Psychiatr. Pol. 2020; 54(4): 641–659
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/123167

A half-century of participant observation in psychiatry. Part II: Affective disorders

Janusz Rybakowski

Poznan University of Medical Sciences,
Department of Adult Psychiatry and Department of Psychiatric Nursing

Summary

The last half-century, thanks to the efforts of outstanding researchers, brought about great progress in the pathogenesis and clinics of affective illnesses. The catecholamine and serotonin hypothesis delineated in the 1960s have retained significant merit. Since the 1990s, the theories have pointed on excessive immune activation and impairment of neuroplasticity under stress. Since the 1970s, a systematic subclassification of unipolar and bipolar affective disorder has proceeded. Epidemiological studies of the last half-century indicated a significantly higher prevalence of depression compared with previous decades. The 21st century brought evidence for a greater frequency of various forms of bipolar affective disorder. During the last 50 years, the etiopathogenesis, diagnosis and treatment of affective disorders were my favorite and fascinating clinical and research topics. This initiated in 1970 when I began my work in the Department of Psychiatry, Medical Academy in Poznan, on account of the introduction of lithium salts for the treatment of these disorders. In 1976–1977, I received a fellowship of the National Institutes of Health at the University of Pennsylvania in Philadelphia and participated in research that elucidated the mechanism of lithium transport across cell membranes. I carried out the studies on the pathogenesis of affective disorders for more than 40 years afterward. They concerned abnormalities of transport across cell membranes, the activity of stress system, excessive pro-inflammatory activation, molecular genetics, dysfunctions of cognition and neurotrophins, especially the brain-derived neurotrophic factor (BDNF). At the beginning of the 21st century, I coordinated two Polish epidemiological projects DEP-BI and TRES-DEP. For my research on bipolar disorders, I received many international awards. I am also the author of the book *The faces of manic-depressive illness* which had three Polish editions as well as English and Russian versions.

Key words: affective disorders

Introduction

The second part of the triptych associated with 50 years of my activity in psychiatry concerns affective disorders. The contemporary concept of these disorders has been marked by two dates: dichotomic division of mental disorders into *dementia praecox* and *manisch-depressives Irresein* by the German psychiatrist, Emil Kraepelin, in 1899 [1], and showing different inheritance of unipolar and bipolar affective disorder by Swiss psychiatrist, Jules Angst [2], and Swedish psychiatrist of Italian origin, Carlo Perris [3], in1966. Affective disorders, for which recently more popular term is 'mood disorders', are relatively frequent, and both kinds (uni – and bipolar) may affect even up to 15% of the population during the lifetime. The etiopathogenesis, diagnosis and treatment of extreme emotions, moods and activity were in this half-century my favorite and fascinating clinical and research topics. It was partly linked with my pursuit of lithium administration in these disorders.

Studies on the etiopathogenesis, diagnosis and epidemiology of affective disorders in the last half-century

In the 1960s, the catecholamine and indolamine (serotonin) concepts of the pathogenesis of affective disorders were delineated. The recognition as to the creators of catecholamine theory should be given to American psychiatrists such as Joseph Schildkraut (1934–2006) and William Bunney, working during this time in the National Institutes of Mental Health (NIMH) in Bethesda. In his article from 1965, Schildkraut, based on pharmacological data, postulated a deficit of noradrenaline in depression and its excess in mania [4]. Shortly afterward he moved to Harvard University in Boston, where he continued his research on the role of the noradrenergic system in psychiatric disorders and on affective disorders in prominent artists.

In the same year, William (Bill) Bunney together with John Davis published a similar article where, in connection with pharmacological action of imipramine, monoamine oxidase inhibitors and reserpine, they suggested a significant role of noradrenaline in the etiopathogenesis of depression [5]. Bunney was working in NIMH for many years and acquired a reputation of the greatest researcher of the neurobiology of affective disorders in the USA. In 1975, he updated the catecholamine theory of affective disorders by adding to noradrenaline its precursor, dopamine, which at that time was flourishing as a brain neurotransmitter [6]. When I was in the USA in 1977, receiving the National Institutes of Health's fellowship, Bunney arranged for me a visit to the NIMH, where I had an opportunity to acquaint his numerous excellent colleagues such as, e.g., Robert Post, Daniel van Kammen or Monte Buchsbaum, who have played a significant role for biological psychiatry in America. For many years, William Bunney has been a professor of psychiatry in the Irvine School of Medicine, University of California.

The serotonin theory postulates a deficiency of serotonin in depression, without a reference to manic states. Its originators were a British psychiatrist, Alec Coppen

(1923–2019), working at that time in the neuropsychiatric center in Epsom, Surrey, and Soviet psychopharmacologists from the Bechterew psychoneurological research center in Leningrad, Izyaslav Lapin (1930–2012) and Grigori Oxenkrug. The fundamental papers of both Coppen and the Soviet authors were published in 1969 [7, 8].

Alec Coppen was one of the most prominent representatives of the European biological psychiatry of affective disorders. In his paper from 1969, he postulates a deficit of the serotonergic system in depression [7]. Coppen was also the exponent and researcher of many other pathogenic and therapeutic concepts of affective disorders concerning, among others, abnormal neurotransmission, water and electrolyte imbalance and metabolic disturbances. He became a great supporter of lithium administration and it is thought he was the first who evidenced the antisuicidal activity of this ion [9].

Izyaslav (Slava) Petrowich Lapin can be regarded as the originator of Russian experimental psychopharmacology. In his article from 1969, he suggested that the therapeutic action of antidepressant drugs is associated with augmentation of serotonergic neurotransmission, which is impaired in depression. Lapin also indicated that the reason of serotonin deficiency in depression may be a shift of tryptophan metabolism from 'serotonin' to ±kynurenine' pathway [8]. Therefore, he can be also named a creator of the kynurenine concept of the pathogenesis of depression. Besides having characteristics of the prominent researcher, Professor Lapin was a man of multiple talents (music, painting) and a friend of Elena Bonner and Andrei Sakharov. When meeting him at scientific conferences I was impressed by his excellent knowledge of the Polish language.

The co-author of the article from 1969, Grigori Oxenkrug, emigrated to the USA in the1980s. He carried on with psychopharmacological and neurobiological research, also on the kynurenine theory of depression. In recent years, he works as a professor of psychiatry and director of the *Psychiatry and Inflammation* program at Tufts University in Boston.

For more than 30 years, the neurotransmitter theories dominated both the views and research on the pathogenesis of affective disorders. This was fostered by the fact that they allowed in a convincing although a little mechanistic way to explain the action of antidepressant drugs. However, even in the 21st century, taking into account new data on serotonin, noradrenaline and dopamine, including the role of multiple receptors and transporters of these neurotransmitters, the mechanism of action of the majority of antidepressant drugs can be interpreted according to this model.

