

Staging of unipolar affective illness

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Summary

In this article, a concept of staging of unipolar affective illness (recurrent depression) is presented. In respective subchapters, three most important aspects of this issue have been discussed: 1) staging of unipolar affective illness; 2) staging of treatment-resistant depression; and 3) conversion of unipolar into bipolar affective illness. The evidence for so called neuroprogression of the illness, accumulated in recent years, has allowed for a classification of staging based on a concept of allostasis and allostatic load. In the course of illness, changes in neuroendocrine system (mainly hypothalamic-pituitary-adrenal axis), immunological system, mechanisms of oxidative stress, neurotransmitters, neurotrophic factors as well as structural and functional changes of the brain occur. In their paper published in 2007, Fava and Tossani elaborated a concept of staging of unipolar affective illness, presenting a continuum model of five consecutive stages with specific clinical features. In the present paper, a concept of treatment-resistant depression and staging of treatment-resistance is presented in the context of several models. An important determinant of treatment-resistant depression is so called subthreshold bipolarity which is connected with worse efficacy of antidepressant drugs. In the course of illness, there is a possibility of changing diagnosis from recurrent depression into bipolar affective illness. The studies on this issue show that frequency of such diagnostic conversion is 1.5% of depressed patients per year.

Key words: unipolar affective illness, staging, treatment-resistant depression, conversion into bipolar disorder

Staging of mental disorders

In recent years, the concept of staging has been increasingly used in regard to mental illnesses and mental disorders. Albert Broders, an American pathologist, is thought to be the precursor of this term because he, as early as in 1920s, proposed to numerate the stages of cancer, with each stage having independent prognostic importance [1]. Besides oncology, the concept of staging of given disease has been

commonly used in such fields of medicine as cardiology, nephrology, rheumatology, hepatology and neurology.

The most important paper for psychiatry in this respect is that of Fava and Kellner, published 20 years ago [2]. The authors presented a proposal of staging for such mental disorders as schizophrenia, bipolar disorder, recurrent depression, panic disorder, disorders connected with psychoactive substances, anorexia and bulimia. In recent years, the greatest interest has been focused on the concepts of staging of schizophrenia and affective disorders. The concept of staging for bipolar disorder was presented in "Psychiatria Polska" in 2012 [3]. This article pertains to the most important aspects of staging of unipolar affective disorder or periodic recurrent depression. In subsequent subchapters, three main aspects of the above issue will be discussed: 1) staging of unipolar affective disorder, 2) staging of treatment-resistant depression, 3) diagnostic conversion of unipolar affective disorder into bipolar affective disorder.

Staging of unipolar affective disorder (periodic depression)

The evidence for illness neuroprogression, accumulated in recent years, enabled to work out a classification of staging of unipolar affective disorder (UD), based on the concept of allostasis and allostatic load. The concept of allostasis, conceived in 1988 by Sterling and Eyer, assumes that in the organism occur dynamic changes in parameters of so-called mediators of allostasis, which aim at maintaining ballance and stability of internal environment in response to changing physical and social external influences [4]. The mediators of allostasis include neuroendocrine system, autonomic nervous system and immunological system, together with substances produced by these systems, such as hormones of the hypothalamic-pituitary-adrenal (HPA) axis, catecholamines and cytokines. Regaining a state of balance, that is state of allostasis, is connected with, among others, altered diurnal cortisol secretion and chronic increase of proinflammatory cytokines. With prolonging effect of stressors on organism and exhaustion of compensatory mechanisms, the state of allostatic load develops, exerting noxious, and sometimes irreversible effect on the functioning of the whole organism. Eventually, the brain, a superior controller of allostatic systems starts to bear a burden of allostatic load, expressed, among others, as disturbances in plasticity and structural changes [5].

