The Development of the Bipolar Spectrum Theory: Concept, Clinical Presentation, and Diagnostics

Zsuzsanna Belteczki[1]

[1] *SZSZBVK- Nagykállói Sántha Kálmán Tagkórház*

In my narrative paper, I describe the development of the bipolar spectrum concept and its clinical heterogeneity observed in everyday practice. I review relevant findings from biological marker research and phenomenology-based screening tools. Furthermore, I provide an overview of the advantages and disadvantages of the bipolar spectrum theory, as well as the challenges of diagnosis.

(Neuropsychopharmacol Hung 2025; 27(4): 282–295)

Keywords: bipolar disorder, bipolar spectrum disorder, biomarker, psychodiagnostics

THE SPECTRUM PERSPECTIVE ON BIPOLAR DISORDER: EVOLUTION OF THE CONCEPT

The concept of the bipolar disorder (BD) spectrum dates back to antiquity, appearing in the works of Aretaeus and Avicenna (Altinbas et al., 2011). However, Kraepelin was the first to propose that there is a continuum between psychotic and less severe affective disorders, which merges without sharp boundaries with personality predisposition and "normality" (Kraepelin, 1921).

The dimensional perspective was supported by Kretschmer and later by Bleuler. In their classification of affective disorders, they distinguished between cyclothymic temperament, cycloid "psychopathy", and manic-depressive illness (Kretschmer, 1921; Bleuler, 1922; Fountoulakis, 2015).

According to Angst's simple model, the classification is as follows:

M: severe mania, D: severe depression, m: hypomania, d: less severe depression. Different combinations constitute the bipolar spectrum (MD/DM = BD-I; mD = BD-II; md = cyclothymia) (Angst, 1978).

Klerman revived this concept in the 20th century, distinguishing six subtypes:

1. mania (+/– depression)
2. hypomania (+/– depression)
3. hypomania with depressive symptoms
4. mania or hypomania resulting from substance use or physical illness
5. depression with a family history suggestive of bipolar disorder
6. unipolar mania (– depression) (Klerman, 1981).

According to a later theory, the bipolar spectrum disorder (BSD) encompasses recurrent major depressive disorder (MDD), dysthymia, cyclothymia, depressive, hyperthymic, and cyclothymic temperament, as well as mixed mood episodes, hypomania and BD types I and II (Akiskal & Mallya, 1987; Akiskal, 2000; Gonda & Vazquez, 2014).

It has long been recognized that the clinical manifestations of both bipolar and unipolar affective disorders include several "intermediate" phenotypes, ranging from the mildest to the most severe forms. In his 1981 review article, Rihmer was among the first in the international literature to apply the terminology

of the unipolar and bipolar affective spectrum (Rihmer,1981). In contrast to BSD, the unipolar depressive spectrum encompasses only depressive conditions. These include subthreshold depressive symptoms, dysthymia/persistent depressive disorder, MDD and chronic or treatment-resistant depression (TRD). This continuum aids in understanding the subclinical forms recognized as risk factors for MDD, as well as comorbidity and the associated biological and cognitive markers (Akiskal et al., 1995; Angst & Merikangas, 1997; Judd & Akiskal, 2000).

In the early 1980s, Koukopoulos adopted a different approach, focusing on the analysis of specific mood episodes. He argued that the DSM-III BD/MDD dichotomy was inadequate because most affective episodes were not stylistically pure, than mixed, making it impossible to establish a stable and valid nosology for a phenomenon that was rare or even non-existent (Koukopoulos et al., 2007).

Akiskal, followed by Pinto and Perugi, broadened the concept of the bipolar spectrum by introducing the "soft BSD" concept, according to which depressive and hypomanic symptoms, as well as temperamental traits, are mixed (Akiskal & Pinto, 1999a; Perugi & Akiskal, 2002). Affective temperaments (AFTs) are behavioural endophenotypes corresponding to the inner core of personality. They represent fundamental affective dispositions, imparting emotional colouring to experiences and perceptions and shaping behavioural and emotional responses, biological rhythms and activity levels (Akiskal & Akiskal, 1992a; Tomassini et al., 2009; Gonda et al., 2009; Rihmer et al., 2010; Silva et al., 2017).

Underlying this is the cyclothymic–anxious–sensitive disposition, which results in mood reactivity and interpersonal sensitivity (Perugi & Akiskal, 2002; Rihmer et al., 2013).

Their classification is as follows:

BD-½: schizo-bipolar disorder: mood-incongruent psychotic symptoms are present;

BD-I: full-blown mania: characterized by euphoric, ecstatic mood, aggressive manifestations, grandiose delusions, loss of self-reflection and judgment, uncontrolled activity, and severe impairment of interpersonal functioning;

BD-I ½: depression with protracted, intense hypomanic symptoms;

BD-II: characterized by depressive and hypomanic episodes. A major depressive episode (MDE) is severe, with hypomania lasting at least four days;

BD-II ½: MDE develops on the basis of cyclothymic temperament. In such cases, mood swings without apparent cause, sensitivity, pessimism, guilt, sleep disturbances, and feelings of dissatisfaction are common. "Dark hypomania" (increased activity and irritability alongside a negative affective state) is particularly characteristic. The cyclothymic temperament shows a distinctive pattern of hypomanic or irritable and mild depressive moods, with corresponding fluctuations in cognition and behaviour. Kraepelin described this temperament as an alternation between the two basic types: hyperthymic and depressive;

BD-III: recurrent depression followed by antidepressant-induced hypomania. It is common for BD to occur in the family;

BD-III ½: hypomania and/or depression associated with psychoactive substance use. BD is often masked or exacerbated by the use of such substances, which further impair mood regulation.

BD-IV: MDE develops on a hyperthymic temperament background; this temperament type is explosive, cheerful, high-energy, associated with leadership roles, risk- and novelty-seeking, socially norm-defying, generous and spendthrift;

BD-V: recurrent depression with dysphoric hypomania. The latter indicates a mixed episode, with racing thoughts, psychomotor agitation and a depressive mood;

BD-VI: dementia with late-onset depression and mixed affective symptoms;

(Kraepelin 1921; Possl J, von Zerssen 1990; Akiskal és Pinto, 1999a; Perugi és Akiskal, 2002; Angst, 2007; Tomassini et al., 2009; Rihmer et al., 2010; Vazquez és Gonda, 2013; Silva et al., 2017; Cervona et al., 2021; Deliyannides, 2024).

Ghaemi's concept is detailed, taking into account features such as family history, AFTs, clinical features of MDE, and psychopharmacological properties (phase shift, resistance) (Ghaemi, 2004; Hede et al., 2019). His theory partially overlaps with Akiskal's definition.

Ghaemi conceptualizes BSD as requiring simultaneous fulfilment of criteria A and B or fulfilment of one item from criteria C, two items from criteria D, or both items from C.

The items are as follows:

A: at least one MDE;

B: no spontaneous hypomanic/manic symptoms;

C: 1. BD among first-degree relatives;
2. antidepressant-induced hypomania/mania;

D: if none of the items from C are present, six of the nine items from D must be met:
1. hyperthymic personality;

2. recurrent MDEs (more than three);
3. short MDEs (lasting on average less than three months);
4. atypical depressive features (increased appetite and excessive sleepiness);
5. MDE with psychotic symptoms;
6. early-onset MDE (onset before age 25);
7. postpartum depression;
8. reduced antidepressant efficacy (acute response present, but no prophylactic response);
9. reduced treatment response—MDE unresponsive to more than three antidepressants (Ghaemi, 2004).

In diagnostic systems, DSM-III distinguished BD, defined by the presence of a manic episode, from unipolar depression (DSM-III, 1980). In DSM-IV, BD-I and BD-II—previously separated by Dunner—were differentiated (Dunner, 1976; DSM-IV, 1994). In DSM-5, alongside a more precise definition of episode duration, specifiers were introduced (with anxiety, mixed, melancholic, atypical, mood-congruent/incongruent psychotic features, catatonia, and rapid cycling) (DSM-5, 2013). For a BD-I diagnosis in DSM-5, the criteria for a manic episode must be met. A manic episode may be preceded or followed by hypomanic or depressive episodes. For a BD-II diagnosis, the criteria for at least one current or past hypomanic episode and one current or past MDE must be met (DSM-5, 2013). Although DSM-5 TR does not mention BSD, conditions related to BD in which not all diagnostic criteria are fulfilled are categorized under "other specified bipolar and related disorders" (DSM-5 TR, 2024; Kaltenboeck et al., 2016; Hede et al., 2019). The use of standardized diagnostic criteria in both ICD-11 and DSM-5 TR has improved diagnostic accuracy; however, the wide variety of symptom combinations and overlap with other psychiatric disorders results in significant clinical heterogeneity (DSM-5 TR, 2022; ICD-11, 2024; Oliva et al., 2024).