In the 1970s, besides the abnormalities in neurotransmission, a possibility of the pathogenic role of water and electrolyte disturbances in affective disorders was raised. This was undoubtedly associated with showing psychotropic properties of lithium, the element belonging, similar to sodium and potassium, to the first group of the Mendeleev's periodic table. Among water and electrolyte disturbances, abnormalities of cation transport across the cell membrane, including lithium transport and the activity of adenosine triphosphatase (ATPase), came to the fore. The data were gathered, among others, from studies performed in Philadelphia, indicating that in affective disorders lithium transport by the so-called lithium-sodium countertransport system is dimin-

ished, which is reflected in erythrocytes by the higher erythrocyte lithium index [10]. Also, impaired activity of sodium-potassium ATPase during depression and mania was showed, among others, on the erythrocyte model [11, 12].

Contemporary molecular-genetic research has shown a connection between abnormalities of various ATPase variants and a predisposition to affective disorders, especially to bipolar disorder. Darier's disease is a dermatologic condition characterized by disturbances of keratinization of skin, nails and mucous membranes. It is caused by a mutation in the *ATP2A2* gene associated with the activity of calcium ATPase isoform (Ca^{2+} ATP-ase) and inherited in an autosomal dominant manner. A number of cases showing family co-morbidity of Darier's disease and bipolar disorder has been reported. Swedish researchers, on the basis of a population study, found that patients with Darier's disease have a 4.3-fold higher risk of bipolar disorder compared with the general population [13]. Wilson's disease is caused by mutations in the *ATP7B* gene coding the ATPase associated with copper transport across the cell membrane. Italian researchers showed that patients with Wilson's disease have nearly 13-fold increased risk for bipolar disorder and nearly 6-fold increased risk for depression, compared with the general population [14].

In the 1990s, new avenues of exploring the pathogenesis of affective disorders were initiated. One of these points to pathological activation of the immune system. The case for the 'inflammatory' hypothesis of affective disorders may be a frequent occurrence of the so-called acute phase response as well as increased secretion of pro-inflammatory cytokines in depression. The outstanding exponent of this concept has been a Belgian psychiatrist, Michael Maes, currently working in Thailand, who published many articles on this topic, also in collaboration with Polish researchers. His recent paper summarizes both the mechanisms of immune-inflammatory activation in depression and bipolar disorder as well as the responsive processes, the so-called Compensatory Immune-Regulatory System Reflex (CISR) [15]. A prominent researcher of the inflammatory concept of affective disorders was Anna Służewska (1951–1999), working at the Department of Adult Psychiatry in Poznan, who passed away due to a tragic death. In recent years, the attention has also been paid to immune activation within the central nervous system called neuroinflammation, where the most important role is played by microglia cells. In these mechanisms, genetic and epigenetic factors as well as gut microbiota may also be relevant [16]. The results of studies have brought upon the attempts of the therapeutic use of drugs modifying the activity of the immune system in affective disorders.

The second path of pathogenic research in affective disorders assumes the impairment of neuroplasticity under the influence of stress. A prominent American neuroscientist, Ronald Duman (1954–2020), showed in 1995 that antidepressant drugs increase the expression of the brain-derived neurotrophic factor (BDNF) gene in the hippocampus [17]. Two years later, the researchers from Yale University, led by him, published the article *Molecular and cellular theory of depression*. They hypothesized that in depressive patients there is an impairment of neurotrophic processes and neurogenesis, and that antidepressant drugs can normalize this [18]. Further studies in this

direction have searched for the drugs in affective disorders with new mechanisms of action – not related to the neurotransmitter concepts.

The last fifty years brought about a lot of evidence for the role of various neuroendocrine systems in the pathogenesis of affective disorders. A reciprocal relationship between mental and endocrine disorders was emphasized in the 1960s by a Swiss psychiatrist, Manfred Bleuler, a son of Eugen, the creator of the term 'schizophrenia' [19]. In affective disorders, most research has been dedicated to the 'stress' axis (limbic-hypothalamic-pituitary-adrenal – LHPA) in the context of its disturbances and the role of stressful events, both in childhood and preceding an episode of the illness. Both in unipolar and bipolar affective disorders, various disturbances of the LHPA axis have been found such as hypercortisolemia, increased corticotropin-releasing hormone (CRH) secretion and abnormal activity of glucocorticoid receptors [20, 21]. A range of data shows the possibility of therapeutic influence in affective disorders by acting on the LHPA axis.

From the area of stress axis descends the first diagnostic test for affective disorders, the dexamethasone suppression test (DST), indicating the hyperactivity of the LHPA axis in depression. Its originator is Bernard (Barney) Carroll (1940–2018), whose fundamental publication comes from 1982 [22], although had been preceded by a number of earlier research. Bernard Carroll graduated in medicine at the University of Melbourne and emigrated to the USA in 1971. He worked at different universities, among others the University of Pennsylvania, University of Michigan, and in 1982–1990 he was a chairman of the Department of Psychiatry, Duke University in Durham. In 1998, he moved to Carmel in California, where he was scientifically active until the end of life, publishing many articles, including those on the ethics in scientific research. The city Carmel-by-the Sea-has 4,000 inhabitants and is notable for streets having no numbers and in 1986–1988 Clint Eastwood was its mayor.

In the last two decades, a significant role of stress of early life (childhood trauma) for the development and course of affective disorders has been highlighted. In their pioneering study of 1999, published in *Molecular Psychiatry*, Israeli researchers found that a loss of a parent, mainly before 9 years of age, results in the 3.8-fold risk of developing depression and 2.8 risks for bipolar disorder in the adulthood [23]. Many studies performed in the last 20 years demonstrated that in persons experiencing various childhood trauma (e.g., emotional, physical and sexual abuse or neglect) there is an increased risk of developing unipolar or bipolar mood disorders and their course is more severe. Several mechanisms of this phenomenon, including genetic and epigenetic ones, have been discovered [24, 25].

Among other neuroendocrine systems, a significant relationship with affective disorders has been demonstrated for the thyroid axis and the 'reproductive' axis in women. Mood disorders make a risk factor for developing thyroid dysfunction, and thyroid hormones can be employed for augmentation of pharmacological treatment of these disorders. Whereas the periods of significant changes in sex hormones, such as perimenstrual, perinatal and perimenopausal ones, can predispose to the occurrence or exacerbation of affective disorders [26].

The last half-century brought about systematic progress in genetic research of affective disorders. Probably, the most important discovery in the 1970s was the demonstration of a linkage between bipolar affective disorder and color-blindness. Several families showed the co-occurrence of bipolar affective disorder and protanopia, known as preconditioned with chromosome X inheritance. It was first reported by Julien Mendlewicz, the eminent Belgian psychiatrist, the long-time Editor-in-Chief of *Neuropsychobiology*, whiose parents lived near Wloclawek, Poland [27]. Nevertheless, the genes located on chromosome X cannot be responsible for all cases of bipolar disorder because this excludes father-son inheritance, and a situation when both father and son have bipolar disorder is not a rarity in clinical conditions.