The concept of neuroprogression assumes that psychosocial and physical stressors together with existing vulnerability (genetic factors, cellular damage) lead to the first episode of illness. In contrast, further episodes appear to be more independent of occurring stressors. Post [6] was the first who introduced this concept as kindling theory, focusing on the problem of treatment resistance. Interactions of biochemical factors result in cellular damage, increased apoptosis and reduction in growth and survival of neurons. These processes lead to increase of treatment-resistance and vulnerability to further episodes. Additionally, each episode is associated with progressive deterioration of cognitive functions and global functioning, as well as with structural changes within the brain.

UD is characterized by chronic inflammatory state and cell-mediated immune activation independent of the presence of the pathogen. In recent meta-analyses, increased levels of proinflammatory cytokines: interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α) and activation of T-cells (lymphocytes), caused by elevated level of serum soluble IL-2 receptor, have been confirmed. Furthermore, alterations in levels of inflammatory markers, such as C-reactive protein (CRP), correlate with the number of previous depressive episodes [7], and levels of IL-1 and TNF- α are considerably higher in patients with three and more depressive episodes. Each episode intensifies inflammatory response and increases probability of new episode. Excessive inflammatory response is connected with a reduction in the brain-derived neurotrophic factor (BDNF) expression, what increases neurotoxicity, cell death, myelin and endothelium damage and free radicals production [8].

Decreased levels of antioxidants, such as coenzyme Q10, vitamin E, zinc, glutathione, as well as lowered activity of antioxidant enzymes, including glutathione peroxidase, occur in UD [9]. Excessive oxidative and nitrosative stress leads to peroxidation of lipids, damage of proteins, DNA and mitochondria and to initiation of autoimmune responses, directed against neoepitops of fatty acids and proteins [10]. The damage caused by oxidative-nitrosative stress (e.g. excessive production of nitric oxide or impairment in mitochondrial oxidative metabolism) and subsequent autoimmune responses are the main causes of illness neuroprogression, leading to disturbances in cell signalling, mitochondrial damage, impairment of axon regeneration and intensification of apoptosis.

Neurobiological disturbances induced by stress, psychoactive substances abuse and subsequent episodes, presented as a methylation of DNA and methylation or acetylation of histones, are written down on epigenetic level and may persist longitudinally, being a kind of preserved "biological scar" or memory trace that increase vulnerability for the emergence of further episodes [11].

Dysfunction of serotonergic system in UD is characterized by increased activity of the enzyme metabolizing tryptophan (indoleamine 2,3-dioxygenase, IDO) (probably caused by proinflammatory cytokines) through kynurenine pathway, which leads to a decrease of serotonin and tryptophan levels and elevation of serum and brain levels of kynurenic and quinolinic acid. Noxious catabolites of tryptophan cause an impairment of antioxidant defence, intensification of oxidative stress, decrease of ATP production by mitochondria, increase of excitotoxicity and reduction of neurogenesis [12]. It was also demonstrated that in patients with UD, especially in those with melancholia, significantly higher titers of antiserotonin antibodies occur, compared with control group, and autoimmune processes are more intense in patients with three prior episodes, than in those with one or two episodes. It shows that autoimmune response directed against serotonin may cause significant disturbance of this neurotransmitter metabolism and it is significantly associated with the number of previous episodes [13].

A connection has been suggested between depressive symptoms and the effect of inflammatory response on noradrenergic system, related to a decrease of adrenergic axons density caused by interferon- α . Furthermore, patients with UD have a diminished

turnover of homovanilic acid, the primary dopamine metabolite, and repeated stress can lead to a sensitization of dopaminergic mesolimbic system by increased levels of glucocorticoids [14]. Portella et al. [15] demonstrated alterations of glutamatergic acid and choline levels, depending on illness duration. Glutaminic acid levels in ventro-medial prefrontal cortex measured with magnetic resonance spectroscopy were negatively correlated with duration of illness, and choline levels showed positive correlation in this respect.