According to the classification of the major diagnostic systems, MDD and BD are clearly distinguished; however, in everyday practice, mood disorders are heterogeneous and dynamic in nature, and their clinical profiles vary (Rihmer, 1978; Fountoulakis, 2015).

From a dimensional perspective, BD and MDD represent the two ends of a spectrum, with depressive and (hypo)manic symptoms appearing in varying degrees and combinations across the spectrum (Chakrabarty & Yatham, 2019).

BSD, as thus defined, does not have clear diagnostic criteria and is likely a heterogeneous group of conditions (Hede et al., 2019). The BSD concept has been supported by several studies with 5–15-year follow-up. Two of these formed part of the STEP-BD programme. These studies showed that 9–40% of patients with MDD experienced a manic or hypomanic episode during follow-up, leading to a change in diagnosis to BD (Akiskal et al., 1995; Truman et al., 2007; El-Mallakh et al., 2008; Reddy, 2012).

Today, the concept of BSD reflects two complementary perspectives:

1. The spectrum of severity, which encompasses psychotic and nonpsychotic major and minor bipolar disorders;
2. The proportional model, which, based on Kleist's original idea, considers depression and mania as separate components, and further distinguishes major and minor mood disorders within these (Kleist, 1937; Fountoulakis, 2015).

To establish a BSD diagnosis, a logical or clinical link should be identified that connects the various conditions. In studies, certain features of MDE have been highlighted as potential predictors of BD/BSD. These include psychomotor agitation, aggressiveness, subthreshold hypomania, mixed symptoms, association with certain affective temperaments (cyclothymic, hyperthymic, irritable), anxiety, substance use, and a family history of affective disorder (Verdolini et al., 2017; Hede et al., 2019).

Several authors emphasize the relationship between TRD and BD/BSD. In 57% of TRD cases, the 32-item Hypomania Checklist was positive, and 11.6% of patients met DSM-IV criteria for BD (Angst et al., 2005; Döme et al., 2021). The rate of depression resistant to antidepressant monotherapy is 41–65% among BD patients, compared to 18–32% in MDD, and according to most (though not all) findings, this also applies to BSD (Perlis et al., 2011; Rihmer et al., 2016). It is now recognized that the bipolar nature of MDD (even at a subsyndromal level) is one of the most common causes of TRD (Correa et al., 2010; Rihmer et al., 2016; 2017; Perugi et al., 2019; Bschor & Kiralski, 2016).

PREVALENCE OF BSD

Given the lack of standardized diagnostic criteria for BSD, prevalence estimates for this spectrum of disorders vary substantially, largely depending on sample characteristics and the operationalization of diagnostic thresholds (Hede et al., 2019).

One study estimated the prevalence of BSD at 6% in the general population, whereas a prospective 20-year longitudinal investigation suggested that up to 24% of the population may be affected (Judd & Akiskal, 2003; Angst et al., 2003; Ferrari et al., 2011; Hede et al., 2019).

In a large clinical sample, using more leniently operationalized criteria, BSD was diagnosed in 40% of psychiatric outpatients (Akiskal & Benazzi, 2005; Hede et al., 2019).

Based on a survey conducted on a representative sample, the lifetime prevalence rates of BD-I and BD-II in the Hungarian population were 2.9% and 2.0%, respectively, ranking among the highest worldwide. When the lifetime prevalence of cyclothymia (2.2%) is included, the three most prominent forms of BSD affect 7.1% of the adult population in Hungary (Szádóczky et al., 1998; 2000). Consistent with these findings, in a normative adult sample in Hungary, the prevalence of cyclothymic, hyperthymic, and irritable temperaments (referred to as the "three bipolar temperaments") was 4.2%, 3.0%, and 2.7%, respectively, amounting to a total of 9.9% (Rózsa et al., 2008).

According to recent international studies, the aggregated lifetime prevalence of BD-I ranges from 0.6% to 1.4%, that of BD-II from 0.4% to 0.5%, and that of BSD is 3.8% (including bipolar disorder with subthreshold symptoms) (Merikangas et al., 2011; 2011; Kim et al., 2011; Azorin & Belzeaux, 2015; Hede et al., 2019). The lifetime prevalence of cyclothymia has been estimated at approximately 0.4–1% (Azorin & Belzeaux, 2015). In the United States, among primary care patients, the use of the Mood Disorder Questionnaire (MDQ) yielded a positive screening result for lifetime BD in 9.8% of cases (Hirschfeld et al., 2000; Hede et al., 2019).

The rate at which BSD transforms into "classic" BD also remains unclear. According to Azorin and Belzeaux, during a five-year follow-up period, 5–15% of patients with type II bipolar disorder may experience a manic episode. In cyclothymia, the risk of developing type I or II BD is estimated at 15–50% (Azorin & Belzeaux, 2015).

Other studies indicate that in adults followed for 5–10 years, transition from BD-II to BD-I occurs in 5–7.5% of cases. In children and adolescents, however, prospective follow-up over 2–4 years shows a substantially higher transformation rate of 20–25%, suggesting that BD-II may be a less stable condition in younger patients (Birmaher et al., 2009; Alloy et al., 2012). For more accurate diagnosis, Ghaemi's BSD criteria should be considered a predictor to be assessed in patients presenting with major depressive episodes (MDE) (Ghaemi, 2004)

The Heterogeneity of BSD and Its Presentation in Clinical Practice

In everyday practice, patients usually present with depression and anxiety, often suffering from atypical depressive symptoms and mood reactivity (Fountoulakis, 2015). In such cases, dysphoric or irritable ("dark") hypomania is more characteristic than the euphoric form, and benzodiazepine abuse may occur as a form of self-medication.

The diagnosis of BSD/BD is further complicated by the fact that euphoric ("sunny") hypomania is often not recognized as a pathological condition by either the patient or their relatives (Fountoulakis, 2015). In many cases, mood fluctuations begin during adolescence, persist throughout life, and the polarity, severity, and duration of a given episode—as well as accompanying symptoms such as anxiety or psychotic features—are often unpredictable. These changes may be seasonal or, in females, associated with the menstrual cycle.

Given this heterogeneous clinical presentation, the term "multipolar mood disorder" may be more appropriate than BSD (Fountoulakis, 2015).

It is also common for the severity or duration of a given episode to fall short of the diagnostic criteria, presenting instead with subthreshold or minor symptoms (Fountoulakis, 2015). In such patients, episodic dysphoric hypomania is characteristic, often accompanied by mood instability, irritability, difficulties in impulse-regulation, impaired decision-making, interpersonal problems, and paranoid thoughts. Consideration of the temperament concept is therefore highly important and useful (Fountoulakis, 2015; Spoorthy et al., 2019). These phenomena support a dimensional rather than a categorical conception of the disorder (Fountoulakis, 2015).

Cyclothymia (cyclothymic disorder) is an important component of BSD and represents an attenuated form of bipolar disorder, typically beginning before the age of 21. It is characterized by spontaneous or reactive, persistent mood fluctuations. Accordingly, it involves rapid, short cycles of subsyndromal depressive and hypomanic episodes, with a continuous or intermittent course and rare euthymic periods (Rihmer et al., 2010; Fountoulakis, 2015; DSM-5-TR, 2024; Perugi et al., 2017).

Cyclothymia-related features, such as sensitivity, emotional dysregulation, impulsivity, emotional reactivity, and limited self-efficacy, combine to produce chronic interpersonal and professional difficulties and internal conflicts (Ratheesh et al., 2023). Cyclothymia is characterized by frequent use of multiple psychoactive substances, affecting up to 50% of patients, and is considered self-medication. Approximately 10–20% of patients with MDD exhibit a cyclothymic temperament, with the proportion being much higher in BD—which is unsurprising, since cyclothymia is a prodrome of BD-I or BD-II, in other words, a subaffective or "embryonic" form of the disease (Akiskal et al., 1979a; Rihmer et al., 2010). However, hyperthymic temperament is twice as common in BD-I and BD-II depression (45% and 41%, respectively) as in MDD (23%) (Pompili et al., 2014).

