JOURNAL OF PSYCHOPATHOLOGY 2024;30:31-37
DOI: 10.36148/2284-0249-N456

Review

Mood instability as prodrome of bipolar disorder

Riccardo Guglielmo[1], Andrea Escelsior[1,2], Mario Amore[1], Gianluca Serafini[1,2]

[1] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, University of Genoa, Genoa, Italy; [2] IRCCS Ospedale Policlinico San Martino, Genoa, Italy

SUMMARY

Bipolar disorder and affective disorders exhibit progressive trajectories, involving central and peripheral biological changes and diverse clinical courses. This review explores the development of clinical staging models for bipolar disorder, aiming to identify critical points in the disorder's progression. Staging models, whether disorder-specific or transdiagnostic, offer a promising avenue for tailoring treatments based on social factors and patient resilience.

A key aspect in the field of affective disorders is the study of prodromal symptoms. Recognizing prodromal symptoms, particularly mood instability, provides an important opportunity for timely intervention. Prospective studies utilizing neuroimaging and genetic tools in at-risk youth show promise in predicting future affective lability and potential full expression of the disorder.

Challenges persist in the research concerning affective disorders, including the lack of clear definitions for stages and specific personality traits predicting mood disorders. Endophenotypes and biomarkers present potential tools to reduce heterogeneity, offering more precise diagnoses and tailored treatments. Early white matter abnormalities may serve as markers of bipolar disorder pathophysiology, suggesting the potential for early interventions.

In conclusion, recognizing prodromal symptoms is crucial for early interventions in affective disorders. Psychoeducation enhances patient compliance and outcomes, emphasizing ongoing awareness of prodromal symptoms during remission. Continued treatment in the residual phase aligns with a staging method for long-term prevention. The evolving landscape of affective disorders research calls for a nuanced understanding to advance comprehension and treatment.

Key words: mood instability, bipolar, prodromal, staging

Introduction

Bipolar disorder (BD) and more generally affective disorders are progressive conditions. BD may present with progressive central and peripheral biological alterations, as well as a heterogeneous clinical course of the illness. The trajectory of major affective disorders is characterized by specific lifetime epochs, including early lifetime trauma, childhood precursor disorders, clinical symptomatic state (i.e., recurrent depressive and manic episodes alternating with euthymic phases), suicidal behaviors, brain alterations stages, neurocognitive deficits, and a residual stage with functional impairments. The staging model (Fig. 1) defines clinically evident points in the course of a disease that are detectable, reflecting a certain level of severity in terms of risk of loss of autonomy, and which could be valid predictors of prognosis or therapeutic responses [1]. After Fava and Kellner's preliminary work in 1993 [2] developing clinical staging models for major psychiatric disorders based on the longitudinal development, major efforts have been made to understand BD through linking the pathological rewiring of the brain that takes place in parallel with clinical progression to the stages of the disorder. In contrast to other branches of medicine, biological staging in psychiatry is hampered by a lack of clear nomenclature regarding clinical staging, due to the fact that both etiology and pathophysiology of psychiatric disorders are still

Riccardo Guglielmo
E-mail: ricguglielmo@gmail.com

How to cite this article: Guglielmo R, Escelsior A, Amore M, et al. Mood instability as prodrome of bipolar disorder. Journal of Psychopathology 2024;30:31-37. https://doi.org/10.36148/2284-0249-N456