The studies in UD have demonstrated a hyperactivation of HPA axis and disturbances in feedback mechanism manifested by increased cortisol levels and disturbances of diurnal cortisol secretion, dysfunction of glucocorticoid receptors, elevated secretion of corticotrophin-releasing hormone (CRH) and abnormal results of dexamethasone suppression test. Maes et al. [16] found that hyperactivity of HPA axis can be associated with higher production of proinflammatory cytokines, and that impaired feedback mechanism of HPA axis in depression can result from processes dependent on IL-2 and IL-1beta. A correlation between the lack of suppression of cortisol secretion in dexamethasone test and illness duration, and a risk of recurrence has been reported [17], as well as a correlation between increased secretion of ACTH and cortisol in the dexamethasone/CRH test and the number of recent episodes and recurrence risk [18].

Abnormal levels of neurotrophic factors levels in depression, mainly decreased levels of BDNF, leading to impairment of neurogenesis in hippocampus and to decreased survival of cells through intensification of apoptosis, have been demonstrated. Additionally, BDNF level may correlate with severity and recurrence of UD. The BDNF level is lower in patients before treatment, compared to treated ones, and the decrease in BDNF level may delay improvement. Decreased BDNF expression may cause a vulnerability to illness, as a consequence of diminished neuronal reserve and neuronal survival [19].

All components of allostatic load are connected with the brain changes parallel to a stage of illness, thus providing the evidence for structural neuroprogression. The main finding, confirmed in several meta-analyses, is a decreased volume of the hippocampus related to the number of previous episodes, but also to the duration of illness [20, 21]. Structural changes in other brain regions, such as amygdala, orbitofrontal cortex, anterior cingulate cortex, basal ganglia and pituitary gland, have also been demonstrated [22]. A positive correlation between the number of previous episodes and a decrease of insular cortex volume, as well as negative correlation with metabolism in subgenual anterior cingulate cortex measured by positron emission tomography (PET), has been reported [23].

Fava and Tossani, in their paper from 2007 [24], developed the concept of staging of UD as a continuum model of five consecutive stages. The first stage (prodromal phase) is characterized by the presence of risk factors without any depressive symptoms (stage 1a) or by subdepressive symptoms not achieving severity of the depressive episode (stage 1b). The most frequent symptoms include anxiety, restlessness and irritability, as well as anhedonia and sleep disturbances. The symptoms which correlate to the greatest extent with the occurrence of depressive episode are: feeling of worthlessness

ness and death wish. At this stage, stressful life events influence prodromal symptoms and persons who have experienced life adversities, and show symptoms of illness, are more vulnerable to the occurrence of depression [25]. Prodromal symptoms (e.g. anxiety, irritability) are connected with decreased serotonin metabolism in the central nervous system, disturbances of 5HT1A and 5HT2 receptors and of the HPA axis function [26].

The first episode of depression (stage 2) may occur after intensification of subdepressive symptoms. Subsequent is the residual phase (stage 3) where full remission occurs without any symptoms of illness (stage 3a) or dysthymia (stage 3b) can be diagnosed. The presence of residual symptoms is connected with negative prognosis, risk of recurrence, suicide, or chronic course [27]. The staging model emphasizes similarity between prodromal and residual symptoms and their association with increased risk of relapse. It turned out that 70% of residual symptoms appear also in prodromal phase of the illness, with 90% rate for generalized anxiety and irritability [28]. The remaining, most frequent residual symptoms are: decrease of everyday activity, depressed mood, feeling guilty, lack of appetite, fatigue and insomnia.

The 4th stage is characterized by recurrences (stage 4a), and if dysthymia was previously present, the diagnosis of “double depression” is made (stage 4b). The most important risk factors of recurrence are the presence of residual symptoms, together with the altered parameters of biological markers (e.g. the dexamethasone suppression test). In the stage 5, the course of illness is chronic, with the duration of episode over two years, without any remission period.

Somatic illnesses comorbid with depression can be considered as resulting from the number of previous episodes. In this context, co-morbidity has close connection with premature deaths of patients, because the number of potential lost years of life has been estimated as 13-28 years, mostly due to cardiovascular illnesses [29]. Depression also makes a risk factor for lifetime development of dementia: an association between the number of the previous episodes and the risk of lifetime dementia was found, with the two-fold increased risk after 4 episodes and increased risk after every subsequent episode [30]. Cusci et al. [31] reported that the number of prior episodes correlated with a decrease of empathy, and Gorwood et al. [32] observed correlation between impairment of delayed memory (delayed recall) and the number of previous episodes and illness duration.