Numerous studies have demonstrated that in bipolar depression, the use of antidepressants— particularly those with dual mechanisms of action—carries a two- to threefold higher risk of phase switching and the development of mixed episodes compared to true MDD (Koukopoulos et al., 2007; Grunze, 2008; Olgiati & Serretti, 2023). Such patients often have a family history of BD and, despite being depressed, exhibit a hyperthymic temperament (Fountoulakis, 2015). Consequently, many patients initially diagnosed with MDD—especially during their first major depressive episode—may actually be "pseudo-unipolar," partly because over 50% of BD-I cases begin with a depressive episode (Fountoulakis, 2015; Oliva et al., 2024). Furthermore, multiple studies have shown that 35–40% of individuals diagnosed with unipolar MDD according to DSM-IV/5 criteria exhibit clinically significant subsyndromal hypomanic symptoms. This suggests that a substantial proportion of such patients actually fall within the bipolar spectrum, and their depressive symptoms often show an inadequate response to antidepressant monotherapy (see the section on TRD above) (Zimmermann et al., 2009; Rihmer & Gonda, 2011; Rihmer et al., 2013; Rihmer et al., 2016).

BIOMARKERS IN BD/BSD

1. Genetic Markers

Twin and family studies suggest that the heritability of BD ranges from 60 to 90% (Johansson et al., 2019; Oliva et al., 2024). A large genome-wide association study (GWAS) identified 64 independent genetic loci associated with BD (Oliva et al., 2024). These genes play a role in ion channel regulation (e.g., CACNA1C, ANK3), synaptic signalling, and neurotransmission (e.g., GRIN2A, ODZ4), and neuroplasticity (NCAN, SYNE1), as well as in cellular signalling and neurodevelopmental processes (TRANK1) (Oliva et al., 2024). Some loci overlap with genetic risk factors for other psychiatric disorders, including schizophrenia, MDD, childhood psychiatric disorders, and problematic alcohol use, indicating a shared genetic architecture (Oliva et al., 2024).

However, in mood disorders, individual polymorphisms and aggregated polygenic risk scores explain only a fraction (2–3%) of the phenotypic variance. Some studies have reported differences in the association of circadian rhythm-regulating genes with BD and MDD, but no discriminating variants have been identified. One study found that subclinical hypomanic symptoms in patients with MDD were associated with higher BD polygenic risk scores, but this result could not be replicated (Mistry et al., 2018; Chakrabarty & Yatham, 2019). Genetic markers hypothesized to link cyclothymic and hyperthymic temperaments with BD have also not been clearly established; although one study found an association between these temperaments and BD-related CLOCK gene variants, the results did not remain significant after statistical correction (Greenwood et al., 2013; Chakrabarty & Yatham, 2019). Thus, it remains uncertain whether BSDs share the genetic diathesis of BD (McCarthy et al., 2012; Chakrabarty & Yatham, 2019).

In contrast to the other four AFTs grouped under a single superfactor, in hyperthymic temperament the "ll" genotype of the serotonin transporter gene—closely related to serotonergic activity of the central nervous system—occurs significantly more frequently than carriage of the "ss" or "sl" alleles (Gonda et al., 2006).

Perinatal effects, childhood trauma, light conditions, and climate changes may contribute as gene–environment interaction risk factors (Oliva et al., 2024). Gene–environment interactions may be mediated by epigenetic mechanisms (such as DNA methylation, histone modifications, non-coding RNA activity, and chromatin remodelling) (Scaini et al., 2020; Oliva et al., 2024).

2. Structural Markers

Lesions in the grey and white matter of the frontal and subcortical regions can be detected in both BD and MDD, but research findings have not consistently replicated these differences. In addition, pharmacological treatment has a significant modifying effect (Chakrabarty & Yatham, 2019). Deep white

matter hyperintensities (WMH) are among the most common neuroimaging findings in BD, primarily observed in the prefrontal and limbic structures.

These regions are associated with emotion regulation, reward, and cognitive processing. The underlying mechanisms of WMHs are thought to involve disturbances in immune response and inflammatory regulation (Serafini et al., 2016; Saccaro et al., 2023; Silva et al., 2024).

At the cellular and subcellular levels in BD, reductions in the number of synapses, interneurons, neurons, and oligodendrocytes have been demonstrated, along with dendritic atrophy, mitochondrial and endoplasmic reticulum damage, elevated intracellular Ca2+ levels, significant oxidative stress, and apoptotic signals (Kim et al., 2017; van der Wijk et al., 2024; Oliva et al., 2024).

3. Functional Markers

Disturbances in emotional regulation and processing are core features of BD. In BD, hyperactivation of subcortical/limbic structures (amygdala, parahippocampal gyrus, basal ganglia) can be observed alongside reduced activity in the dorso- and ventrolateral prefrontal cortex and the anterior cingulate cortex, as well as dysfunctional connectivity between prefrontal and limbic regions (Chen et al., 2011; Vargas et al., 2013; Chakrabarty & Yatham, 2019). This pattern is observable not only in response to emotional stimuli but also during cognitive tasks, suggesting that deficits in "top-down" cognitive control are present in both emotional and neutral contexts (Chen et al., 2011; Vargas et al., 2013; Chakrabarty & Yatham, 2019). Some studies have also demonstrated frontal hypoactivation in individuals with cyclothymic temperament (Chakrabarty & Yatham, 2019).

According to the reward hypersensitivity model, individuals with BSD are more sensitive to positive stimuli related to anticipated rewards, as well as to negative stimuli associated with failures. This model proposes that such heightened sensitivity can lead to extreme mood fluctuations: excessive activation may trigger (hypo)manic symptoms, while excessive deactivation may result in depressive symptoms (anhedonia, amotivation) (Chakrabarty & Yatham, 2019; Walsh et al., 2024). A positive feedback loop exists between reward and mood, whereby reward leads to elevated mood, while heightened mood amplifies the reward experience (Alloy et al., 2015; Chakrabarty & Yatham, 2019).

4. Cognitive Markers

In BD, multiple cognitive domains are impaired, with these deficits detectable not only during acute affective episodes but also in the euthymic state (Torres et al., 2007; Chakrabarty & Yatham, 2019). Findings are inconsistent regarding whether differences exist among the various forms of BSD. According to a meta-analysis, patients with BD-I performed worse than those with BD-II in global cognition, verbal memory, processing speed, and executive functions, although the effect sizes of these differences were small (Bora, 2018; Chakrabarty & Yatham, 2019). Another meta-analysis found no differences in executive functions between the two groups or between patients and healthy controls (Dickinson et al., 2017; Chakrabarty & Yatham, 2019). Verbal memory impairment has been considered in several studies as an endophenotype of BSD (Chakrabarty & Yatham, 2019).

5. Peripheral Markers

5/1. Inflammatory Markers

Although elevated levels of inflammatory markers—such as T-cell activation, interleukin (IL)-2, 4, 6, 10, tumour necrosis factor (TNF)-alpha, as well as soluble TNF receptor-1, soluble IL-6 and IL-2 receptors, and IL-1 receptor antagonist—have been demonstrated in cases of BD, these alterations were not specific to affective disorders (Chakrabarty & Yatham, 2019; Oliva et al., 2024). C-reactive protein levels were also found to be elevated in BD patients during both euthymic and manic episodes (Oliva et al., 2024). Dysfunction of the hypothalamic-pituitary-adrenal axis increases inflammation and oxidative stress, thereby enhancing stress sensitivity, with these changes exerting neurotoxic effects (Oliva et al., 2024).

5/2. Brain-Derived Neurotrophic Factor (BDNF) Levels

Research has produced contradictory results regarding BDNF levels in different forms of BSD. Generally, BDNF levels decrease with repeated episodes and with increasing age, in both bipolar depression and in MDD, although some studies suggest that this decrease is more pronounced in BD. During treatment, BDNF levels may normalize (Chakrabarty & Yatham, 2019). From a psychiatric perspective, in otherwise healthy

hypertensive patients, a hyperthymic temperament was associated with significantly higher BDNF levels (Nemcsik et al., 2016).

