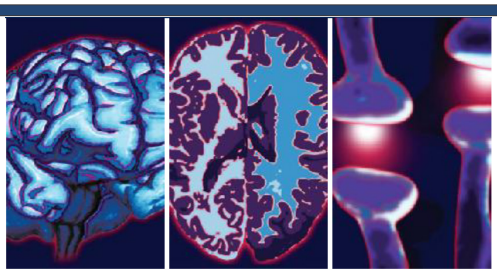
Perspective



Bipolar Disorder Clinical Progression Multiple Sclerosis Type Group Classification: A New Perspective on Subtyping.

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Introduction

Bipolar disorder was first systematically described in the historical record by Hippocrates (460–337 BC). For many years, there has been no clear definition or research on this disease. Starting in the 19th century, the concepts of mania and melancholia and the connection between them became the focus of attention again, and the definition of "modern" bipolar disorder began to be formed [1].

The first attempt to categorize and standardize mental illness in the DSM-I (1952) classified manic-depression as a psychotic disorder "characterized by a varying degree of personality integration and a failure to test and evaluate external reality in various spheres" [2]. With the DSM-II, manic depression was characterized as a "manic-depressive illness" and classified under Affective Disorders. In the DSM-II, these disorders are detailed as being characterized by a "single disorder of mood, either extreme depression or elation, that dominates the mental life of the patient" [3]. The DSM-III (1980) characterizes disease with specific diagnostic criteria and major dissimilarity from previous versions, describing the symptoms and criteria required for the diagnosis of "episode" [4]. Another improvement in this edition is the differentiation of depression into unipolar and bipolar types. Although the mixed episode was defined in detail in DSM-IV, no major diagnostic change was observed. Rapid-Cycling Bipolar Disorder (RCBD) is defined in this edition as a condition in which the patient experiences four or more episodes of mania and/or major depression per year [5]. And the last one, the criteria for all episodes (manic, hypomanic, and depressive) in the DSM-V, generally remained the same, except for the novelty of including drug- and substance-induced episodes in the diagnosis [6].

Despite many years of diagnostic changes and acceptance, there is no widely accepted disease subtyping classification yet. The difficulties and differences in the diagnostic criteria for bipolar disorder stem from the fact that patients belong to a broad spectrum rather than a single disease. The wide range of treatment responses, life-long attacks, and severity of attacks among the patients necessitate classification regarding the course of the disease. It is worth considering and researching whether the disease prognosis subtypes used in multiple sclerosis can be revised to include bipolar disorder because it progresses with attacks and remissions, has significant neurological pathology, and has familial comorbidity with bipolar disorder [7].

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Multiple Sclerosis Phenotypes

Multiple Sclerosis (MS), a chronic disease of the Central Nervous System (CNS) with demyelination and axonal degeneration, is characterized by heterogeneity in the symptoms, disease course, and outcomes. The first formally defined MS phenotypes were proposed in 1996 by the U.S. National Multiple Sclerosis Society Advisory Committee [8].

The most common MS phenotype is relapsing-remitting MS, found in about 85% of patients and characterized by alternating periods of neurological dysfunction episodes and periods of relative clinical stability free of new neurological symptoms. Relapses result in residual deficits in almost half of episodes, leading to stepwise neuronal impairment. The severity of inflammatory pathology and frequency of relapses, most prominent in young adulthood, decrease with advanced disease and age. Most untreated relapsing-remitting MS patients progress into the secondary progressive MS phenotype, with a median time to the progressive phase of about 19 years after the onset of MS [9]. About 15% of patients will develop a primary progressive phenotype, characterized by the lack of an initial remission-relapsing pattern and progression from the disease onset [10].

Bipolar Disorder Clinical Progression MS Type Group

Classification

When classifying the clinical course of bipolar disorder, the term "stage" is used, implying that all patients constitute a homogeneous group and that their illness will progress in stages. Dividing all patients diagnosed with bipolar disorder into stages creates the perception that each patient will progress to the next stage. When using the term "group" in clinical course classification, the heterogeneous nature of the disease and its subtyping are highlighted. For these reasons, the term "group" is used in the clinical course classification of bipolar disorder and MS subtyping.

Multiple Sclerosis (MS) is a chronic and progressive disease characterized by periods of relapse. The disease typically begins in young adulthood, and the duration of untreated illness is associated with increased morbidity and mortality [11]. Bipolar disorder, with its relapses beginning in young adulthood, is also a progressive disease, contributing to morbidity and mortality. Relapses in both diseases are associated with increased inflammation [12,13]. Considering the many common features of the two diseases, the idea arises that the clinical classification system used for many years in MS can also be applied to the clinical course of bipolar disorder. A comparison of clinical functioning across years across bipolar disorder clinical progression MS model groups are shown in Figure 1.