The staging model of UD not only allows us to assess severity of the illness, but also takes into consideration other factors, such as the presence of social support, adaptive mechanisms, resilience, reaction to stressful events, losses experienced in the past, premorbid personality and personality traits, as well as patient motivation and cooperation in treatment. Apart from diagnosing during current episode, the staging method locates each patient on the continuum of the illness, providing the most optimal therapeutic strategy and evaluation of outcome. In response to these needs, the concepts of staging of UD related to the stages of treatment-resistance have been developed in the recent years.

**Table 1. Staging of unipolar affective disorder
(according to Fava and Tossani (2007), modified)**

Stage	Characteristic
Stage 1 (prodromal phase)	Risk factors without any depressive symptoms (stage 1a) or with subdepressive symptoms, not achieving severity of the depressive episode (stage 1b)
Stage 2	First episode of depression
Stage 3	Residual phase with full remission (stage 3a) or dysthymia (stage 3b)
Stage 4	Recurrence (stage 4a) or "double depression" if dysthymia was presented previously (stage 4b).
Stage 5	Chronic course of illness (duration of depressive episode over two years)

Staging of treatment-resistant depression

The concept of treatment-resistant depression (TRD) was introduced 40 years ago [33] and since then much attention has been paid to its criteria and therapeutic strategies. The staging of treatment-resistant depression is a part of broader approach to the concept of staging of UD. The knowledge about staging of the illness can help to optimize treatment and predict further course in patients who, hitherto, have been perceived uniformly, both in prognostic and therapeutic aspects, because of having the same diagnosis [34].

Most commonly used definition of TRD is a lack of remission following two courses of treatment with antidepressants of different mechanisms of action, which were used in adequate doses and for sufficient time, with patient being fully cooperating. Some researchers suggest including to TRD criteria the lack of efficacy of electroconvulsive therapy (ECT) and relapse within the same episode after significant clinical improvement [35, 36].

A sufficient time for treatment means at least 6-8 weeks of using maximal tolerated therapeutic doses of antidepressants, properly matched to a given patient, i.e. taking into account type of depression, type of affective disorder, as well as limitations and contraindications for the drug.

Duration of antidepressant treatment necessary to reach a good therapeutic result in patients with TRD may last even 10 weeks, and in elderly patients, a significant improvement may appear after 12 or more weeks. It has been also assumed that the diagnosis of treatment-resistant depression requires minimum of 16 points on 17-items Hamilton Depression Rating Scale (HDRS) [37].

The resistance to pharmacological treatment of depression can be modulated by various additional factors – clinical, biological and socio-demographic ones. One should take into account the type of depression (melancholic, psychotic, atypical), comorbidity with other psychiatric disorders (especially anxiety disorders, personality disorders, alcohol or psychoactive substance abuse), as well as sex and age of illness onset. Some data show that the therapeutic effect of tricyclic antidepressants (TCA) is weaker in women than in men, on the other hand, the effect of selective serotonin reuptake

inhibitors (SSRI) and monoamine oxidase inhibitors (MAOI) is better in women than in men. Some researches revealed that family history of affective disorders has been associated with earlier onset and chronic course of the illness, which are themselves risk factors of treatment-resistant depression [38, 39].

In the last review of this issue published in 2012, Ruhe et al. [40] mention several models of staging of treatment-resistant depression. The first model, suggested by Thase and Rush in 1997 [41] identifies 5 stages of treatment resistance of depression. Their classification is based on the number and type of antidepressants that have been ineffective; in the order from more often used (TCA, SSRI) to less often methods (MAOI, ECT). Stage 1 means at least one treatment failure of antidepressant from two main groups. Stage 2 is defined as at least two ineffective treatments with two antidepressants from two different groups. Stage 3 fulfils the criteria of stage 2 plus failure of adequate treatment with TCA. Stage 4 fulfils the criteria of stage 3 plus failure of adequate treatment with MAOI. Stage 5 fulfils the criteria of stage 4 plus failure of treatment with ECT. Limitation of this model results from not taking into account a degree of intensity of each therapy – with respect to dose and duration, and also not considering the role of augmentation and combination therapy.