5/3. Other Biomarkers

Morning cortisol levels are elevated in euthymic bipolar patients compared to controls. Insulin-like growth factor-1 (IGF-1) levels were also found to be elevated during manic episodes, and increased levels of antibodies against NMDA receptors were observed in individuals with manic BD. However, these markers are not specific to BD and may also occur in other psychiatric disorders or inflammatory conditions (Oliva et al., 2024).

DIAGNOSIS OF BSD

Currently, the diagnosis is still phenomenology-based. The recognition of BSD requires brief, easy-to-administer screening tools that can be used in patients with depression (Baldassano, 2005).

The most commonly used tools are:

Mood Disorder Questionnaire (MDQ)

The MDQ is a self-report questionnaire based on DSM-IV criteria and clinical experience that can be completed in a short time—approximately 5 minutes (Hirschfeld et al., 2000). It contains 13 questions addressing mood (elevated/irritable), increased self-confidence, reduced need for sleep, pressured speech, racing thoughts, distractibility, increased activity, excessive sociability, heightened work or sexual energy, risk-taking behaviour, interest in new activities, and exaggerated or unusual behaviour. Two additional questions concern the simultaneity of symptoms and functional impairment (Hirschfeld et al., 2000).

For a diagnosis, at least seven symptoms must be present simultaneously, and the level of difficulty caused by these symptoms must be at least moderate. The advantage of the MDQ is its good specificity (particularly for BD-I), while its limitation is lower sensitivity (especially for BD-II) (Hirschfeld et al., 2000).

32-Item Hypomania Checklist (HCL-32)

The HCL-32 is a 32-item self-report questionnaire, validated in several countries, designed to aid identification of hypomanic symptoms in individuals with MDE. A score of 14 or higher indicates that the individual may potentially have a bipolar disorder (Angst, 2005). The HCL-32 is capable of detecting both the "sunny" and "dark" aspects of hypomania; however, it does not distinguish between BD-I and BD-II (Angst et al., 2005). According to Gamma's study, the HCL-32 demonstrated 82% sensitivity and 57% specificity when evaluated against DSM-IV criteria. When bipolar-specific specifiers are applied, specificity can be increased to 73% (Gamma et al., 2013). The Hungarian version of the questionnaire was developed by Rihmer and colleagues and is included in Appendix X of the guideline "On the Diagnosis and Therapy of Bipolar Affective Disorder" (Rihmer et al., 2017).

Bipolar Spectrum Diagnostic Scale (BSDS)

The BSDS is a self-report questionnaire that describes bipolar symptoms in the form of a narrative story. It consists of two parts. The first part is a story containing 19 positive statements, where the patient marks which statements apply to them; the second part is a simple multiple-choice question assessing how well the described story fits the individual ("this story fits me very well, or almost perfectly; this story fits me fairly well; this story fits me to some degree, but mostly does not; this story does not really describe me").

Scoring is as follows: 19 points or more → high probability of BSD; 11–18 points → moderate probability; 6–10 points → low probability; below 6 points → BSD is unlikely (Baldassano, 2005). The maximum score is 25 and the optimal threshold for BSD probability is a minimum of 13 points (Ghaemi et al., 2005).

When comparing the MDQ and the BSDS, it was found that the MDQ identifies individuals with BD-I more effectively than those with BD-II or BD not otherwise specified (BD-NOS). In contrast, the BSDS showed equal sensitivity in identifying BD-I, BD-II, and BD-NOS, making it a useful tool for recognizing BD subtypes, although further validation in clinical populations is required (Ghaemi et al., 2005).

Hypomanic Personality Scale (HPS)

The HPS was developed to identify individuals at elevated risk of bipolar disorder (BD) (Eckblad & Chapman, 1986). Goodwin and Jamison (2007) noted that heightened neuroticism, extraversion, cyclothymic and hyperthymic temperamental

features, and novelty seeking may be associated with BD. However, the considerable variability in findings has precluded generalization. These characteristics may hypothetically represent (a) independent risk factors, (b) early, attenuated manifestations of BD, or (c) models reflecting a genetic predisposition (Goodwin & Jamison, 2007). The questionnaire was administered in a non-clinical sample, and four factors were identified as being associated with BD: mood lability; creativity, productivity, and grandiosity; excessive sociability; and the "exceptional" personality (Rawling et al., 2000). A major limitation of the HPS is its length, as it comprises 48 items. Moreover, since it was conceptualized as a personality assessment tool, it primarily captures enduring personality styles rather than transient states (Eckblad & Chapman, 1986).

The Bipolarity Index (BI)

The Bipolarity Index (BI) is a clinical rating scale developed to quantify the extent of bipolar features in both a patient's psychiatric history and current presentation. It was introduced by Ghaemi and colleagues with the specific aim of assisting in differentiation between bipolar I disorder (BD-I), bipolar II disorder (BD-II), and major depressive disorder (MDD), given that bipolar disorder is frequently underdiagnosed or misdiagnosed (Ghaemi et al., 2002).

The BI provides a dimensional assessment of the severity of bipolar features and is designed to estimate the likelihood that an individual is affected by a bipolar spectrum disorder (BSD). Importantly, the instrument can be applied in both retrospective and cross-sectional research contexts (Ghaemi et al., 2002).

The BI comprises five dimensions, each rated on a scale from 0 to 20, resulting in a total score ranging from 0 to 100. The five dimensions are as follows:

1. Symptoms and signs: presence of classic manic or hypomanic symptoms.
2. Age at onset: early onset, defined as onset before 21 years of age.
3. Course of illness: episodic pattern with spontaneous remissions.
4. Treatment response: lithium responsiveness and worsening with antidepressant therapy.
5. Family history: presence of bipolar disorder or related affective disorders in first-degree relatives (Ghaemi et al., 2002).

According to established thresholds, a total score above 70 indicates a high likelihood of bipolar disorder and a score between 50 and 70 suggests a moderate likelihood, while a score below 50 is more consistent with MDD (Ghaemi et al., 2002). The BI thus offers a structured and quantitative framework for distinguishing BDs from MDD, complementing clinical judgment and facilitating more accurate diagnosis.

TEMPS-A (The Temperament Evaluation of Memphis, Pisa, Paris, and San Diego)

Based on the well-established association between personality and affective disorders, and following several modifications and refinements, Akiskal and colleagues developed the TEMPS-A (Akiskal & Akiskal, 1992a; Akiskal et al., 2005b; Rovai et al., 2013). This self-administered questionnaire is designed to quantify affective temperaments (ATs), namely depressive (DT), cyclothymic (CT), hyperthymic (HT), irritable (IT), and anxious (AT). The instrument evaluates multiple domains including emotional reactivity, cognitive and psychomotor characteristics, circadian patterns, and socio-behavioural traits (Akiskal et al., 1998b; Rovai et al., 2013).

The questionnaire contains 110 items for women and 109 for men, and can typically be completed in under 15 minutes (Akiskal et al., 2005b). Items are rated in a dichotomous yes/no format. At item 111, respondents are asked to select one statement from six alternatives that they consider to be most representative of themselves for the majority of their lifetime (Akiskal et al., 2005a, 2005b; Előry et al., 2011). The TEMPS-A has been validated in more than 25 languages and compared with other temperament and personality assessment tools. The Hungarian version was adapted and validated by Rihmer and colleagues (Rózsa et al., 2006; 2008; Rovai et al., 2013).

Research consistently demonstrates that the prevalence of dominant temperaments is markedly higher among individuals with affective disorders compared to the general population. Depressive temperament (DT) has been identified as a risk factor for major depressive disorder (MDD) and is associated with antidepressant-induced hypomania (Akiskal & Akiskal, 1992a; Rihmer et al., 2010). Anxious temperament (AT) is a significant predictor of both anxiety and depressive disorders, particularly generalized anxiety disorder. Hyperthymic temperament (HT) shows a strong association with bipolar spectrum disorders (BSD) and, uniquely, has been found to exert a protective effect against suicide (Akiskal et al., 2003; Rihmer et al., 2010; Walsh et al., 2012).