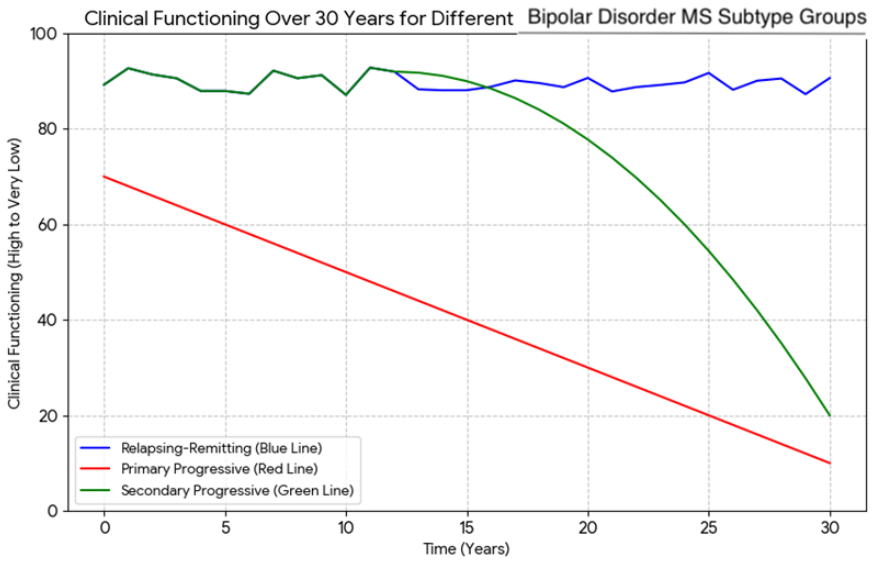

Figure 1. Clinical Functioning Across Years in Bipolar Disorder MS Subtype Groups.

Relapsing-remitting bipolar disorder group

"Classical" bipolar disorder patients, first described by psychiatrists and included in clinical studies, progress with mood attacks and periods of remission. The progression of attacks, which is the diagnostic feature of the disease, covers most patients with bipolar disorder as well as the MS patient group phenotype. Relapsing-remitting bipolar disorder corresponds to Clinical Stage 2 in the clinical course classification made by Berk et al. in 2007 and to Stage 3 due to the recurring nature of the attacks [14]. In their 2009 classification, Kapczinski et al. defined relapsing-remitting bipolar disorder as Stage I patients with BD who present well-established periods of euthymia and the absence of overt psychiatric morbidity between episodes—and Stage II—patients who present rapid cycling [15]. The high permeability between Stages I and II necessitated grouping these groups together. Patients with relapsing episodes are at high risk for rapid cycling, making it impossible to make a definitive distinction; the lifetime rate of rapid cycling is approximately 10% within a year [16].

In the Kupka and Hillegers's staging model classified patients experiencing their first episode as Stage 2, and patients who relapse but recover intermittently as Stage 3 [18]. Most individuals with first-episode bipolar disorder experience relapse during the course of their illness, with annual relapse rates estimated at 21.9%–26.3% [19]. Given the high relapse rates and functional loss, it is necessary to classify patients with their first episode according to their clinical course. The Relapsing-Remitting Group encompasses Stages 2 and 3 in Kupka and Hillegers's 2012 classification.

In their 2014 clinical classification, Duffy et al. divided patients with relapses into Stage 2, Stage 3, and Stage 4a, using various criteria [17]. The "MS Model" proposed in this article, however, places patients diagnosed with bipolar disorder without progressive deterioration into the Relapsing-Remitting group, taking into account the variable nature of the disease and demonstrating the need for effective treatment to prevent future relapses.

A comparison of the bipolar disorder MS subtype grouping model with other bipolar disorder clinical course classification studies is presented in Table 1.

Table 1: Comparison of bipolar disorder staging models with the bipolar disorder clinical progression Multiple Sclerosis (MS) model groups.