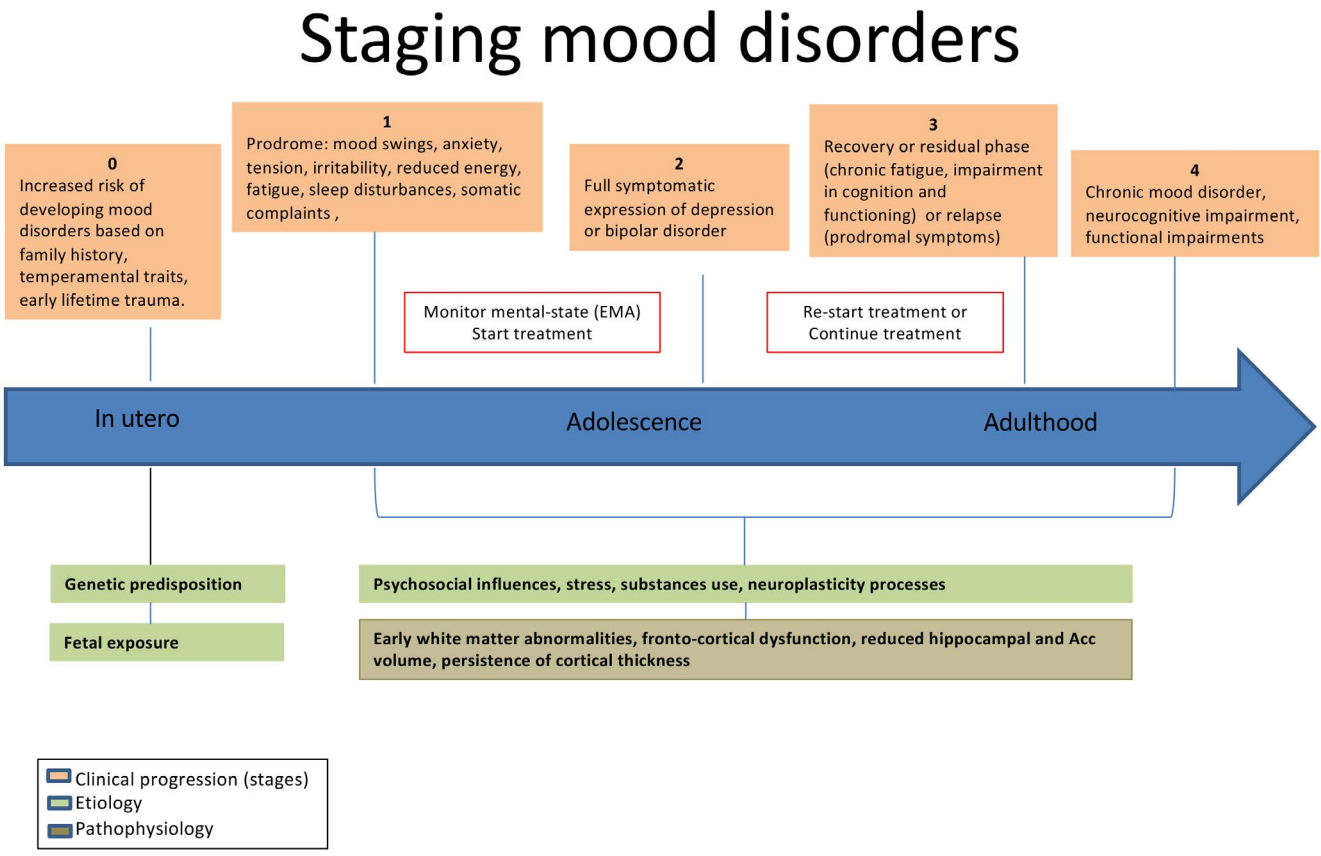

FIGURE 1. *Possible stages pathways from in utero to adulthood. This figure describes a heuristic model to link developmental stages of mood disorders with the timing of the biological and psychosocial underpinnings of etiological and pathophysiological events. ACC anterior cingulate cortex, EMA Ecological momentary assessment*