The second classification is the European Staging Method [42]. The basis for this model is the lack of improvement after one adequate treatment with antidepressant, given in therapeutic dose for 6-8 weeks. Treatment-resistant depression (TRD) denotes the resistance to two or more attempts of proper treatment, with following duration of the therapy: for TRD 1: 12-16 weeks; for TRD 2: 18-24 weeks; for TRD 3: 24-32 weeks; for TRD 4: 30-40 weeks; for TRD 5: 36 weeks – 1 year. Treatment-resistant chronic depression means the resistance to different therapeutic strategies, including potentiation, with duration of the therapy for at least 12 months. This classification introduces a concept of chronic treatment-resistant depression, which stands for an episode of treatment-resistant depression lasting more than a year, despite adequate treatment.

The next model of staging for the TRD is the Massachusetts General Hospital Staging Method (MGH-S) [43]. This classification takes into account the number and intensity of treatment failures, and also all activities aimed to optimize each therapeutic intervention, with special focus on ECT failure. The model to the greatest extent accommodates for various factors influencing treatment-resistance of depression, and thus may be more reliable than other classifications. Its limitation is connected with the quality of data, which are obtained from patient or medical records. Some reservations can be also raised for its scoring, corresponding to each therapeutic attempt which has not been empirically confirmed: 1) lack of the therapeutic response to any adequate treatment (at least 6 weeks of proper dose of antidepressant) with any registered antidepressant gives an estimation of the intensity of resistance as 1 point for each attempt of treatment; 2) Optimization of dose and duration of the treatment, augmentation or combination therapy (according to Massachusetts General Hospital Antidepressant Treatment Questionnaire) increases total result by 0.5 point for each attempt or augmentation; 3) The use of ECT increases total result by 3 points. Research comparing the Massachusetts General Hospital Staging Method and the Staging Model

of Thase and Rush indicates that the first one is much more useful to predict the lack of remission, although, the results obtained with both of these models were strongly correlated.

The last classification presented here is the Maudsley Staging Method (MSM) [44]. It is a multidimensional model, taking into account the number of treatment failures (including augmentation and ECT) as well as factors connected with depression, such as intensity of symptoms and duration of depressive episode. According to this model the staging of present episode is a digital result between 3 and 15. The MSM model proved to be useful for estimating both short- and long-term results of the treatment of depression; patients with higher score on admission had greater probability that they will not reach remission on release from hospital; higher score on MSM was also connected with longer duration of depressive symptoms following 7 years after hospitalization. Scored parameters for MSM are: duration of depressive episode, 3 points for chronic course (> 24 months), intensity of symptoms – from subthreshold (1 point) to very severe with psychotic features (5 points); number of treatment failures – with 5 levels, e.g. level 1 means treatment failure with 2 antidepressants and it scores 1 point, level 5 means more than 10 ineffective treatments with antidepressants and it scores 5 points. For each augmentation and for ECT, 1 point is given.

In recent years, the issue of treatment-resistant depression is increasingly considered in the context of patients' population in which spectrum of bipolar affective disorder, or so-called subthreshold bipolarity is recognized. It has been demonstrated that such a population makes a significant percentage of patients diagnosed with first or subsequent episode of depression. The study of German researchers published in 2009 included 2210 persons, aged 14-24, living in Munich district. The features of subthreshold bipolarity were found in 41.4% of patients among 488 people diagnosed with current or past depressive episode [45]. In 2011, Angst et al. [46] presented the results of BRIDGE trial performed on 5635 patients with depressive episode. 903 patients (16%) fulfilled DSM-IV criteria for bipolar affective disorder, additionally, in 31% of patients some features of bipolarity were revealed (bipolar specifier criteria).