Moreover, HT (and to a lesser extent CT) appears to contribute to the development of bipolar I disorder. Cyclothymic temperament (CT) demonstrates high sensitivity (88%) for bipolar II disorder, carries significant predictive value for the conversion of MDD into BD-II, and is linked to poorer clinical outcomes in such cases (Kochman et al., 2005; Akiskal et al., 2006; Rihmer et al., 2010; Belteczki et al., 2021). Both CT and IT have been shown to correlate with borderline pathology and impulsivity (Akiskal & Akiskal, 1992a; Rihmer et al., 2010; Walsh et al., 2012). In patients with IT, the first episode of bipolar disorder is more frequently manic, and the occurrence of psychotic symptoms, mixed episodes, and aggressive behaviours is significantly more common (Kesebir et al., 2005).

SCID-5-CV (Structured Clinical Interview for DSM-5, Clinical Version)

The SCID-5-CV is a semi-structured, systematic instrument designed to assess lifetime (hypo) manic and depressive episodes, as well as DSM-5 criterion-based symptoms, thereby reducing the risk of misdiagnosis, particularly in cases of BD-II or bipolar spectrum disorders (BSD) (First et al., 2016). The SCID differentiates MDD from BD and allows for the classification of BD-I, BD-II and cyclothymic disorder, although a detailed patient history is required.

The SCID can be used in combination with screening instruments such as the MDQ, HCL-32, and TEMPS-A. It also aids in excluding mood disturbances secondary to substance use or medical conditions (First et al., 2016). However, several factors limit its practical application: administration requires a partially trained clinician, the interview is time-consuming (typically taking 1–2 hours), and it relies on patient self-reflection and memory, meaning hypomanic episodes may remain unreported or unnoticed (First et al., 2016; Shabani et al., 2021). The instrument is also less sensitive in detecting "soft" or subthreshold forms of bipolarity (Shabani et al., 2021).

The SCID Hypomania Module (SCID-Hba) provides greater detail and personalized questioning, resulting in higher detection rates of BD-II. It emphasizes increased, goal-directed activity, a sensitive marker of hypomania (Benazzi & Akiskal, 2005).

The diagnosis of BD/BSD is further complicated by the fact that approximately two-thirds of patients present with comorbid psychiatric disorders (Léda-Rêgo et al., 2024; Oliva et al., 2024). Lifetime prevalence rates of co-occurring psychiatric conditions in BD are as follows: anxiety disorders 40% (with panic disorder being the most common at 18%, followed by generalized anxiety disorder and social phobia at 13%), substance use disorders 30–56%, behavioural addictions 33%, ADHD 18–19%, borderline personality disorder and impulse-control disorders 15–22%, obsessive-compulsive disorder 9–10%, post-traumatic stress disorder 10%, and eating disorders 10–20% (Yacipi et al., 2018; Preuss et al., 2021; Hossein et al., 2019; Léda-Rêgo et al., 2024; Oliva et al., 2024).

The association between psychiatric comorbidity and BD is clinically significant, as comorbid conditions are linked to earlier age at onset, more frequent relapses, a more complex clinical presentation, poorer functioning, and increased risk of suicide (Léda-Rêgo et al., 2024).

Artificial Intelligence (AI) in BSD Diagnostics

AI-based tools are becoming increasingly important in supporting diagnosis of BSD, as research has largely moved beyond the paradigm of examining a single biomarker (Oliva et al., 2024). This is particularly relevant because BSD denotes heterogeneous states that exist on a spectrum and are prone to misdiagnosis.

AI can integrate clinical, digital, and neurobiological data, enabling early detection (Oliva et al., 2024). While AI cannot replace clinical assessment and follow-up, machine learning methods can aid in analysing the symptomatic and temporal patterns of BSD/BD (Dwyer et al., 2018). Moreover, analysis and integration of linguistic and emotional markers, polygenic risk patterns, sensor data on sleep, activity, and circadian rhythms, as well as fine structural and functional differences in neuroimaging studies, can also support accurate diagnosis (Boral et al., 2023; Hajek et al., 2022; Saccaro et al., 2021; Guglielmi et al., 2023).

Advantages of the BSD Concept:

1. Promotion of genetic and biomarker research
2. Identification of cases mistakenly diagnosed as unipolar depression

In bipolar depression, mixed, atypical, psychotic, and catatonic symptoms are more common, as well as an earlier age of onset and postpartum onset of MDEs. Additionally, there is a higher occurrence of shorter but more frequent MDEs, resistance to antidepressant

therapy, tachyphylaxis (diminished drug effect), and familial aggregation of affective disorders or bipolar disorder compared to unipolar depression (Rihmer et al., 2014; Oliva et al., 2024).

3. Validation of subsyndromal states
4. Possibility of early intervention
5. Raising awareness of the relationship between BD and MDD (Reddy et al., 2012)

CONCLUSIONS

In psychiatry, diagnosis is still primarily phenomenological rather than biomarker-based. Accordingly, it is very difficult to draw clear boundaries between health and illness, as well as between normality and pathological states (Fountoulakis, 2015).

In BD, establishing a diagnosis takes on average seven years, due to frequent comorbid psychiatric disorders and the complexity of the symptomatology (three years for BD-I, up to 12 years for BD-II) (Ghaemi et al., 1999; Oliva et al., 2024). The same applies to BSD, as cross-sectional studies do not allow clear differentiation between normal psychological variation and subthreshold disorders; long-term follow-up is required. Additionally, obtaining a family history is important, especially when affective disorders aggregate in the family. Hypomanic episodes lasting fewer than four days can be an important clinical indicator, particularly when recurrent or occurring in the context of familial mood disorders (Fountoulakis, 2015).

Diagnostic difficulties in BD are further compounded by symptom overlap with other psychiatric disorders (primarily MDD and anxiety disorders), the presence of comorbid conditions, high variability in symptom presentation, subthreshold symptoms, lack of insight (especially during hypomanic/manic episodes), age-related factors (early onset), and the limitations of diagnostic screening tools and strategies (Fountoulakis et al., 2015; Desai et al., 2021).

Delays in establishing a BD/BSD diagnosis can lead to functional decline, psychosocial and interpersonal difficulties, and increased suicide risk (30–50% of individuals with BD attempt suicide in their lifetime, and 5–20% die by suicide) (Rihmer et al., 2014; Oliva et al., 2024). However, if the specificity of the diagnosis is "diluted", individuals with normal mood fluctuations may also be classified within the BSD category (Paris, 2015). In such cases, the use of mood stabilisers and/or antipsychotics exposes patients to potential side effects (Paris, 2015).

Corresponding author: Zsuzsanna Belteczki
+36 30 488 9566
E-mail: belteczkizsuzsa@gmail.com

Acknowledgments:
I would like to thank Prof. Dr. Zoltán Rihmer for his valuable guidance in the preparation of this article.

REFERENCES

1. Akiskal HS, Rosenthal RH, Rosenthal TL et al. Differentiation of primary affective illness from situational, symptomatic, and secondary depressions. Archives of General Psychiatry. 1979a;36(6):635-43
2. Akiskal HS, Mallya G. Criteria for the "soft" bipolar spectrum: treatment implications. Psychopharmacol Bulletin 1987;23(1):68-73.
3. Akiskal HS, Akiskal KK. Cyclothymic, hyperthymic, and depressive temperaments as subaffective variants of mood disorders, Tasman A., Riba M.B. Review of Psychiatry. The American Psychiatric Press, Washington, DC; 1992a, 11: 43 – 46.
4. Akiskal HS, Maser JD, Zeller PJ et al. Switching from 'unipolar' to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. Archives of General Psychiatry 1995;52:114–123.
5. Akiskal HS, Placidi GF, Maremmani I ez al. TEMPS-I: delineating the most discriminant traits of the cyclothymic, depressive, hyperthymic and irritable temperaments in a nonpatient population. Journal of Affective Disorders 1998b;51(1):7-19.
6. Akiskal HS, Pinto O. The evolving bipolar spectrum. Prototypes I, II, III, and IV. Psychiatric Clinics of North America 1999a ;22(3):517-534.
7. Akiskal HS. Dysthymia, cyclothymia and related chronic subthreshold mood disorders. In: Gelder M, Lopez-Ibor J, Andreasen N (ed). New Oxford Textbook of Psychiatry. London: Oxford University Press; 2000, pp 736-749.
8. Akiskal HS, Hantouche EG, Allilaire JF. Bipolar II with and without cyclothymic temperament: "dark" and "sunny" expressions of soft bipolarity. Journal of Affective Disorders 2003;73(1-2):49-57.
9. Akiskal HS, Benazzi F. Optimizing the detection of bipolar II disorder in outpatient private practice: toward a systematization of clinical diagnostic wisdom. The Journal of Clinical Psychiatry 2005;66:914–921.
10. Akiskal HS, Akiskal KK, Haykal RF et al. TEMPS-A: progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. Journal of Affective Disorders 2005a ;85(1-2):3-16.
11. Akiskal HS, Mendlowicz MV, Jean-Louis G et al. TEMPS-A: validation of a short version of a self-rated instrument designed to measure variations in temperament. Journal of Affective Disorders 2005b ;85(1-2):45-52.