In the late 1980s, the first American publication presenting the results of the molecular-genetic study appeared. The research team led by Janice Egeland from the University of Miami performed the study in the Old Order Amish population in Pennsylvania, showing that in these persons a predisposition to bipolar affective disorder is associated with DNA markers, located on the short arm of chromosome 11. This was published in a prestigious journal *Nature* [28]. The subsequent studies have not confirmed this phenomenon in other populations. However, they revealed the presence of various 'candidate' genes associated with a predisposition to a bipolar disorder such as *BDNF* gene or tyrosine hydroxylase gene in this location.

Since the 1990s, there have been two decades of genetic research using a method of so-called candidate gene. In this research, polymorphism frequency of a gene coding given substance or enzyme the role of which in the pathogenesis of unipolar or bipolar affective disorder has been proposed, based on the results of biochemical or pharmacological studies, was investigated. The most frequent procedure was case-control design, comparing the frequency of a given polymorphism in affective patients with that of healthy persons. The polymorphisms were also studied using clinical, neurophysiological or cognitive phenotype. Likewise, the attempts were made to assess interaction between a given gene and environmental factors. The conspicuous study in this respect showed that s/l polymorphism of the serotonin transporter gene can determine the risk of developing depression under the influence of stress factors [29].

In the second decade of the 21st century, the most important method of genetic research was the genome-wide association study (GWAS). Encompassing a large number of patients, the method allows for the identification of million or even more polymorphisms of the whole genome. The last summary of the GWAS in depression was presented by Mullins and Lewis [30], and in bipolar disorder by Ikeda et al. [31]. The GWAS studies revealed several dozen genes associated with a predisposition to these disorders. Among them, noteworthy is the *CACNA1C* (Calcium Voltage-Gated Channel Subunit Alpha1 C) gene, associated with calcium ion transport across the membrane. Perhaps it is the only gene so far that translates into a treatment such as the use of calcium channel antagonists in ultra-rapid-cycling bipolar disorder [32].

Following the articles of Angst [2] and Perris [3] from 1966, which grounded the distinction of affective disorders into unipolar and bipolar, further attempts of subclassification of these disorders appeared shortly. As to bipolar disorder, two such proposals

were presented in the 1970s by American psychiatrists. In 1974, David Dunner and Ronald Fieve described a course of bipolar disorder with poor response to lithium. The illness was characterized by rapid changes of episodes, which corresponded with *folie circulaire* described 120 years earlier by the French physician, Jean Pierre Falret [33]. The authors proposed the criterion for the rapid cycling type of the illness as at least four episodes (manic or depressive) in a year [34]. Further investigations showed that rapid cycling bipolar disorder may have distinctive features as to the prevalence and pathogenesis, and its treatment is especially difficult.

The next important step was taken by the article published in 1976. Its first author was again David Dunner, and co-authors were Elliot Gershon and Frederick Goodwin. According to the authors' proposal, if in the course of bipolar disorder apart from depressive states there occur manic episodes of major severity requiring hospitalization or mixed states, this would be bipolar I disorder. In bipolar II disorder, apart from episodes of depression there occur hypomanic states not requiring hospitalization [35]. This subclassification has been introduced to the American diagnostic system DSM. David Dunner is now professor emeritus at the University of Washington, Seattle, being still scientifically active. He was long-time Editor-in-Chief of the journal *Comprehensive Psychiatry*. Recently, together with me, he is a member of a research team led by an Australian psychiatrist, Gordon Parker. The aim of the group is to make a symptomatic distinction of bipolar I and bipolar II disorder [36].

Ronald Fieve (1930–2018) was an enthusiastic exponent of introducing lithium for psychiatric treatment in the USA, and most of his career was made in New York. He was also a proponent of using another element of the first group of the periodic table, rubidium, in the treatment of depression. His concept was based on the opposite pharmacological properties of rubidium and lithium when lithium was known mostly as an antimanic drug [37]. Elliot Gershon, whose roots are in the Eastern borderlands of pre-war Poland, is professor emeritus at the University of Chicago where he worked most of his time receiving many awards for genetic research. Whereas Frederick (Fred) Goodwin, now professor emeritus at George Washington University in Washington, was a director of the National Institutes of Mental Health (NIMH) in 1981–1988. Together with Kay Jamison, he published a 'bible' of bipolar affective disorder *Manic-depressive illness*, in 1990, and the second edition in 2007 [38, 39].

In 1984, a type of affective disorder with the peculiar circannual course was described. In such patients, during the fall-winter time, occurs depression while in the spring-summer period they have either euthymic or elevated mood. This form of the illness was named 'seasonal affective disorder'. The first author of the paper is Norman Rosenthal, a psychiatrist, coming to the USA from South Africa [40]. Further observations showed that there are several variants of seasonality, also associated with unipolar mood disorder. The most advanced research concern depressive states occurring in fall and winter, so-called 'winter depression'. They prompted the development of light therapy which proved effective in the treatment of such depression.

In the 1990s, the already mentioned great researcher of affective disorders, Jules Angst, proposed such new diagnostic categories as brief recurrent depression [41] and

brief hypomania [42]. In the last two decades, he introduced the Hypomania Check List (HCL-32) for the assessment of hypomanic symptoms [43], and declared himself a supporter of the diagnostic concept of unipolar mania [44].

A significant contribution to the diagnosis of affective disorders, especially bipolar disorder, was made by Hagop Akiskal, an American psychiatrist of Armenian origin. His most important accomplishments include the studies on dysthymia [45], a concept of the bipolar spectrum [46], and development of the temperament scale TEMPS-A (Temperament Evaluation of Memphis, Pisa and San Diego-Autoquestionnaire) [47]. Hagop Akiskal is director emeritus of the International Mood Center in San Diego, California, and was the long-time Editor-in-Chief of *Journal of Affective Disorders*. In 2004, he was a guest of the 43rd Polish Psychiatric Association Convention in Warsaw.

Epidemiological studies on depression carried out in the last decades of the 20th century pointed to a greater prevalence of this condition compared with data from the previous years. Currently, it is assumed that the one-year prevalence of depression accounts for the average of 5% of the population and is higher in women than in men [48]. For women, the lifetime risk of depression requiring a therapeutic intervention is about 10%.

In the 21st century, the evidence has been produced for the significant frequency of various forms of bipolar disorder. Current epidemiological data indicate that the lifetime risk for bipolar disorder type I is 1%, whereas for bipolar II and bipolar spectrum combined is about 3.5% [49].

Author's scientific contributions to the pathogenesis, diagnostics and epidemiology of affective disorders

In the field of affective disorders, I found myself in 1970, at a time of the inauguration of my work in the Psychiatric Clinic of Medical Academy in Poznan. It was associated with initiation of studies on the therapeutic action of lithium in these disorders. In 1971, I started a correspondence with Mogens Schou (1918–2005), the greatest contemporary lithium researcher. In 1973, the degree of medicinae doctor was conferred on me for the thesis titled: *A study of some aspect of water and electrolyte metabolism in patients with affective disorders treated with lithium carbonate*. Personal meeting with Mogens Schou took place in 1974 in Copenhagen. As an only representative of my country I participated there in the WHO *International Training Course in Psychopharmacology for Teachers in Medical Schools*. Mogens Schou was a director of this course and the co-director was Ole Jorgen Rafaelsen (1930–1987), a prominent Danish psychiatrist, the long-time chairman of the Department of Psychiatry, University of Copenhagen, who prematurely died in a tragic accident. The Rafaelsen Award is given every two years during the world congresses of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) for distinguished young researchers in psychopharmacology. Whereas since 2001, Mogens Schou awards have been presented by the International Society of Bipolar Disorders for outstanding achievements in the

field of research, as well as educational, organizational and media activity associated with bipolar affective disorder.