The results of the Polish TRES-DEP trial aimed to assess the utility of the Mood Disorder Questionnaire (MDQ) and the Hypomania Checklist-32 (HCL-32) for diagnosing bipolarity among patients with first or recurrent depressive episode and to estimate the role of bipolarity in such patients in the context of worse effect of antidepressants correspond with this results. 150 psychiatric centres from all regions of Poland and for the final analysis 1051 patients (299 men, 752 women) were included in the study. Criteria for bipolarity according to HCL-32 were fulfilled by 37.5% of patients, and according to MDQ, by 20% patients. Persons with positive results of HCL-32 and MDQ were characterized by more frequent family history of psychiatric disorders (depression, bipolar affective disorder, alcoholism, suicidality) and worse course of the disorder (earlier onset, more depressive episodes, more hospitalizations, more suicidal attempts). Significantly greater intensity of bipolar features, according to HCL-32 and MDQ, was found in patients with depression in whom the effect of antidepressant drugs was unfavourable [47].

Worse therapeutic reaction to antidepressant drugs is one of the most significant consequences of subthreshold bipolarity. The author of this article made the review of studies performed in recent years concerning the efficacy of antidepressants in relation to bipolar features and also augmentation of antidepressants by mood stabilizing drugs used in bipolar disorder [48]. The analysis showed a significant relationship between lower efficacy of antidepressants and features of bipolarity in patients with diagnosis of depression. It turned out that not only mood stabilizers of 1st generation (mainly lithium) are effective for augmentation of antidepressants in treatment-resistant depression, but such effect was also observed for mood stabilizers of 2nd generation, such as lamotrigine and atypical antipsychotics (mainly quetiapine, olanzapine, aripiprazol). Some of the latter have already received an official recommendation for such an use.

Table 2. Staging models of treatment-resistance of unipolar affective disorder

Classifications of treatment-resistance of depression	Criteria
Thase and Rush Method [41]	5 stages of treatment resistance of depression Stage 1. ≥ 1 treatment failure of antidepressant from two main groups; Stage 2. ≥ 2 ineffective treatments with two antidepressants from two different groups; Stage 3. criteria of stage 2 plus failure of adequate treatment with TCA; Stage 4. criteria of stage 3 plus failure of adequate treatment with MAOI; Stage 5. criteria of stage 4 plus failure of treatment with ECT
European Staging Method [42]	Lack of improvement after 1 adequate treatment with antidepressant given in therapeutic dose for 6-8 weeks TRD: resistance to ≥ 2 attempts of adequate treatment TRD 1: treatment 12-16 weeks; TRD 2: treatment 18-24 weeks TRD 3: treatment 24-32 weeks TRD 4: treatment 30-40 weeks TRD 5: treatment 36 weeks – 1 year Chronic TRD- resistance to different therapeutic strategies, including potentiation, duration of therapy for at least 12 months
Massachusetts General Hospital Staging Method (MGH-S) [43]	Takes into account the number and intensity of treatment failures, and also all activities aimed to optimize each therapeutic intervention, with special focus on ECT failure

table continued on the next page

Maudsley Staging Method (MSM) [44]	<p>The number of treatment failures (including augmentation and ECT) and intensity of symptoms and duration of depressive episode</p> <p>Scored parameters : duration of depressive episode, intensity of symptoms, number of treatment failures</p> <p>Five levels of resistance:</p> <p>level 1 – treatment failure with 2 antidepressants and it scores 1 point</p> <p>level 5 – more than 10 ineffective treatments with antidepressants and it scores 5 points</p> <p>Each augmentation and ECT scores 1 point</p>
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TCA – tricyclic antidepressant; MAOI – monoamine oxidase inhibitor; ECT – electroconvulsive therapy; TRD – treatment-resistant depression

Diagnostic conversion of recurrent depression into bipolar affective illness

An important element of the course of unipolar affective illness is a possibility of its conversion into bipolar disorder (BD). Subthreshold bipolarity is connected with a resistance of depression to treatment with antidepressant drugs and, on the other hand, treatment-resistant depression can be a risk factor for conversion from unipolar depression into bipolar affective illness. The biggest study on this issue has been performed by Taiwan researchers including two cohorts of depressive patients (1485 in 2000 and 2459 in 2003) in the context of subsequent conversion into BD. In 7.6-12.1% of patients the conversion occurred within 2-3 years, more frequently in patients with treatment-resistant depression (approx. 26%) than with treatment non-resistant depression (approx. 8%) [49].