12. Akiskal HS, Akiskal KK, Perugi G et al. Bipolar II and anxious reactive "comorbidity": toward better phenotypic characterization suitable for genotyping. Journal of Affective Disorders 2006 ;96(3):239-47
13. Alloy LB, Urošević S, Abramson LY et al. Progression along the bipolar spectrum: a longitudinal study of predictors of conversion from bipolar spectrum conditions to bipolar I and II disorders. Journal of Abnormal Psychology, 2012;121(1):16-27.
14. Alloy LB, Nusslock R, Boland EM. The development and course of bipolar spectrum disorders: an integrated reward and circadian rhythm dysregulation model. Annual Review of Clinical Psychology 2015; 11: 213-250.
15. Altinbas K, Smith DJ, Craddock N. Rediscovering the Bipolar Spectrum. Archives of Neuropsychiatry 2011; 48: 167-170.
16. Angst J. The course of affective disorders. II. Typology of bipolar manic-depressive illness. Archiv für Psychiatrie und Nervenkrankheiten 1978; 26: 65–73.
17. Angst J, Merikangas K. The depressive spectrum: diagnostic classification and course. Journal of Affective Disorders 1997;45(1-2):31-39.
18. Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rössler W. Toward a redefinition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. Journal of Affective Disorders 2003; 73 (1–2): 133–146.
19. Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD, Skeppar P, Vieta E, Scott J. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. Journal of Affective Disorders 2005;88(2):217-233.
20. Angst J. The bipolar spectrum. British Journal of Psychiatry 2007;190(3):189-191.
21. Azorin JM, Belzeaux R. Differential Diagnosis and Bipolar Spectrum Disorder. In: Yildiz A, Ruiz P, Nemeroff CB. The Bipolar Book. Oxford University Press, 2015.
22. Baldassano CF. Assessment tools for screening and monitoring bipolar disorder. Bipolar Disorders 2005; 7(1), 8–15.
23. Baldessarini RJ. Aplea for the integrity of the bipolar concept. Bipolar Disorders 2000;2:3–7.
24. Belteczki Z, Rihmer Z, Rozsa S, Ujvari J, Pompili M, Gonda X, Dome P. Affective Temperaments, Panic Disorder and Their Bipolar Connections. Medicina (Kaunas). 2021 19;57(3):289.
25. Benazzi F, Akiskal HS. The modified SCID Hypomania Module (SCID-Hba): a detailed systematic phenomenologic probing. Journal of Affective Disorders 2009;117(3):131-6.
26. Birmaher B, Axelson D, Goldstein B et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. American Journal of Psychiatry. 2009;166(7):795-804.
27. Bleuler E. Die Probleme der Schizoidie und der Syntonie. Zeitschrift für die Gesamte Neurologie und Psychiatrie 1922; 78: 373–399.
28. Bora E. Neurocognitive features in clinical subgroups of bipolar disorder: a metaanalysis. Journal of Affective Disorders 2018; 229: 125-134.
29. Boral S, Dey B, Biswas D et al. Deep learning analysis of clinical notes identifies hidden bipolarity in treatment-resistant depression. Bipolar Disorders 2023;25(4), 345–355.
30. Bschor T, Kilarski LL. Are antidepressants effective? A debate on their efficacy for the treatment of major depression in adults. Expert Review Neurotherapeutics 2016;16(4):367-374.
31. Cervone A, D'Ostuni FP, D'Aietti E et al. Mixed States: Diagnosis, Assessment and Diagnostic Stability. Psychiatria Danubina 2022;34(Suppl 8):38-41.
32. Chakrabarty T, Yatham LN. Objective and biological markers in bipolar spectrum resentations. Expert Review of Neurotherapeutics,2019;19(3):195-209.
33. Chen CH, Suckling J, Lennox BR et al. A quantitative meta-analysis of fMRI studies in bipolar disorder. Bipolar Disorders 2011; 13: 1-15.
34. Correa R, Akiskal H, Gilmer W, Nierenberg AA, Trivedi M, Zisook S. Is unrecognized bipolar disorder a frequent contributor to apparent treatment resistant depression? Journal of Affective Disorders 2010;127(1-3):10-18.
35. Deliyannides DA. Mood Dysregulation – Beyond the Bipolar Spectrum. 2024 Apple Academic Press, Inc. Co-published with CRC Press (Taylor & Francis), pp 15-19.
36. Desai P, Urošević S, Butler M. Addressing challenges in the evidence base for bipolar disorders: Diagnostic accuracy and attrition. Bipolar Disorders 2021;23(4):321-323.
37. Dickinson T, Becerra R, Coombes J. Executive functioning deficits among adults with bipolar disorder (types I and II): a systematic review and meta-analysis. Journal of Affective Disorders 2017; 218: 407-427.
38. Döme P, Kunovszki P, Takács P et al. Clinical characteristics of treatment-resistant depression in adults in Hungary: Real-world evidence from a 7-year-long retrospective data analysis. PLoS One. 2021;16(1):e0245510.
39. DSM-III; Diagnostic and Statistical Manual of Mental Disorders. Third Edition. American Psychiatric Association, Washington DC, 1980.
40. DSM-IV; The Diagnostic and Statistical Manual of Mental Disorder Fourth Edition. American Psychiatric Association, Washington DC, 1994.
41. DSM-5; The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. American Psychiatric Association, Washington DC, 2013.
42. DSM-5 TR;Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision. American Psychiatric Association, Washington DC, 2022.
43. Dunner DL, Gershon ES, Goodwin FK. Heritable factors in the severity of affective illness. Biological Psychiatry 1976; 11(1): 31-42.
44. Dwyer DB, Falkai P, Koutsouleris N. Machine Learning Approaches for Clinical Psychology and Psychiatry. Annual Review of Clinical Psychology 2018;14:91-118.
45. Eckblad M, Chapman LJ. Development and validation of a scale for hypomanic personality. Journal of Abnormal Psychology 1986;95(3):214-222.
46. El-Mallakh RS, Ghaemi SN, Sagduyu K et al. STEP-BD investigators. Antidepressant-associated chronic irritable dysphoria (ACID) in STEP-BD patients. Journal of Affective Disorders 2008;111:372–377.
47. Eory A, Gonda X, Torzsa P et al. Affektív temperamentumok: a neurobiológiai alapoktól a klinikai alkalmazásig [Affective temperaments: from neurobiological roots to clinical application]. Orvosi Hetilap 2011;152(47):1879-1886.
48. Ferrari AJ, Baxter AJ, Whiteford HA. A systematic review of the global distribution and availability of prevalence data for bipolar disorder. Journal of Affective Disorders 2011;134(1-3):1-13.
49. First MP, Williams JBW, Karg RS et al. SCID-CV, APA, 2016.
50. Fountoulakis KN. Bipolar Disorder. Clinical Description. Springer 2015, pp 27-80.
51. Gamma A, Angst J, Azorin J et al. Transcultural validity of the Hypomania Checklist-32 (HCL-32) in patients with major depressive episodes. Bipolar Disorders 2013;15(6):701-712.