In 1973, together with Jerzy Sowiński from the Endocrinology Clinic in Poznan, I published in *Lancet* the letter to the editor, which was one of the first reports in the world pointing to thyroid dysfunctions in a manic and depressive episode of bipolar disorder [50].

My international publications on theoretical and practical aspects of lithium administration allowed me to apply for a foreign fellowship. In 1976, I received a Fogarty fellowship of the National Institutes of Health, USA, which I pursued in 1976–77at the Department of Psychiatry, University of Pennsylvania, Philadelphia, working as a psychiatrist in the Depression Research Unit. I also participated in a research group which was one of the first in the world identifying the mechanism of lithium transport across the cell membrane. It was shown that the most important mechanism of transporting lithium out of the cell is the lithium-sodium countertransport. The chief of the workplace where the experiments were performed was Alan Frazer, eminent psychopharmacologist, especially in the field of antidepressant drugs. In the early 1990s, Alan Frazer became the Chairman of the Department of Pharmacology, the University of San Antonio in Texas, where he has been working until now. He was also the long-term Editor-in-Chief of the *International Journal of Neuropsycho-pharmacology*.

Since my fellowship, I have been keeping close personal and research relationships with Jay Amsterdam, the latter long-time head of the Depression Research Unit at the University of Pennsylvania. I was there several times as a visiting scientist, and we have many collaborative publications. The roots of Jay Amsterdam's family are in Mstow near Czestochowa. I managed to obtain many copies of the birth and marriage certificates of his relatives, among others, the birth certificate of his grandfather, Faivel Amsterdam. Jay Amsterdam is a member of the Advisory Board of *Psychiatria Polska* and the author of many articles published in this journal.

The research performed in Philadelphia made a basis for my habilitation thesis. In 1980, I received a habilitation degree for the thesis *A study of lithium transport across cell membrane in bipolar affective disorder using red blood cell model*.

In 1985, I became the Head of the Department of Psychiatry, Medical Academy in Bydgoszcz, and I was performing this job for 10 years. Shortly before moving to Bydgoszcz, I spent several months in Denmark, in Copenhagen and Aarhus. In the latter place, I was a guest of Mogens Schou, who was at this time director of the Psychopharmacology Research Unit in Risskov hospital, near Aarhus. Knowing my interest in the mechanisms of cation transport, Mogens Schou acquainted me with Jens Skou, the discoverer of the sodium-potassium ATPase, working at the University of Aarhus. For this discovery, Jens Skou was awarded the Nobel Prize in 1997.

After my return from Philadelphia, I was continuing research on cation transport abnormalities in affective disorders both in Poznan, in 1978–85, as well as in Bydgoszcz afterward. Lithium transport across the erythrocyte membrane and the activity of sodium-potassium ATPase were investigated. We confirmed a lower activity of lithium transport out of the cell by the lithium-sodium countertransport in affective disorders,

which was reflected by a higher erythrocyte lithium index, both during acute episode and in remission [51]. In some studies, a decreased activity of sodium-potassium ATPase was showed both in manic and in depressive episodes [52, 53].

In 1995, I came back to Poznan to became the Head of the Department of Adult Psychiatry, Poznan University of Medical Sciences, and I performed this function for 22 years. The research on the neurobiology and psychopharmacology of affective disorders has been going on. One of the topics explored with sorely missed Anna Służewska was an inflammatory hypothesis of depression. In our studies, it was confirmed that in depression, there are features of pathological immune activation such as an elevation of C-reactive protein, alpha-1acid glycoprotein and alpha-chymotrypsin concentration, and an increased secretion of pro-inflammatory interleukins, such as interleukin-1 and interleukin-6. One of these papers, in which Ania is the first author, has until now been quoted 345 times in the Scopus database [54]. In recent years, in collaboration with Szczecin center, we assessed the very small embryonic-like stem cells (VSELs) and neural and glial markers in peripheral blood of patients with bipolar disorder. It was found that in bipolar patients there were features of excessive regenerative and inflammatory processes reflected by increased concentration of the VSELs and the mRNA expression of neural and glial markers in peripheral blood. Increased VSELs level correlated with the duration of illness, which may indicate that it may serve as a marker of its progress [55].

While in Bydgoszcz, several studies were performed on the LHPA axis using the dexamethasone suppression test. A relationship was found between the results of the test and gender and a season of the year [56, 57]. Whereas in Poznan, unique research was made employing the CRH-dexamethasone test, showing that a dysregulation of the LHPA axis in depression in the course of bipolar disorder is greater than in unipolar depression [58]. This paper has been quoted in the Scopus database 178 times.

In collaboration with the Department of Neuropsychology, Medical Academy in Bydgoszcz headed by Professor Alina Borkowska, several studies on cognitive dysfunctions in affective disorders were performed. In the most important paper, which has been quoted in the Scopus database 171 times, it was found that the severity of cognitive dysfunction was greater in bipolar depression compared to recurrent depression [59].

In 1999, the Psychiatric Genetics Unit at the Poznan University of Medical Sciences was constituted, headed by Professor Joanna Hauser, which resulted in several scientific projects in affective disorders. Among the case-control studies using the candidate gene methodology, the association found between bipolar disorder and the polymorphism of the tyrosine kinase FYN gene can be mentioned. The kinase is involved in the interaction between BDNF and glutamatergic receptor NMDA [60]. In another study, such an association was found with polymorphism of the cystathionine beta-synthase gene, associated with the synthesis of homocysteine [61]. In the previous article of the triptych, the study of the matrix metallopeptidase-9 *(MMP-9)* gene in schizophrenia was mentioned, where, for the first time in the world, the association with the 1562C/T polymorphism of the *MMP-9* gene located on chromosome 20q13.12 was demonstrated. A case-control study was also performed in bipolar affective

disorder, comparing 416 patients and 558 healthy persons. The association with the 1562C/T polymorphism of the *MMP-9* gene was also found, however, in contrast to schizophrenia, where a preponderance of C allele was observed, in bipolar disorder, there was a greater frequency of T allele [62].

In the Department of Adult Psychiatry, many studies were performed concerning the role of BDNF in the pathogenesis and treatment of affective disorders. In some of them, a combined neuropsychological and molecular-genetic methodology was used. For the first time in the world, we demonstrated that Val/Met polymorphism of the BDNF gene is associated with a quality of performance on the cognitive tests, connected with the activity of the prefrontal cortex; persons with Val/Val genotype achieve significantly better results [63]. We also revealed that such a phenomenon is characteristic of bipolar disorder and is not present in schizophrenia or healthy subjects [64]. Since it has been found that the Val/Val genotype can predispose to bipolar disorder, our results can indicate an evolutionary trade-off, where a predisposition to the illness can be associated with better cognitive functions in afflicted subjects. The assessment of serum BDNF concentration showed that it is lower during the episode of depression, both unipolar and bipolar, compared to remission. We also found a negative correlation between BDNF concentration and severity of depression [65].