Bipolar affective illness, in 50% of cases, begins with a depressive episode. Variable number of subsequent depressive episodes occur until the evident and diagnosable hypomanic or manic episode appears, and meanwhile, the diagnosis of recurrent depression is made. This may last several years which has been reflected in the results of epidemiological studies indicating that in 1/3 of patients a time lag from first symptoms (mainly depressive) to making diagnosis of BD is about 10 years [50].

The NIMH Collaborative Depression Study including 559 patients with depression showed that during 11-year follow-up: in 8.6% of patients, the diagnosis has been changed into BD II, and in 3.9% of patients into BD I [51]. Much higher figures were obtained by Goldberg et al. [52] in 74 patients with depression during 15-year follow up: in 27% of them, a diagnosis was changed into BD II, and in 19% into BD I.

Angst et al. [53] assessed 406 patients who have been examined for averagely 20 years after first depressive episode. Diagnostic change into BD I had a frequency of 1% of patients per year, and into BD II – 0.5% of patients per year. The risk factors for conversion to BD I included male sex and early onset of illness, and for BD II – female sex, later onset of illness and family history of (hypo)mania. In conclusion,

the authors state that the risk of diagnostic conversion from recurrent depression into bipolar disorder is constant and amounts to 1.5% of depressed population per year and each new episode of depression increases the risk of mania or hypomania.

In 2013, the only Polish study on diagnostic conversion from recurrent depression into bipolar affective illness, coming from Krakow centre, was published. This was a retrospective study of medical records of 122 patients with initial diagnosis of depression, followed-up for 5-37 years (mean 18 years). Diagnostic conversion was ascertained in 40 patients (32.8%), averagely after 9.3 years (+8.6) of observation. The frequency of the conversion was 1.8% per year, and it was more frequent in patients with early onset of illness, greater number of episodes, greater number of hospitalizations, and in patients with depression resistant to treatment with antidepressant drugs [54].

Recent meta-analysis of this issue performed by Baldessarini et al. [55] involved 12 studies, including the Polish study carried out by Dudek et al. [54]. Total population of patients studied was 58,000, the biggest contribution to which was made by the study of Martin et al. [56] including 50,000 patients and by Li et al. [49] study, mentioned earlier. The mean frequency of the conversion from unipolar to bipolar illness in this analysis was 1.79% (CI 1.1-2.48), which is similar to the results of Angst et al. [53], as well as to those of the Polish study [54].

The paper of Danish authors published in 2013 included 8588 patients with unipolar depression having psychotic symptoms, observed in the period of 1995-2007. During this time in 609 of them (7.1%) the diagnosis was changed into bipolar affective illness. Several risk factors of diagnostic conversion were found, such as: early onset of illness, frequent recurrences of depression, living alone, receiving a disability pension, and lower education level [57].

Concluding remarks

As shown in the present article, staging of unipolar affective illness can be considered in several aspects: pathogenic, therapeutic and diagnostic ones. A pathogenic aspect is connected with a neuroprogression of the illness conceptualized in the context of allostasis and allostatic load. This allows for identifying stages of the course of illness, having specific clinical features and biochemical changes. A therapeutic aspect is connected with the resistance of depression to treatment and can be regarded in the context of several staging models of treatment-resistant depression. An important determinant of treatment-resistant depression is so called subthreshold bipolarity which is connected with worse efficacy of antidepressant drugs. A diagnostic aspect deals with a possibility of diagnostic change during the course of illness from recurrent depression into bipolar disorder. The studies of this issue indicate that the frequency of such diagnostic conversion amounts to 1.5% of population of depressed patients per year.

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