52. Gardner R Jr. Mechanisms in manic-depressive disorder: an evolutionary model. Archives of General Psychiatry1982;39(12):1436-1441.
53. Ghaemi SN, Sachs GS, Chiou AM et al. Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? Journal of Affective Disorders 1999;52:135–144.
54. Ghaemi SN, Sachs GS, Chiou AM et al. Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? Journal of Affective Disorders 2002; 67(1–3), 203–210.
55. Ghaemi SN, Hsu DJ, Ko JY et al. Bipolar spectrum disorder: a pilot study. Psychopathology 2004;37(5):222-226.
56. Ghaemi SN, Miller CJ, Berv DA et al. Sensitivity and specificity of a new bipolar spectrum diagnostic scale. Journal of Affective Disorders 2005;84(2-3):273-277.
57. Gonda X, Rihmer Z, Zsombók T, Akiskal KK, Bagdy G, Akiskal HS. The 5HTTLPR plolymorphism of the serotonin transporter gene is associated with affective temperaments as measured by TEMPS-A. Journal of Affective Disorders 2006; 91: 125-131.
58. Gonda X, Fountoulakis KN, Juhasz G et al. Association of the s allele of the 5-HTTLPR with neuroticism-related traits and temperaments in a psychiatrically healthy population. European Archives of Psychiatry and Clinical Neuroscience 2009;259(2):106-113.
59. Gonda X, Vazquez GH. Theoretical and clinical overview of affective temperaments in mood disorders. Psicodebate, 2014; 14 (2):39-58.
60. Goodwin FK, Jamison K. Manic–Depressive Illness. 2nd ed. New York: Oxford University Press, 2007.
61. Greenwood TA, Badner JA, Byerley W et al. Heritability and genome-wide SNP linkage analysis of temperament in bipolar disorder. Journal of Affective Disorders 2013; 150:1031-1040.
62. Grunze HC. Switching, induction of rapid cycling, and increased suicidality with antidepressants in bipolar patients: fact or overinterpretation? CNS Spectrums 2008; 13(9):790–795.
63. Guglielmi L, Bellani M, Marinelli V et al. Polygenic risk scores meet machine learning for bipolar disorder: Ready for clinical translation? Molecular Psychiatry 2023, 28, 601–616.
64. Hajek T, Frankland A, Kolenic M et al. Brain structural signature of familial predisposition for bipolar disorder: findings from the ENIGMA Bipolar Disorder Working Group. Molecular Psychiatry 2022:27, 762–777.
65. Hede V, Favre S, Aubry JM, Richard-Lepouriel H. Bipolar spectrum disorder: What evidence for pharmacological treatment? A systematic review. Psychiatry Research 2019 ;282:112627.
66. Hirschfeld RM, Williams JB, Spitzer RL et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. American Journal of Psychiatry 2000;157(11):1873-1875.
67. Hossain S, Mainali P, Bhimanadham NN et al. Medical and Psychiatric Comorbidities in Bipolar Disorder: Insights from National Inpatient Population-based Study. Cureus. 2019; 12;11(9):e5636.
68. ICD-11; Clinical descriptions and diagnostic requirements for ICD-11 mental, behavioural and neurodevelopmental disorders. World Health Organization, 2024.
69. Johansson V, Kuja-Halkola R, Cannon TD et al. A population-based heritability estimate of bipolar disorder - In a Swedish twin sample. Psychiatry Research 2019;278:180-187.
70. Judd LL, Akiskal HS. Delineating the longitudinal structure of depressive illness: beyond clinical subtypes and duration thresholds. Pharmacopsychiatry 2000;33(1):3-7.
71. Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. Journal of Affective Disorders 2003; 73(1–2):123–131.
72. Kaltenboeck A, Winkler D, Kasper S. Bipolar and related disorders in DSM-5 and ICD-10. CNS Spectrums 2016; 21 (4), 318–323.
73. Kesebir S, Vahip S, Akdeniz F et al. [The relationship of affective temperament and clinical features in bipolar disorder]. Turk Psikiyatri Dergisi 2005;16(3):164-169.
74. Kim JH, Chang SM, Hong JP et al. Lifetime prevalence, sociodemographic correlates, and diagnostic overlaps of bipolar spectrum disorder in the general population of South Korea. Journal of Affective Disorders 2016 ;203:248-255.
75. Kim Y, Santos R, Gage FH, et al. Molecular Mechanisms of Bipolar Disorder: Progress Made and Future Challenges. Frontiers in Cellular Neuroscience 2017; 14:11:30.
76. Kleist K. Zustandsbilder und Krankheitsarten im Lichte der Gehirnpathologie. Psychiatrischneurologische Wochenschrift, 1937; 39:420–422.
77. Klerman GL. The spectrum of mania. Comprehensive Psychiatry. 1981;22(1):11-20.
78. Kochman FJ, Hantouche EG, Ferrari P et al. Cyclothymic temperament as a prospective predictor of bipolarity and suicidality in children and adolescents with major depressive disorder. Journal Affective Disorders 2005;85(1-2):181-189.
79. Koukopulos A, Caliari B, Tundo A et al. Rapid cyclers, temperament, and antidepressants. Comprehensive Psychiatry1983;24(3):249-58.
80. Koukopoulos A, Sani G, Koukopoulos AE et al. (2007) Melancholia agitata and mixed depression. Acta Psychiatrica Scandinavica. Supplementum (433): 50–57.
81. Kraepelin E. Manic-Depressive Insanity and Paranoia. Edinburgh: E&S Livingstone, 1921.
82. Kretschmer E. Physique and Character. New York: Cooper Square Publishers, Inc., 1921; 1970.
83. Léda-Rêgo G, Studart-Bottó P, Abbade P et al. Lifetime prevalence of psychiatric comorbidities in patients with bipolar disorder: A systematic review and meta-analysis. Psychiatry Research 2024 l;337:115953.
84. McCarthy MJ, Nievergelt CM, Kelsoe JR et al. A survey of genomic studies supports association of circadian clock genes with bipolar disorder spectrum illnesses and lithium response. PLoS One 2012;7, e32091.
85. Merikangas KR, Jin R, He JP, Kessler RC et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Archives of General Psychiatry 2011; 68(3):241–251.
86. Mistry S, Harrison JR, Smith DJ et al. The use of polygenic risk scores to identify phenotypes associated with genetic risk of bipolar disorder and depression: a systematic review. Journal of Affective Disorders 2018; 234:148-155.
87. Nemcsik J, László A, Lénárt L et al. Hyperthymic affective temperament and hypertension are independent determinants of serum brain-derived neurotrophic factor level. Annals of General Psychiatry 2016;15:17.
88. Olgiati P, Serretti A. Antidepressant emergent mood switch in major depressive disorder: onset, clinical correlates and impact on suicidality. International Clinical Psychopharmacology 2023;38(5):342-351.
89. Oliva V, Fico G, De Prisco M et al. Bipolar disorders: an update on critical aspects. Lancet Regional Health Europe 2024; 29:48:101135.