In the first decade of the 21st century, I was a coordinator of two large epidemiological studies of affective disorders in Poland. They were possible thanks to research grants obtained from a pharmaceutical company, Sanofi. In 2002, the prevalence of bipolar disorder was assessed using the existing DSM-IV diagnostic criteria for bipolar disorder, type I and II, and the proposed criteria for bipolar spectrum. Besides me, a national coordinator was Andrzej Kiejna, the chairman of the Department of Psychiatry, Medical Academy in Wroclaw. The study was given the acronym title DEP-BI (DEPression-BIpolar) and was aimed at estimating the frequency of bipolar disorder among depressed patients currently receiving outpatient care provided by psychiatrists. The study involved 96 psychiatrists representing all the provinces of Poland (2 to 12 specialists from each province). Each psychiatrist included 7–10 patients, aged 18–65 years, who had undergone at least one episode of depression in the course of unipolar or bipolar affective disorder. The final analysis covered 880 people. The obtained results showed that over 60% of the examined patients who were treated by Polish psychiatrists due to depression showed features of bipolar disorder. Bipolar disorder type I was 10% more frequent in men and type II was 10% more frequent in women. The bipolar spectrum criterion was met by 12% of patients, with a similar percentage of men and women [66]. In the group of bipolar disorders, early-onset depression (before the age of 25), atypical depression (with excessive sleepiness and appetite), depression with psychotic symptoms, postpartum depression, and depression in which treatment with antidepressants did not bring satisfactory results (so-called drug-resistant depression) were more frequent [67].

The study conducted in 2007, which was given the acronym title TRES-DEP (Treatment-RESistant Depression) aimed to assess the features of bipolarity in depressed patients. Besides me, the national coordinators were Andrzej Kiejna, the chairman of the

Department of Psychiatry, Medical University in Wroclaw, and Dominika Dudek, the current chairwoman of the Department of Psychiatry, Jagiellonian University Medical College in Krakow, the Editor-in-Chief of *Psychiatria Polska*, and the president-elect of the Polish Psychiatric Association. The survey involved 150 psychiatric centers from all regions of Poland. Each center included in the study five patients aged 18–77 years with drug-resistant depression and five with drug-responsive depression. For psychometric assessment, the MDQ (Mood Disorder Questionnaire (MDQ) [68] and Hypomania Checklist-32 (HCL-32) [43] were used. The Polish versions of these scales were elaborated and validated during this project [69, 70]. The final analysis included 1,051 patients (299 men, 752 women). In the study group, the 'bipolarity' criteria set out by the HCL-32 were met by 37.5% of the respondents, and the MDQ criteria – by 20% of the respondents. Patients who obtained positive results on the HCL-32 and MDQ were characterized with more family history of mental disorders (depression, bipolar disorder, alcoholism, suicide) and a more severe course of the illness (earlier onset, more depressive episodes, more frequent hospitalizations and suicide attempts). A significantly higher level of 'bipolarity' measured by the HCL-32 and MDQ was observed in depressed patients in whom the effects of antidepressants were less positive [71].

The creator of the HCL-32 is Jules Angst, probably the most prominent living researcher of affective disorders, whose friendship and collaboration in recent two decades have been extremely valuable for me. Jules Angst is professor emeritus of psychiatry at the University of Zurich. In the previous chapter, his enormous contribution to the diagnostics and clinics of affective disorders was presented. Jules Angst participated in many scientific conferences in Poland and several meetings of the Polish Psychiatric Association. In 2014, he was the main lecturer at the annual conference *Neuropsychiatry and Neuropsychology* co-organized by Termedia publisher in Poznan, talking about the classification of affective disorders. In December 2016, his 90th birthday was greatly celebrated in Zurich. On this occasion, I handed him a copy of a fresh publication in *Psychiatria Polska* concerning the first study performed in Poland by Poznan and Krakow centers using the modified hypomania checklist scale (HCL-33) containing versions for both the patient and a close person [72].

As the head of the Department of Adult Psychiatry, I participated in developing the Polish versions of personality scales such as the Temperament Evaluation of Memphis, Pisa and San Diego-Autoquestionnaire (TEMPS-A) and Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE). The creator of the first of them is already mentioned prominent researcher of bipolar disorder, Hagop Akiskal [47]. The scale assesses five temperaments that may occur in affective disorders: cyclothymic, hyperthymic, irritable, depressive, and anxious. The elaboration and validation of the Polish version were made with collaboration of the Clinical Neuropsychology Unit, Collegium Medicum Bydgoszcz, Nicolaus Copernicus University in Torun, headed by Professor Alina Borkowska [73]. The O-LIFE scale, elaborated by the team of a British psychologist, Gordon Claridge, assesses such schizotypy dimensions as unusual experiences, cognitive disorganization, introversion/anhedonia, and impulsive

nonconformity [74]. The Polish version was developed in the Department of Adult Psychiatry [75]. Both scales were widely used in many clinical and pharmacological studies performer in Poznan center.

It has been known that bipolar disorder is over-represented among the people associated with art. In a study performed in the Department of Adult Psychiatry, it was found that bipolar patients showed higher indexes of creativity compared with control subjects. The association between creativity and the features of schizotypy measured by the O-LIFE scale was also observed [76]. For the doctoral dissertation on this topic, Paulina Klonowska received an award of the Polish Psychiatric Association during the Convention in Poznan in 2010.

The study was also performed concerning the effect of childhood trauma on the development and course of bipolar disorder. Compared with the control group, bipolar patients showed a higher level of indices of physical abuse, emotional abuse, sexual abuse, emotional neglect, physical neglect, and also experienced more frequently such negative childhood events as alcoholism, psychiatric illness and suicide in the family, parental abandonment, divorce, death and prolonged separation [77]. Emotional abuse and neglect were the main factors associated with an unfavorable course of the illness [78].

Our research on social cognition in bipolar disorder showed a deficit in mentalization (theory of mind) both during a manic and depressive episode, which corresponds with other studies [79]. However, as the first researchers, we observed an increased affective empathy during a manic episode [80].

In collaboration with Krakow center, the chronobiological studies of bipolar disorder were performed using the BRIAN (Biological Rhythms Interview of Assessment in Neuro-psychiatry) scale. It was found that in bipolar patients the biological rhythms measured by this scale are disturbed and correlated with affective temperaments and schizotypy dimensions [81, 82]. The creator of the BRIAN scale is Flavio Kapczinski, an outstanding Brazilian psychiatrist of the young generation, a descendant of Polish emigrant coming to Brazil at the end of the 19th century. Flavio Kapczinski was a researcher of mood disorders in Porto Alegre, Brazil, where I visited him in 2011. In 2012, he was the main lecturer at the annual conference *Neuropsychiatry and Neuropsychology* in Poznan. For several years, he has been director of the bipolar disorder program at MacMasters University in Hamilton, Canada. He is the author of many papers on the neurobiology of bipolar disorder and a proponent of the concept of the staging of the illness [83].

