where it intensifies secretion of luteinising hormone (LH), stimulates oocyte maturation and increases the number of ovulated oocytes. The neuropeptide has an anti-inflammatory and cell-protecting effect, affects behaviour, participates in sensory perception, memory processes and energy metabolism. Outside the central nervous system, PNX exerts an effect on the heart, ovaries, fatty tissue and pancreatic islets [38].

On the other hand, another (unmarked in this study) neuropeptide – nesfatin-1, may intensify the effect of PNX-14 on the release of reproductive hormones, such as LH, folliculotropin and testosterone in male rats [39]. It also turns out that nesfatin-1 is expressed in neurons of the bed nucleus of the stria terminalis which participates in the development of anxiety, stress and fear [40]. In light of the existing correlation between nesfatin-1 and PNX it is advisable to assess concentrations in further studies on nesfatin-1 and PNX, as well as to study correlations between PNX and nesfatin-1 concentrations.

In our study, higher concentrations of serum SPX were observed in BD children than in the control group. Additionally, in the logistic regression analysis the SPX model obtained statistical significance, pointing to the correlation of higher concentrations of this neuropeptide with increased BD risk in the studied population. However, it should be noticed that despite statistical significance, the correlation was very weak and could be of incidental nature. This can be supported not only by a very low value of OR, but also a moderate, negative correlation between PNX and SPX concentrations. Available literature shows that SPX in animal models reduces insulin secretion and has a strong anorectic, analgesic, anxiolytic and anti-depression effect [41, 42]. However, among BD patients anxiety symptoms are frequent; therefore, it seems that in these patients SPX may not play an anxiolytic role. Similarly with the effect of SPX on appetite – the studied group consisted of individuals with reduced and increased appetite, but also those with no changes in this respect. Further studies on SPX should also be directed towards defining the correlations between SPX concentration and individual BD

episodes (mixed episode, depression, mania/hypomania) and symptoms occurring in their course (e.g. anxiety, changes in appetite or weight).

In studies on children with obesity and hypertension a significantly lower median of SPX concentration can be observed as compared to children with normal weight and arterial blood pressure [43, 44]. It is also believed that increased serum SPX concentration may indicate a response to physical exercise [45]. Patients during manic or mixed episodes manifest psychomotor agitation and are overactive; however, during depressive episodes they manifest psychomotor retardation.

Kisspeptin in animal and human models modulates glucose-stimulated insulin secretion, food intake and/or energy expenditure. It is also engaged in animals in the control of reproductive behaviour, and in humans – in the modulation of sexual and emotional brain processing [41]. It is also believed to be a key regulator of puberty onset and fertility control [46]. Furthermore, it reveals anti-depressive and anxiety-suppressing effects [41]. Despite these activities, our study suggests that kisspeptin does not play a key role in BD, since no statistically significant difference was observed between concentrations of this neuropeptide in patients and the control group. However, it should also be taken into consideration to what extent pharmacotherapy in BD patients affected the concentration of this and the remaining neuropeptides in venous blood serum, since e.g. quetiapine (mood stabiliser) therapy, in the study of Nikisch et al. [47] affected the NPY-LI level (NPY – like immunoreactivity) in CSF, and changes in its concentration may prove in the future to be a marker of response to treatment [47]. On the other hand, in a study on rats, olanzapine reduced the expression of mRNA NPQ/SPX in the brainstem, and increased the level of mRNA SMIM20/PNX [48]. Hence, in future studies it is necessary to take into consideration the effect of applied pharmacotherapy on the concentrations of selected neuropeptides, and also to observe changes in these concentrations over time under the effect of the applied therapy.

Broadening knowledge on neuropeptide participation in the course of mood disorders may in the future help to develop therapeutic interventions directed to PNX or SPX signalling pathways. However, there are still numerous questions and controversies which should be studied, before the possible therapeutic potential of neuropeptides is established [41].

Conclusions

1. BD is statistically significantly correlated with a reduced PNX concentration and increased SPX concentration in the serum of BD patients.
2. BD occurrence does not reveal any correlation with serum kisspeptin levels.
3. PNX concentration decrease is a statistically significant, strong predictor of BD risk growth in the studied group, with the odds ratio equalling OR = 0.154.
4. SPX concentration increase is a statistically significant, however very weak predictor of BD risk increase.

Study limitations

The study does not include the effect of applied psychotropic medications, coexisting disorders, types of BD episodes and symptoms in individuals of the studied group. The size of the control group is also a limitation of this study.

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