largely unknown. Nevertheless, several clinical staging models of BD have been developed over time since Fava and Kellner's first study [2]. Most of these models focus on traditional diagnostic categories [3-7], while others are transdiagnostic models that attempt to capture the non-specific and fluid early stages of the disorder [8]. Transdiagnostic staging models are probably optimal for the study of the at-risk and prodromal phases, while disorder-specific models might be useful to understand the late stage of the full expressed disorder [9]. Criticisms concerning the disorder-specific approach argued that the model is more applicable to the late stages with an established illness, and it does not incorporate an "at risk" phase, which is a critical element of all medical models of staging [7]. Critics of the transdiagnostic model argued that it may promote a hierarchical model which is biased toward psychotic disorders over other disorders given that operationalization of stages are more reliant on functional level rather than phenomenology [7]. Staging affective disorders could be helpful in delivering tailored treatments to the patient. By using the staging model, clinicians may weigh factors such as patients' social support and their adaptation, resilience and reaction to previous conflicts, threats or losses assess motivation and compliance with treatment, modeling the choice of the intervention. The traditional nosological diagnosis of affective disorders emphasizes a cross-sectional description of syndromes and is based on clusters of symptoms and does not take into consideration some features, including family history of mental illness, prodromal patterns, traumas, severity of the recurring pattern of the disease, suicidal behaviors, neurocognitive deficits, and deteriorated outcome characteristics. As such, affective disorders are not stage-defined, although diagnostic criteria based on staging may provide more appropriate and targeted treatments to prevent further episodes and progression into the later stages, which are characterized by functional and

cognitive decline [3]. In this context a relatively neglected, clinical important issue, is the study of prodromal symptoms in mood disorders. Appraisal of prodromal symptoms may be of practical value providing challenging insights into the pathogenesis and course of major affective disorders in a longitudinal perspective, according to a staging model of the illness. The definition of a prodromal phase would benefit from the joint use of symptom identification, biomarkers, and neuroimaging [10].

Prodromal phase

The term "prodrome" derives from the Latin word *prodromus*, which in turn stems from the Greek *prodromos*. In medicine, prodromes can be identified with the early symptoms and signs of a disease that differ from those of the acute clinical phase. The prodromal phase refers to the time interval between the development of prodromal symptoms and the onset of the characteristic manifestations of the fully developed illness [11]. Recognizing and detecting the prodromal symptoms of affective disorders may lead to a more timely and effective treatment of relapse and recurrence [11]. The construct of prodromes is in line with a staging model that considers the longitudinal development of illness [2]. This model defines the extent of progression of a disorder for an individual at a particular point in time (e.g., prodromal, acute, and residual phases). Until the 1990s, staging was largely neglected in psychiatry, in contrast to other medical disciplines. Over the time, the construct of prodromes and staging of affective disorders has been increasingly recognized as important components of clinical assessment. The concept of prodromes in mood disorders has been known for a long time thanks to the first studies of Hays in 1964 [12], Hopkinson in 1965 [13], Winokur and Paykel in 1976 [14,15] and Young and Grabler in 1985 [16], among others. It was with studies from the late 1980s onwards that standardized methods began to be used for the assessment of prodromal symptoms allowing a definition of the construct of prodromes in mood disorders. The study of Fava et colleagues [17] was one of the first studies to focus on the prodromal symptoms of depression using a semi structured interview. Their study revealed that all of the depressed patients displayed at least one prodromal symptom, particularly generalized anxiety and irritability and other non-specific symptoms like impaired work and initiative, fatigue, and initial and delayed insomnia [17]. However, the early stages of mood disorders are diffuse and non-specific, and several relatively non-specific psychopathological presentations have been reported as antecedents to the full symdromal onset. In line with these preliminary studies, reviews about prodromal symptoms in symptomatic patients identified several, although not specific, prodromal symptoms in four specific areas: cognitive, emotional, physical and psychomotor [10,11]. Prodromal symptomatology exists before the onset of unipolar depression and the overall rates of prodromal symptoms ranged from 26 to 100% [10]. Anxiety, tension, irritability, reduced energy, fatigue, sleep disturbances, and somatic complaints were the most commonly reported prodromal symptoms [10]. Regarding the duration of the prodromal phase, the results are influenced by the different methodological tools used, and it ranges from less than a month to several years. However, the mean durations are long enough to indicate that there may be the possibility of effective early interventions in many patients.