90. Paris J. Overdiagnosis in Psychiatry: How Modern Psychiatry Lost Its Way While Creating a Diagnosis for Almost All of Life's Misfortunes University Press. 2015.
91. Perlis RH, Uher R, Ostacher M et al. Association between bipolar spectrum features and treatment outcomes in outpatients with major depressive disorder. Archives of General Psychiatry 2011;68(4):351-360.
92. Perugi G, Akiskal HS. The soft bipolar spectrum redefined: focus on the cyclothymic, anxious-sensitive, impulse-dyscontrol, and binge-eating connection in bipolar II and related conditions. Psychiatric Clinics of North America 2002 ;25(4):713-737.
93. Perugi G, Hantouche E, Vannucchi G. Diagnosis and Treatment of Cyclothymia: The "Primacy" of Temperament. Current Neuropharmacology 2017;15(3):372-379.
94. Perugi G, Pacchiarotti I, Mainardi C et al. & BRIDGE-II-MIX Study Group. Patterns of response to antidepressants in major depressive disorder: Drug resistance or worsening of depression are associated with a bipolar diathesis. European Neuropsychopharmacology 2019;29(7):825-834.
95. Pompili M, Innamorati M, Gonda X et al. Characterization of patients with mood disorders for their prevalent temperament and level of hopelessness. Journal of Affective Disorders 2014;166:285-291.
96. Possl J, von Zerssen D. A case history analysis of the "manic type" and the "melancholic type" of premorbid personality in affectively ill patients. European Archives of Psychiatry and Clinical Neuroscience 1990;239(6):347-355.
97. Preuss UW, Schaefer M, Born C et al. Bipolar Disorder and Comorbid Use of Illicit Substances. Medicina (Kaunas). 2021; 7;57(11):1256.
98. Ratheesh A, Hammond D, Watson M et al. Bipolar At-Risk Criteria and Risk of Bipolar Disorder Over 10 or More Years. JAMA Network Open 2023;6(9):e2334078.
99. Rawlings D, Barrantes-Vidal N, Claridge G et al. A factor analytic study of the Hypomanic Personality Scale in British, Spanish and Australian samples. Personality and Individual Differences 2000; 28(1):73-84.
100. Reddy MS. The bipolar spectrum. Indian Journal of Psychological Medicine 2012;34(1):1-4.
101. Rihmer Z. A depresszió nosologiai problémái. Orvosképzés 1978; 53:255-260.
102. Rihmer Z. Az endogén depresszió korszerű nozológiája. Orvosi Hetilap 1981; 122: 2519-2525.
103. Rihmer Z, Akiskal KK, Rihmer A et al. Current research on affective temperaments. Current Opinion of Psychiatry. 2010;23(1):12-18.
104. Rihmer Z, Gonda X. Antidepressant-resistant depression and antidepressant-associated suicidal behaviour: the role of underlying bipolarity. Depression Research and Treatment 2011;2011:906462.
105. Rihmer Z, Dome P, Gonda X. Antidepressant response and subthreshold bipolarity in "unipolar" major depressive disorder: implications for practice and drug research. Journal of Clinical Psychopharmacology 2013;33(4):449-452.
106. Rihmer Z, Gonda X, Torzsa P et al. Affective temperament, history of suicide attempt and family history of suicide in general practice patients. Journal of Affective Disorders 2013;149(1-3):350-354.
107. Rihmer Z, Szekeres Gy, Döme P. A bipoláris (mániás-depressziós) betegség klinikuma. In: Rihmer Z (szerk.) Depresszió, bipoláris betegség és öngyilkosság-prevenció. Oriold és társai; 2014, pp 89-120.
108. Rihmer Z, Gonda X, Rihmer A et al. Antidepresszívum-rezisztens depresszió és a bipoláris spektrum kapcsolata - diagnosztikai és terápiás szempontok. Psychiatrica Hungarica 2016; 31 (2):157-168.
109. Rihmer Z, Szekeres Gy, Pestality P et al. A bipoláris affektív betegségek diagnosztikájáról és terápiájáról. Psychiatria Hungarica 2017; 32: 178-224.
110. Rovai L, Maremmani AG, Rugani F et al. Do Akiskal & Mallya's affective temperaments belong to the domain of pathology or to that of normality? European Review for Medical and Pharmacological Sciences 2013;17(15):2065-2079.
111. Rózsa S, Rihmer A, Ko N et al. Az affektív temperamentum: a TEMPS-A kérdöívvel szerzett hazai tapasztalatok [Affective temperaments: psychometric properties of the Hungarian TEMPS-A]. Psychiatr Hungarica 2006;21(2):147-160.
112. Rózsa S, Rihmer Z, Gonda X et al. A study of affective temperaments in Hungary: internal consistency and concurrent validity of the TEMPS-A against the TCI and NEO-PI-R. Journal of Affective Disorders 2008;106(1-2):45-53.
113. Saccaro LF, Amatori G, Cappelli A et al. Portable technologies for digital phenotyping of bipolar disorder: A systematic review. Journal of Affective Disorders 2021;295:323-338.
114. Saccaro LF, Crokaert J, Perroud N et al. Structural and functional MRI correlates of inflammation in bipolar disorder: A systematic review. Journal of Affective Disorders 2023; 325:83–92.
115. Scaini G, Valvassori SS, Diaz AP et al. Neurobiology of bipolar disorders: a review of genetic components, signaling pathways, biochemical changes, and neuroimaging findings. Brazilian Journal of Psychiatry 2020;42(5):536-551.
116. Serafini G, Pompili M, Innamorati M et al. The impact of periventricular white matter lesions in patients with bipolar disorder type I. CNS Spectrums 2016;21(1):23-34
117. Shabani A, Masoumian S, Zamirinejad S, Hejri M, Pirmorad T, Yaghmaeezadeh H. Psychometric properties of Structured Clinical Interview for DSM-5 Disorders-Clinician Version (SCID-5-CV). Brain and Behavior 2021;11(5):e01894.
118. Silva RF, Mograbi DC, Amadeo LN et al. The relationship between affective temperament and suicide attempt, clinical history and current subclinical symptoms in bipolar disorder. Diversitates International Journal, 2017 (3):65-79.
119. Silva T, Nunes C, Ribeiro A et al. White matter hyperintensities in bipolar disorder: systematic review and meta-analysis. Frontiers in Psychiatry 2024; 26;15:1343463.
120. Spoorthy MS, Chakrabarti S, Grover S. Comorbidity of bipolar and anxiety disorders: An overview of trends in research. World Journal of Psychiatry 2019;9(1):7-29.
121. Szádóczky E, Papp Zs, Vitrai J et al. The prevalence of major depressive and bipolar disorders in Hungary. Results from a national epidemiologic survey. Journal of Affective Disorders 1998;50(2-3):153-162.
122. Szádóczky E, Papp Zs, Vitrai J et al. A hangulat- és szorongásos zavarok előfordulása a felnőtt magyar lakosság körében. Orvosi Hetilap, 2000; 14117-14122.
123. Tomassini A, Struglia F, Stratta P et al. Affective temperaments and residual symptoms in patients with mood and anxiety disorders. International Journal of Psychiatry in Clinical Practice 2009;13(1):31-35.
124. Torres IJ, Boudreau VG, Yatham LN. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatrica Scandinavica Supplementum 2007; 434:17-26.

125. Truman CJ, Goldberg JF, Ghaemi SN et al. Self-reported history of manic/hypomanic switch associated with antidepressant use: Data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). The Journal of Clinical Psychiatry 2007;68:1472–1479.
126. Yapici Eser H, Kacar AS, Kilciksiz CM et al. Prevalence and Associated Features of Anxiety Disorder Comorbidity in Bipolar Disorder: A Meta-Analysis and Meta-Regression Study. Frontiers in Psychiatry. 2018; 27;9:229.
127. van der Wijk I, Bélteczki Zs, Döme P. The role of oxidative stress in the pathomechanism of major mood disorders: a narrative review with a special focus on uric acid. Neuropsychopharmacologia Hungarica 2024; XXVI, 2: 105-124.
128. Vargas C, Lopez-Jaramillo C, Vieta E. A systematic literature review of resting state network-functional MRI in bipolar disorder. Journal of Affective Disorders 2013;150: 727-735.
129. Varo C, Murru A, Salagre E et al. Behavioral addictions in bipolar disorders: A systematic review. European Neuropsychopharmacology 2019 ;29(1):76-97.
130. Vazquez GH, Gonda X. Affective Temperaments and Mood Disorders: A Review of Current Knowledge. Current Psychiatry Review 2013; 9:21-32.
131. Verdolini N, Perugi G, Samalin L et al. BRIDGE-II-Mix Study Group. Aggressiveness in depression: a neglected symptom possibly associated with bipolarity and mixed features. Acta Psychiatrica Scandinavica 2017;136(4):362-372.
132. Walsh RFL, Klugman J, Moriarity DP et al. Reward sensitivity and social rhythms during goal-striving: An ecological momentary assessment investigation of bipolar spectrum disorders. Journal of Affective Disorders 2024;344:510-518.
133. Zimmermann P, Brückl T, Nocon A, et al. Heterogeneity of DSM-IV major depressive disorder as a consequence of subthreshold bipolarity. Archives of General Psychiatry 2009;66(12):1341-1352.

A bipoláris spektrum elmélet koncepció fejlődése, klinikai kép, diagnosztika

Narratív írásomban bemutatom a bipoláris spektrum koncepció fejlődését, és annak a mindennapi gyakorlatban észlelt klinikai heterogenitását. Ismertetem a biológiai marker kutatás releváns eredményeit, a fenomenológiai alapú szűrőeszközöket. Áttekintést nyújtok a bipoláris spektrum elmélet előnyeiről és hátrányairól, a diagnosztika nehézségeiről.

Kulcsszavak: bipoláris zavar, bipoláris spektrum zavar, biomarker, pszichodiagnosztika