My fascination with bipolar affective disorder culminated in the book *Oblicza choroby maniakalno-depresyjnej* (*The faces of manic-depressive illness*), released by Poznan publisher Termedia in 2008 and 2009, and the third expanded and supplemented edition appeared in 2018 [84]. The second edition was also published in English [85] and Russian [86].

Together with Jan Jaracz, I developed *Leksykon manii i depresji* (*Lexicon of mania and depression*), published by Termedia in 2010 [87]. With Dominika Dudek and Marcin Siwek, I edited the books: *Choroba afektywna dwubiegunowa – wyzwania*

diagnostyczne (*Bipolar affective disorders – diagnostic challenges*) [88] and *Choroba afektywna dwubiegunowa – wyzwania terapeutyczne* (*Bipolar affective disorders – therapeutic challenges*) [89].

The studies on bipolar disorder brought me an international reputation which was reflected in numerous awards. In 2012 I received the Lifetime Achievement Award of European Bipolar Forum, and in 2015 – the Lifetime Achievement Award in Biological Psychiatry from the World Federation of the Societies of Biological Psychiatry. In 2018, the Mogens Schou Research Award from the International Society of Bipolar Disorder was conferred on me. During the ISBD conference in Mexico City, my award was recommended by Robert Post, the great expert in affective disorders, the originator of the 'kindling' hypothesis in their pathogenesis [90].

Thus, I can appraise my half-century work as a psychiatrist dealing with bipolar affective disorder as greatly satisfactory.

References

1. Kraepelin E. *Psychiatrie. Ein Lehrbuch für Studierende und Ärzte*, 6 Auflage. Leipzig: Barth; 1899.
2. Angst J. *Zur Ätiologie und Nosologie endogener depressiver Psychosen*. Berlin: Springer; 1966.
3. Perris C. *A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. I: Genetic investigation*. Acta Psychiatr. Scand. 1966; 42(Suppl 194): 15–44.
4. Schildkraut JJ. *The catecholamine hypothesis of affective disorders: A review of the supporting evidence*. Am. J. Psychiatry 1965; 122(5): 509–522.
5. Bunney WE Jr, Davis JM. *Norepinephrine in depressive reactions. A review*. Arch. Gen. Psychiatry 1965; 13(6): 483–494.
6. Bunney WE Jr. *The current status of research in the catecholamine theories of affective disorders*. Psychopharmacol. Commun. 1975; 1(6): 599–609.
7. Coppen A. *Defects in monoamine metabolism and their possible importance in the pathogenesis of depressive syndromes*. Psychiatr. Neurol. Neurochir. 1969; 72(2): 173–180.
8. Lapin IP, Oxenkrug GF. *Intensification of the central serotoninergic processes as a possible determinant of the thymoleptic effect*. Lancet 1969; 1(7586): 132–136.
9. Coppen A, Standish-Barry H, Bailey J, Houston G, Silcocks P, Hermon C. *Does lithium reduce the mortality of recurrent mood disorders?* J. Affect. Disord. 1991; 23(1): 1–7.
10. Rybakowski J, Frazer A, Mendels J, Ramsey TA. *Erythrocyte accumulation of the lithium ion in control subjects and patients with primary affective disorder*. Commun. Psychopharmacol. 1978; 2(2): 99–104.
11. Naylor GJ, Dick DA, Dick EG, Le Poidevin D, Whyte SF. *Erythrocyte membrane cation carrier in depressive illness*. Psychol. Med. 1973; 3(4): 502–508.
12. Naylor GJ, Dick DA, Dick EG, Worrall EP, Peet M, Dick P. *Erythrocyte membrane cation carrier in mania*. Psychol. Med. 1976; 6(4): 659–663.
13. Cederlöf M, Bergen SE, Långström N, Larsson H, Boman M, Craddock N et al. *The association between Darier disease, bipolar disorder, and schizophrenia revisited: A population-based family study*. Bipolar Disord. 2014; 17(3): 340–344.

14. Carta MG, Sorbello O, Moro MF, Bhat KM, Demelia E, Serra A et al. *Bipolar disorders and Wilson's disease*. BMC Psychiatry 2012; 12: 52.
15. Maes M, Carvalho AF. *The compensatory immune-regulatory reflex system (CIRS) in depression and bipolar disorder*. Mol. Neurobiol. 2018; 55(12): 8885–8903.
16. Fries GR, Walss-Bass C, Bauer ME, Teixeira AL. *Revisiting inflammation in bipolar disorder*. Pharmacol. Biochem. Behav. 2019; 177: 12–19.
17. Nibuya M, Morinobu S, Duman RS. *Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments*. J. Neurosci. 1995; 15(11): 7539–7547.
18. Duman RS, Heninger GR, Nestler EJ. *A molecular and cellular theory of depression*. Arch. Gen. Psychiatry 1997; 54(7): 597–606.
19. Bleuler M. *Psychiatrie und Endokrinologie. Geschichte ihrer Beziehungen in den letzten dreissig Jahren*. Acta Psychiatr. Scand. 1965; 41(3): 411–418.
20. Belvederi Murri M, Prestia D, Mondelli V, Pariante C, Patti S, Olivieri B et al. *The HPA axis in bipolar disorder: Systematic review and meta-analysis*. Psychoneuroendocrinology 2016; 63: 327–342.
21. Menke A. *Is the HPA axis as target for depression outdated, or is there a new hope?* Front. Psychiatry 2019; 10; 101.
22. Carroll BJ. *The dexamethasone suppression test for melancholia*. Br. J. Psychiatry 1982; 140: 292–304.
23. Agid O, Shapira B, Zislin J, Ritsner M, Hanin B, Murad H et al. *Environment and vulnerability to major psychiatric illness: A case control study of early parental loss in major depression, bipolar disorder and schizophrenia*. Mol. Psychiatry 1999; 4(2): 163–172.
24. Jaworska-Andryszewska P, Rybakowski J. *Negative experiences in childhood and the development and course of bipolar disorder*. Psychiatr. Pol. 2016; 50(5): 989–1000.
25. Jaworska-Andryszewska P, Rybakowski JK. *Childhood trauma in mood disorders: Neurobiological mechanisms and implications for treatment*. Pharmacol. Rep. 2019; 71(1): 112–120.
26. Tichomirowa MA, Keck ME, Schneider HJ, Paez-Pereda M, Renner U, Holsboer F et al. *Endocrine disturbances in depression*. J. Endocrinol. Invest. 2005; 28(1): 89–99.
27. Mendlewicz J, Linkowski P, Guroff JJ, Van Praag HM. *Color blindness linkage to bipolar manic-depressive illness. New evidence*. Arch. Gen. Psychiatry 1979; 36(13): 1442–1447.
28. Egeland JA, Gerhard DS, Pauls DL, Sussex JN, Kidd KK, Allen CR et al. *Bipolar affective disorders linked to DNA markers on chromosome 11*. Nature 1987; 325(6107): 783–787.
29. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H et al. *Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene*. Science 2003; 301(5631): 386–389.
30. Mullins N, Lewis CM. *Genetics of depression: Progress at last*. Curr. Psychiatry Rep. 2017; 19(8): 43.
31. Ikeda M, Saito T, Kondo K, Iwata N. *Genome-wide association studies of bipolar disorder: A systematic review of recent findings and their clinical implications*. Psychiatry Clin. Neurosci. 2018; 72(2): 52–63.
32. Goodnick PJ. *The use of nimodipine in the treatment of mood disorders*. Bipolar Disord. 2000; 2(3 Pt 1): 165–173.
33. Falret JP. *Mémoire sur la folie circulaire, forme de maladie mentale caractérisée par la reproduction successive et régulière de l'état maniaque, de l'état mélancolique et d'un intervalle lucide plus ou moins prolongé*. Bulletin de l'Académie de Médicine 1854; 19: 382–415.