To better investigate and study the prodromes of mood disorders, a series of prospective cohort studies have taken place in more recent years. Of particular relevance in this area are the studies of Angst et al. [18] and Tijssen et al. [19]. These studies recruited large community samples and conducted follow-up assessments for up to 15 and 10 years respectively. The Zurich cohort study [18] investigated bipolar spectrum disorder (BSD), rather than BD I. Moreover, the sample was enriched by identifying high-risk subjects (high scores on the Symptom Checklist-90R) and included a control group of a sample of average scorers on the same checklist. Tijssen et al. [19] recruited a sample of young adults at random from the population register for the Munich area by excluding subjects with symptoms attributed to alcohol or substance use, and subjects with a past or current diagnosis of BD at baseline. Both studies provide evidence of clinical features/symptoms preceding the onset of BD. The most commonly reported putatively prodromal features were affective swings and depressive mood. Particularly in the study by Angst et al. [18], mood swings (frequent ups and downs), probably due to a lability and/or immaturity of the mood-regulating system, was the strongest risk factor for the subsequent diagnosis of a BSD, greater even than a family history of mania. This result was in agreement with a previous study of Akiskal et al. who found that mood lability was also the strongest predictor of a diagnostic change from unipolar to BD II disorders in a 11-year prospective study of 559 patients [20]. A recent systematic literature review has further confirmed this finding, showing that longitudinal studies demonstrated a significant association between prospectively identified affective lability in cohorts without BD and subsequent diagnoses of BD or BSD [21].

Affective liability is a sudden, exaggerated, unpredictable, and inappropriate change in emotion. It could be defined as a tendency to experience frequent, rapid fluctuations of intense affect, as well as the inability to regulate these fluctuations or their behavioral sequelae [22]. Whilst the clinical significance of this instability is

now recognized even in the DSM 5 criteria for BD and others mood and related disorders, very little is known about underlying neural mechanisms of mood instability. Difficulties in regulating mood are often also seen in youth at risk to develop mood and anxiety disorders further supporting its predictive nature. Preliminary evidence shows that a combination of clinical and neural measures at MRI scan could predict future affective lability factor scores in youth at risk for BD and thus may indicate risk for future BD [23]. Particularly, future affective lability factor scores such as mixed/mania, irritability, and anxiety/depression, could be predicted by neural function and gray matter structure in brain regions supporting brain reward and emotion processing [23]. This is in agreement with studies showing alterations of cortical thickness in adults with BD, BD at-risk youth and adults, and depressed youth relative to healthy controls [24]. These findings are too small and inconsistent to serve as diagnostic makers, they might be of particular relevance for within-subject comparisons in the context of neurodevelopment and longitudinal staging of BD. Since there is a substantial heritability of cortical thickness, stress response and cerebral glutamate levels [24], neuroimaging and genetic tools and clinical assessements might be combined to increase their clinical utility. For example, reduced cortical thickness along with glutamatergic abnormalities found in BD and subjects at risk, could be the result of the underlying susceptibility genes (i.e. glutamatergic system) and environmental factors (i.e. stress) during life, acting on the fragility of the cortical structure leading to the clinical expression of BD [24,25]. The possibility of being able to identify, by means of objective data (i.e., neuroimaging, genetics, electrophysiological) combined with through clinical assessments, subjects at risk of developing future affective lability and consequently a possible BD, opens the door to early intervention in these subjects. Particularly, younger patients enhanced neuroplastic potential and targeting these patients at early stages of illness is beneficial in preventing cortical deterioration. These early interventions may take the form of psychotherapeutic, pharmacological and/or social interventions, within the broader framework of a holistic intervention. For instance, physical activity has been shown to be able to induce neuroplasticity in medial temporal cortical regions in subjects with early psychosis [26].

Apart from symptomatic prodromes such as affective lability, it is necessary to know and identify the social risk factors of mood disorders. In a holistic bio-psycho-social approach to the staging and development of mood disorders, the clinician should always pay attention to various environmental factors that cumulatively to the genetic risk, favor the onset of the disorder. In this context, research on monozygotic twins discordant for mood disorders attempted to demonstrate how different environmental events can trigger the development of a mood disorder. As is well known, among the most important factors are intimate love relationship, degree of planfulness, occupational stressors and major traumatic life events [27,28]. Typically, monozygotic twin studies tend to agree that the differences between twin pairs grow substantially over the human life span, emphasizing the importance of cumulative environmental experiences. Most of this research pointed out how temperamental differences can magnify themselves across the life courses, describing a process called cumulative continuity, i.e. individuals actively seek out environments that are compatible with their dispositions [29]. This means that individuals' affective temperaments can lead them to select environments that, in turn, reinforce and sustain those same behavior pattern across the life course through the progressive accumulation of its own consequences [27].

Hence the importance for the clinician to work with the patient in the clinical practice in order to identify symptomatic prodromes and social risks factors to develop effective strategies to carefully manage them. It is recommended to monitor the person's mental state, possibly with new digital assessment methods, and encourage a healthy lifestyle, be knowledgeable about the symptoms of the disorder, and know when to ask for professional help. Nowadays, among the various tools available to the clinician to monitor a patient's daily life and response mechanisms to stressors, we can mention the ecological momentary assessment (EMA). EMA describes a type of data collection that allows clinicians and researchers to gather detailed insight into the daily lives of patients by inquiring about the subjects' mental state in the moment, avoiding memory recall bias. EMA techniques provide methods by which a patient can report on symptoms, affect, behavior and cognitions close in time to experience, and these reports are obtained many times over the course of a day [30].

Discussion

Research on prodromal symptoms and staging of mood disorders has not yet provided the expected impact in clinical practice. It remarks that the traditional, linear and oversimplified medical models in psychiatry should be supplanted by an updated multifactorial model. It is necessary to carefully consider the predisposition to disease, the time and manner of symptoms presentation, multiple disease forms, variable adaptive responses, and the role of social and cultural factors. One of the main difficulties with this approach is where to locate prodromal symptoms that precede the first depressive or manic episode and how to describe subthreshold affective syndromes. To date, still, we do not have a

clear definition of the stages of mood disorders, prodromal symptoms are still too unspecific, and we have no specific personality trait predicting affective disorders. While the recognition of prodromal symptoms may help the clinician to psycho-educate the patient and his family, there are no specific pharmacological treatments in specific stages. The data respect specific treatments in specific stages are still too scarce and this is especially pertinent for early subthreshold stages of illness. A central issue in research into the prodromal symptoms and staging of mood disorders is the great phenotypic heterogeneity of these and the absolute lack of biomarkers. In contrast to other branches of medicine, psychiatry suffers from a diagnostic and classification system that is not based on pathophysiology and etiology, being dependent on nosological tradition, expert consensus, psychometric reliability, and clinical utility. In this context, the definition of stages in affective disorders would benefit from the joint use of symptom identification, biomarkers, and endophenotypes [24,31,32]. Dissecting psychiatric macro phenotypes into biologically valid components presumes the ability to make diagnoses more certain, specific, and amenable to tailored treatments. Particularly, research on endophenotypes is of a great value as it has the merit to reduce heterogeneity by defining biological traits that are more direct expressions of gene effects. The search of endophenotypes has a prevention potential as they can be used to identify individuals who are at risk of developing a mental disorder. Naturally, endophenotypes could contribute to a clinically useful reclassification that will improve the treatment of mental disorders [24]. To date, there is considerable evidence to support a possible developmental etiology of mood disorders. Particularly, the presence of abnormalities already presents at the beginning of these disorders and even in young at-risk subjects confirms this hypothesis. For instance, there is substantial evidence that early white matter abnormalities (WMAs) with resulting fronto-limbic dissociation play a central role in the pathophysiology of BD [33]. Starting from the fetal period, the interplay between environmental risk factors such as stress and infections, and the genetic susceptibility of different systems like immune, circadian and glutamatergic systems among others, shape a vulnerable brain. Early WMAs might be the result of this vulnerable brain on which new stressors are added in young adulthood which favour the onset and progression of the full disorder as the brain does not have the appropriate resilience to resist [24]. Importantly, studies on BD show that these WMAs may be at least partially normalized by medications via glutamatergic neuroplasticity processes. Interestingly, mood stabilizers have well-documented neuroprotective and neurotrophic effects in vivo and in vitro. For instance, long-term lithium treatment increases total grey matter volume [34], enhances levels of N-acetyl-aspartate, a marker of neuronal viability [35]; and increases diffusion tensor imaging (DTI) measures of axial diffusivity (AD) in several white matter fibre tracts, including interhemispheric, limbic, and large frontal, parietal, and fronto-occipital connections in the brains of BD patients, correlating with its clinical efficacy [36]. This suggests that lithium and other drugs might counteract the detrimental influences of BD on white matter structure, contributing to the functional integrity of the brain [36]. Taken together, these data encourage research on the use of specific types of medication, psychoeducation, and psychotherapy from the earliest stages of the disorder.