34. Dunner DL, Fieve RR. *Clinical factors in lithium carbonate prophylaxis failure*. Arch. Gen. Psychiatry 1974; 30(2): 229–233.
35. Dunner DL, Gershon ES, Goodwin FK. *Heritable factors in the severity of affective illness*. Biol. Psychiatry 1976; 11(1): 31–42.
36. Parker G, Tavella G, Ricciardi T, Hadzi-Pavlovic D, Alda M, Hajek T et al. *Refined diagnostic criteria for the bipolar disorders: Phase two of the AREDOC project*. J. Affect. Disord. 2020 (in press).
37. Fieve RR, Meltzer H, Dunner DL, Levitt M, Mendlewicz J, Thomas A. *Rubidium: Biochemical, behavioral, and metabolic studies in humans*. Am. J. Psychiatry 1973; 130(1): 55–61.
38. Goodwin FK, Jamison KR. *Manic depressive illness*. Oxford: Oxford University Press; 1990.
39. Goodwin FK, Jamison KR. *Manic-depressive illness. Bipolar disorders and recurrent depression*, 2nd ed. Oxford: Oxford University Press; 2007.
40. Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Davenport Y et al. *Seasonal affective disorder: A description of the syndrome and preliminary findings with light therapy*. Arch. Gen. Psychiatry 1984; 41(1): 72–80.
41. Angst J. *Recurrent brief depression. A new concept of depression*. Pharmacopsychiatry 1990; 23(2): 63–66.
42. Angst A. *The emerging epidemiology of hypomania and bipolar II disorder*. J. Affect. Disord. 1998; 50(2–3): 143–151.
43. Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD et al. *The HCL-32: Towards a self-assessment tool for hypomanic symptoms in outpatients*. J. Affect. Disord. 2005; 88(2): 217–233.
44. Angst J, Grobler C. *Unipolar mania: A necessary diagnostic concept*. Eur. Arch. Psychiatry Clin. Neurosci. 2015; 265(4): 273–280.
45. Akiskal HS. *Dysthymia: Clinical and external validity*. Acta Psychiatr. Scand. Suppl. 1994; 383: 19–23.
46. Akiskal HS, Pinto O. *The evolving bipolar spectrum. Prototypes I, II, III, and IV*. Psychiatr. Clin. North Am. 1999; 22(3): 517–534.
47. Akiskal HS, Akiskal KK. *Special issue: TEMPS: Temperament Evaluation Temperament Evaluation of Memphis, Pisa, Paris and San Diego*. J. Affect. Disord. 2005; 85(1–2): 1–2.
48. Paykel ES, Brugha T, Fryers T. *Size and burden of depressive disorders in Europe*. Eur. Neuropsychopharmacol. 2005; 15(4): 411–423.
49. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M et al. *Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication*. Arch. Gen. Psychiatry 2007; 64(5): 543–552.
50. Rybakowski J, Sowiński J. *Free-thyroxine index and absolute free-thyroxine in affective disorders*. Lancet 1973; 1(7808): 889.
51. Rybakowski J, Potok E, Strzyzewski W. *The activity of the lithium-sodium countertransport system in erythrocytes in depression and mania*. J. Affect. Disord. 1981; 3(1): 59–84.
52. Rybakowski J, Potok E, Strzyzewski W. *Decreased activity of ouabain-dependent sodium and potassium fluxes in erythrocytes during depression and mania*. Act. Nerv. Super. (Praha) 1983; 25(1): 72–74.
53. Rybakowski JK, Lehmann W. *Decreased activity of erythrocyte membrane ATPases in depression and schizophrenia*. Neuropsychobiology 1994; 30(1): 11–14.

54. Służewska A, Rybakowski J, Bosmans E, Sobieska M, Berghmans R, Maes M et al. *Indicators of immune activation in major depression*. Psychiatry Res. 1996; 64(3): 161–167.

55. Ferensztajn-Rochowiak E, Kucharska-Mazur J, Tarnowski M, Samochowiec J, Ratajczak MZ, Rybakowski JK. *Stem cells, pluripotency and glial cell markers in peripheral blood of bipolar patients on long-term lithium treatment*. Prog. Neuropsychopharmacol. Biol. Psychiatry 2018; 80(Pt A): 28–33.

56. Płocka M, Matkowski K, Lehmann W, Kanarkowski R, Rybakowski J. *Test hamowania deksametazonem u mężczyzn i kobiet z depresją endogenną i schizofrenią*. Psychiatr. Pol. 1992; 26(5): 373–380.

57. Rybakowski J, Plocka M. *Seasonal variations of the dexamethasone suppression test in depression compared with schizophrenia: A gender effect*. J. Affect. Disord. 1992; 24(2): 87–91.

58. Rybakowski JK, Twardowska K. *The dexamethasone/corticotropin-releasing hormone test in depression in bipolar and unipolar affective illness*. J. Psychiatr. Res. 1999; 33(5): 363–370.

59. Borkowska A, Rybakowski JK. *Neuropsychological frontal lobe tests indicate that bipolar depressed patients are more impaired than unipolar*. Bipolar. Disord. 2001; 3(2): 88–94.

60. Szczepankiewicz A, Rybakowski JK, Skibinska M, Dmitrzak-Weglarz M, Leszczynska-Rodziewicz A, Wilkosc M et al. *FYN kinase gene: Another glutamatergic gene associated with bipolar disorder?* Neuropsychobiology 2009; 59(3): 178–183.

61. Permoda-Osip A, Dmitrzak-Weglarz M, Hauser J, Rybakowski JK. *Are genes connected with homocysteine metabolism associated with bipolar disorder?* Neuropsychobiology 2014; 69(2): 107–111.

62. Rybakowski JK, Skibinska M, Leszczynska-Rodziewicz A, Kaczmarek L, Hauser J. *Matrix metalloproteinase-9 gene and bipolar mood disorder*. Neuromolecular Med. 2009; 11(2): 128–132.