Research on prodromal symptoms and staging of mood disorders introduced by Fava & Kellner in the 1990s [2] is still relevant and deserves more attention. There are still several unmet needs. Despite great advances in neuroimaging, structural, and functional neuroimaging explain not more than 2% of the variance in mood disorders, so it is of little use for diagnosis [37]. Hence the growing importance of combining different biological markers such as genetic risk scores, neuroimaging, and psychosocial assessments in disease prediction algorithms. As already discussed, this could be done even better by reducing phenotypic heterogeneity through the study of endophenotypes. This would make it possible to assess the effect of various combined treatments (e.g., drugs, psychotherapy, psychosocial treatments) on the progression of mood disorders and establish the risk/benefit ratio of starting treatment at an early stage of the disorder. New treatment approaches capable to enhance neuroplasticity and neuroprotection, working on the glutamate system, may enhance psychosocial interventions and deserve more attention as a potential treatment in the early stages of the disorder.

Conclusions

The timely recognition of prodromal symptoms and environmental crisis factors in individual patients may facilitate early intervention upon relapse, since prodromal symptoms of relapse tend to mirror those of the initial episode [17]. This could be implemented by having a history of illness progression, and investigating prodromal symptoms when the patient is judged as being in remission. After the acute phase, it may be difficult to assess whether partial or full remission occurred without knowing the patient well before the onset of the disorder. Residual symptoms may be caused by a partial persistence of the disorder or an aggravation of a pre-existing abnormal personality traits. Such an aggravation may be caused by various factors like, for instance, life events and stressors [2]. This makes it possible to significantly shorten the duration of the episode [38] by initiating phar-

macotherapy and/or psychotherapy when the same symptoms appear again, before the full manifestations of the disorder. Moreover, according to a staging method [2] research suggested consistency of the prodromal symptom profile and duration within individuals across depressive episodes and similarities between prodromal and residual symptoms of the same depressive episode [10]. This implies that treatment directed toward the residual phase (i.e. sequential model) might provide long-term benefits in preventing relapse compared to just one course of treatment [39]. Before discontinuing or decreasing medication on discharging the patient from psychotherapy, psychiatrists may educate patients and their families to be particularly aware of the specific symptoms that preceded the illness episode and rapidly notify the psychiatrist. Psychoeducation of the patient, based on the explanation of how to recognize prodromes and the benefits and risks of treatments, has shown to improve compliance and outcomes as well as reduce relapse in affective disorders.

Acknowledgments

This work was supported by #NEXTGENERATIONEU (NGEU) and funded by the Italian Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022)

Conflict of interest statement

The authors have no conflicts of interest to declare.

Funding

The authors have no funding to declare.

Author's contributions

The authors have contributed equally to this paper.

References

1 Gonnella JS, Hornbrook MC, Louis DZ. Staging of disease. A case-mix measurement. JAMA 1984;251:637-44.

2 Fava GA, Kellner R. Staging: a neglected dimension in psychiatric classification. Acta Psychiatr Scand 1993;87:225-30. https://doi.org/10.1111/j.1600-0447.1993.tb03362.x

3 Cosci F, Fava, GA. Staging of mental disorders: systematic review. Psychother Psychosom 2013;82:20-34. https://doi.org/10.1159/000342243

4 Duffy A. Toward a comprehensive clinical staging model for bipolar disorder: integrating the evidence. Can J Psychiatry 2014;59:659-66. https://doi.org/10.1177/070674371405901208

5 Berk M, Conus P, Lucas N, et al. Setting the stage: from prodrome to treatment resistance in bipolar disorder. Bipolar Disord 2007;9:671-8. https://doi.org/10.1111/j.1399-5618.2007.00484.x

6 Kapczinski F, Dias VV, Kauer-Sant'anna M, et al. Clinical implications of a staging model for bipolar disorders. Expert Rev Neurother 2009;9:957-66. https://doi.org/10.1586/ern.09.31

7 Kupka R, Duffy A, Scott J, et al. Consensus on nomenclature for clinical staging models in bipolar disorder: A narrative review from the International Society for Bipolar Disorders (ISBD) Staging Task Force. Bipolar Disord 2021;23:659-678. https://doi.org/10.1111/bdi.13105

8 Mcgorry PD, Hickie IB, Yung AR, et al. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Aust N Z J Psychiatry 2006;40:616-22. https://doi.org/10.1080/j.1440-1614.2006.01860.x

9 Berk M, Post R, Ratheesh A, et al. Staging in bipolar disorder: from theoretical framework to clinical utility. World Psychiatry 2017;16:236-244. https://doi.org/10.1002/wps.20441

10 Benasi G, Fava GA, Guidi J. Prodromal Symptoms in Depression: A Systematic Review. Psychother Psychosom 2021;90:365-372. https://doi.org/10.1159/000517953

11 Fava GA, Kellner, R. Prodromal symptoms in affective disorders. Am J Psychiatry 1991;148:823-30. https://doi.org/10.1176/ajp.148.7.823

12 Hays P. Modes of Onset of Psychotic Depression. Br Med J 1964;2:779-84. https://doi.org/10.1136/bmj.2.5412.779

13 Hopkinson G. The Prodromal Phase of the Depressive Psychosis. Psychiatr Neurol (Basel), 1965;149:1-6. https://doi.org/10.1159/000128798.

14 Winokur G. Duration of illness prior to hospitalization (onset) in the affective disorders. Neuropsychobiology 1976;2:87-93. https://doi.org/10.1159/000117535

15 Paykel ES, Prusoff BA, Tanner J. Temporal stability of symptom patterns in depression. Br J Psychiatry 1976;128:369-74. https://doi.org/10.1192/bjp.128.4.369

16 Young MA, Grabler P. Rapidity of symptom onset in depression. Psychiatry Res 1985;16:309-15. https://doi.org/10.1016/0165-1781(85)90122-2

17 Fava GA, Grandi S, Canestrari R, et al. Prodromal symptoms in primary major depressive disorder. J Affect Disord 1990;19:149-52. https://doi.org/10.1016/0165-0327(90)90020-9

18 Angst J, Gamma A, Endrass J. Risk factors for the bipolar and depression spectra. Acta Psychiatr Scand Suppl 2003;15-9. https://doi.org/10.1034/j.1600-0447.108.s418.4.x

19 Tijssen MJ, Van Os J, Wittchen HU, et al. Evidence that bipolar disorder is the poor outcome fraction of a common developmental phenotype: an 8-year cohort study in young people. Psychol Med 2010;40:289-99. https://doi.org/10.1017/S0033291709006138

20 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. Arch Gen Psychiatry 1995;52:114-23. https://doi.org/10.1001/archpsyc.1995.03950140032004

21 Taylor RH, Ulrichsen A, Young AH, et al. Affective lability as a prospective predictor of subsequent bipolar disorder diagnosis: a systematic review. Int J Bipolar Disord 2021;9:33. https://doi.org/10.1186/s40345-021-00237-1.