63. Rybakowski JK, Borkowska A, Czerski PM, Skibińska M, Hauser J. *Polymorphism of the brain-derived neurotrophic factor gene and performance on a cognitive prefrontal test in bipolar patients*. Bipolar Disord. 2003; 5(6): 468–472.

64. Rybakowski JK, Borkowska A, Skibinska M, Hauser J. *Illness-specific association of val66met BDNF polymorphism with performance on Wisconsin Card Sorting Test in bipolar mood disorder*. Mol. Psychiatry 2006; 11(2): 122–124.

65. Filuś J, Rybakowski J. *Badania stężenia czynnika neurotrofowego pochodzenia mózgowego (BDNF) w surowicy krwi u chorych na depresję*. Farmakoter. Psychiatr. Neurol. 2009; 25(1): 23–29.

66. Rybakowski JK, Suwalska A, Lojko D, Rymaszewska J, Kiejna A. *Bipolar mood disorders among Polish psychiatric outpatients treated for major depression*. J. Affect. Disord. 2005; 84(2–3): 141–147.

67. Rybakowski JK, Suwalska A, Lojko D, Rymaszewska J, Kiejna A. *Types of depression more frequent in bipolar than in unipolar affective illness: Results of the Polish DEP-BI study*. Psychopathology 2007; 40(3): 153–158.

68. Hirschfeld RM, Williams JB, Spitzer RL, Calabrese JR, Flynn L, Keck PE Jr et al. *Development and validation of a screening instrument for bipolar spectrum disorder: The Mood Disorder Questionnaire*. Am. J. Psychiatry 2000; 157(11): 1973–1875.

69. Kiejna A, Pawłowski T, Dudek D, Lojko D, Siwek M, Roczeń R et al. *The utility of Mood Disorder Questionnaire for the detection of bipolar diathesis in treatment-resistant depression*. J. Affect. Disord. 2010; 124(3): 270–274.

70. Rybakowski JK, Angst J, Dudek D, Pawłowski T, Łojko D, Siwek M, Kiejna A. *Polish version of the Hypomania Checklist (HCL-32) scale: The results in treatment-resistant depression*. Eur. Arch. Psychiatry Clin. Neurosci. 2010; 260(2): 139–144.
71. Rybakowski JK, Dudek D, Pawłowski T, Łojko D, Siwek M, Kiejna A. *Use of the Hypomania Checklist-32 and the Mood Disorder Questionnaire for detecting bipolarity in 1051 patients with major depressive disorder*. Eur. Psychiatry 2012; 27(8): 577–581.
72. Łojko D, Dudek D, Angst J, Siwek M, Michalak M, Rybakowski J. *The 33-item Hypomania Checklist (HCL-33) – A study of the consistency between self – and external assessments in Polish bipolar patients*. Psychiatr. Pol. 2016; 50(6): 1085–1092.
73. Borkowska A, Rybakowski JK, Drozdz W, Bielinski M, Kosmowska M, Rajewska-Rager A et al. *Polish validation of the TEMPS-A: The profile of affective temperaments in a college student population*. J. Affect. Disord. 2010; 123(1–3): 36–41.
74. Claridge G, McCrerry C, Mason O, Bentall R, Boyle G, Slade P et al. *The factor structure of 'schizotypal' traits: A large replication study*. Br. J. Clin. Psychol. 1996; 35(1): 103–115.
75. Dembińska-Krajewska D, Rybakowski J. *The assessment of schizotypy by the O-LIFE (Oxford-Liverpool Inventory for Feelings and Experiences) in patients with schizophrenia and affective disorders*. Psychiatr. Pol. 2016; 50(6): 1147–1156.
76. Rybakowski JK, Klonowska P. *Bipolar mood disorder, creativity and schizotypy: An experimental study*. Psychopathology 2011; 44(5): 296–302.
77. Jaworska-Andryszewska P, Abramowicz A, Kosmala A, Klementowski K, Rybakowski J. *Trauma wczesnodziecięca w chorobie afektywnej dwubiegunowej*. Neuropsychiatria i Neuropsychologia 2016; 11(2): 39–46
78. Jaworska-Andryszewska P, Rybakowski JK. *Childhood trauma in mood disorders: Neurobiological mechanisms and implications for treatment*. Pharmacol. Rep. 2019; 71(1): 112–120.
79. Bodnar A, Rybakowski JK. *Mentalization deficit in bipolar patients during an acute depressive and manic episode: Association with cognitive functions*. Int. J. Bipolar Disord. 2017; 5: 38.
80. Bodnar A, Rybakowski JK. *Increased affective empathy in bipolar patients during a manic episode*. Braz. J. Psychiatry 2017; 39(4): 342–345.
81. Dopierala E, Chrobak AA, Kapczinski F, Michalak M, Tereszko A, Ferensztajn-Rochowiak E et al. *The Biological Rhythms Interview of Assessment in Neuropsychiatry in patients with bipolar disorder: Correlation with affective temperaments and schizotypy*. Braz. J. Psychiatry 2016; 38(4): 325–328.
82. Dopierala E, Chrobak A, Kapczinski F, Michalak M, Tereszko A, Ferensztajn-Rochowiak E et al. *A study of biological rhythm disturbances in Polish remitted bipolar patients using the BRIAN, CSM, and SWPAQ scales*. Neuropsychobiology 2016; 74(2): 125–130.
83. Kapczinski F, Magalhães PV, Balanzá-Martinez V, Dias VV, Frangou S, Gama CS et al. *Staging systems in bipolar disorder: An International Society for Bipolar Disorders Task Force Report*. Acta Psychiatr. Scand. 2014; 130(5): 354–363.
84. Rybakowski J. *Oblicza choroby maniakalno-depresyjnej*, 3rd ed. supplemented. Poznan: Termedia Medical Publishing House; 2018.
85. Rybakowski J. *The faces of manic-depressive illness*. Poznan: Termedia Publishers; 2009.
86. Rybakowski J. *Liki maniakalno-depressivnogo rasstroistva*. Moskwa: Isdatelstwo DOM; 2018.
87. Rybakowski J, Jaracz J, editors. *Leksykon depresji i manii*. Poznan: Termedia Medical Publishing House; 2010.

88. Dudek D, Siwek M, Rybakowski J, editors. *Choroba afektywna dwubiegunowa – wyzwania diagnostyczne*. Poznan: Termedia Medical Publishing House; 2012.
89. Dudek D, Siwek M, Rybakowski J, editors. *Choroba afektywna dwubiegunowa – wyzwania terapeutyczne*. Poznan: Termedia Medical Publishing House; 2013.
90. Post RM. *Transduction of psychosocial stress into the neurobiology of recurrent affective disorder*. Am. J. Psychiatry 1992; 149(8): 999–1010.

Address: Janusz Rybakowski
Poznan University of Medical Sciences
Department of Adult Psychiatry
60-572 Poznań, Szpitalna Street 27/33
e-mail: janusz.rybakowski@gmail.com