22 Marwaha S, HE Z, Broome M, et al. How is affective instability defined and measured? A systematic review. Psychol Med 2014;44:1793-808. https://doi.org/10.1017/S003329171300240

23 Bertocci MA, Hanford L, Manelis A, et al. Clinical, cortical thickness and neural activity predictors of future affective lability in youth at risk for bipolar disorder: initial discovery and independent sample replication. Mol Psychiatry 2019;24:1856-1867. https://doi.org/10.1038/s41380-018-0273-4

[24] Guglielmo R, Miskowiak KW, Hasler G. Evaluating endophenotypes for bipolar disorder. Int J Bipolar Disord 2021;9:17. https://doi.org/10.1186/s40345-021-00220-w

[25] Guglielmo R, Hasler G. The neuroprotective and neuroplastic potential of glutamatergic therapeutic drugs in bipolar disorder. Neurosci Biobehav Rev 2022;142:104906. https://doi.org/10.1016/j.neubiorev.2022.104906

[26] Woodward ML, Lin J, Gicas KM, et al. Medial temporal lobe cortical changes in response to exercise interventions in people with early psychosis: a randomized controlled trial. Schizophr Res 2020;223:87-95. https://doi.org/10.1016/j.schres.2020.05.043.

[27] Kendler KS, Halberstadt LJ. The road not taken: life experiences in monozygotic twin pairs discordant for major depression. Mol Psychiatry 2013;18:975-84. https://doi.org/10.1038/mp.2012.55

[28] Kendler KS, Eaves LJ, Loken EK, et al. The impact of environmental experiences on symptoms of anxiety and depression across the life span. Psychol Sci 2011;22:1343-52. https://doi.org/10.1177/0956797611417255

[29] Allport GW. Personality: a psychological interpretation. New York, NY: Holt, Rinehart & Winston 1937.

[30] Moskowitz DS, Young SN. Ecological momentary assessment: what it is and why it is a method of the future in clinical psychopharmacology. J Psychiatry Neurosci 2006;31:13-20.

[31] Hasler G, Drevets WC, Manji HK, et al. Discovering endophenotypes for major depression. Neuropsychopharmacology 2004;29:1765-81. https://doi.org/10.1038/sj.npp.1300506

[32] Hasler G, Drevets WC, Gould TD, et al. Toward constructing an endophenotype strategy for bipolar disorders. Biol Psychiatry 2006;60:93-105. https://doi.org/10.1016/j.biopsych.2005.11.006

[33] Benedetti F, Yeh PH, Bellani M, et al. Disruption of white matter integrity in bipolar depression as a possible structural marker of illness. Biol Psychiatry 2011;69:309-17. https://doi.org/10.1016/j.biopsych.2010.07.028

[34] Moore GJ, Bebchuk JM, Wilds IB, et al. Lithium-induced increase in human brain grey matter. Lancet 2000b;356:1241-2. https://doi.org/10.1016/s0140-6736(00)02793-8

[35] Moore GJ, Bebchuk JM, Hasanat K, et al. Lithium increases N-acetyl-aspartate in the human brain: in vivo evidence in support of bcl-2's neurotrophic effects? Biol Psychiatry 2000a;48:1-8. https://doi.org/10.1016/s0006-3223(00)00252-3

[36] Benedetti F, Bollettini I, Barberi I, et al. Lithium and GSK3-beta promoter gene variants influence white matter microstructure in bipolar disorder. Neuropsychopharmacology 2013;38:313-27. https://doi.org/10.1038/npp.2012.172

[37] Winter NR, Leenings R, Ernsting J, et al. Quantifying Deviations of Brain Structure and Function in Major Depressive Disorder Across Neuroimaging Modalities. JAMA Psychiatry 2022;79:879-888. https://doi.org/10.1001/jamapsychiatry.2022.1780

[38] Kupfer DJ, Frank E, Perel JM. The advantage of early treatment intervention in recurrent depression. Arch Gen Psychiatry 1989;46:771-5. https://doi.org/10.1001/archpsyc.1989.01810090013002.

[39] Guidi J, Fava GA. Sequential Combination of Pharmacotherapy and Psychotherapy in Major Depressive Disorder: A Systematic Review and Meta-analysis. JAMA Psychiatry 2021;78:261-269. https://doi.org/10.1001/jamapsychiatry.2020.3650