Yazici MS subtype grouping model (2025)	Berk et al. staging model (2007)	Kapczinski et al. staging model (2009)	Kupka & Hillegers staging model (2012)	Duffy et al staging model (2014)
Relapsing-Remitting Bipolar Disorder Group	Stage 2- First threshold mood episode	Stage I- Well-defined periods of euthymia without overt psychiatric symptoms	Stage 1D- increased risk, with recurrent Major Depressive Episodes	Stage 2- Positive family history + minor mood disorder and/ or clinically significant mood symptoms
	Stage 3a- Recurrence of subthreshold mood symptoms	Stage II- Symptoms in interepisode periods related to comorbidities	Stage 2A- 1st manic episode (BD I diagnosis) without previous history of depressive episode(s) and without depression immediately preceding or following 1st manic episode	Stage 3- Positive family history + major depressive disorder, single, or recurrent

	Stage 3b- First threshold relapse Stage 3c- Multiple relapses		Stage 2B- 1st hypomanic (BD II diagnosis) or manic episode (BD I diagnosis) without previous history of depressive episode(s) but with depression immediately preceding or following 1st (hypo)manic episode	
			Stage 2C- 1st hypomanic (BD I diagnosis) or manic episode (BD I diagnosis) with previous history of depressive episode(s), with or without depression immediately preceding or following 1st (hypo)manic	Stage 4A- Classical episodic bipolar disorder (BDI, II, NOS) with or without psychotic features in episodes and good quality of remission
			Stage 2D- 1st depression after hypomanic episode (BD II diagnosis)	
			Stage 3A- Recurrence of subsyndromal depressive or manic symptoms after the diagnosis of BD	
			Stage 3B- Recurrent BD(recurrence of any depressive, hypomanic, or manic/mixed episode) and with full symptomatic and functional recovery between episodes	

Secondary Progressive Bipolar Disorder Group	Stage 4- Persistent unremitting illness	Stage III- Marked impairment in cognition and functioning	Stage 3C- Recurrent BD (recurrence of any depressive, hypomanic, or manic/mixed episode), with subsyndromal symptoms and/ or impaired functioning between episodes	Stage 4A- Non-classical bipolar disorder (cyclic mania, mixed mania, BDI, II, NOS) typically not fully remitting and often attenuated psychotic symptoms
				Stage 4B- Classical bipolar disorder with residual symptoms: Reflecting burden of illness effects (addiction, medical comorbidity, non-optimal treatment)
Primary Progressive Bipolar Disorder Group	Stage 4- Persistent unremitting illness	Stage IV- Unable to live autonomously owing to cognitive and functional impairment	Stage 4A- Chronic depressive, manic or mixed episode(s), without symptomatic and functional recovery for 2 years	Stage 4B- Psychotic spectrum bipolar disorders (schizoaffective: poorly remitting) chronic fluctuating and cognitive and functional decline
			Stage 4B- Rapid cycling (≥ 4 mood episodes/ year), without symptomatic and functional recovery for 2 years	

Primary progressive bipolar disorder group

A subgroup of bipolar disorder patients with an early onset, familial history, and severity and frequency of exacerbations that are significantly higher than those of "classical" patients draws attention in clinical practice [20]. The characteristics of this group are a low response to drug therapy, low adherence to treatment, a high suicide rate, persistently low functionality, and the absence of a significant remission period. In patients with bipolar disorder, cognitive impairment develops in proportion to the number and duration of attacks; patients who experience frequent and long attacks, or rather, who do not fully recover between attacks, have intense cognitive impairment [21]. For this group, which can also be classified as treatment-resistant bipolar disorder, the use of depot antipsychotics and clozapine stands out as a significant difference in treatment from the relapsing remitting group [22].

Secondary progressive bipolar disorder group

It seems possible for patients who started with a remission-relapsing form of bipolar disorder but did not receive adequate treatment, had substance use disorder [23], and experienced

an increase in attacks due to organic medical disease to pass into the progressive phase after a while. Cognitive deterioration becomes particularly pronounced in a group of bipolar disorder patients with advancing age, and as the duration of illness increases, cognitive performance and clinical functioning decline significantly [24]. Patients previously classified as relatively benign relapsing-remitting bipolar disorder may later experience progressive deterioration; the "Secondary Progressive Bipolar Disorder Group" subtype is recommended for this subgroup.

Summary

Bipolar disorder patients form a heterogeneous group from onset to overall prognosis. This diversity is not fully reflected in clinics and research, leading to ineffective treatments and failure of research. The prognosis subtype groups used in multiple sclerosis for about twenty-five years can also be applied to bipolar disorder.

Conclusion

There is a need to categorize this heterogeneous patient group to investigate the etiological factors of bipolar disorder and to find highly valid results in clinical studies. The fact that severe patients seen in clinical practice are not fully included in the diagnosis systems and treatment algorithms pushes psychiatrists to take risks in treatment. It will help to classify patients according to disease progression, speed up treatment selection, and reduce the expectation rate for treatment to realistic levels. Conducting special studies on subgroups will increase the probability of successful treatment for patients. Disease progression should be decisive when new diagnostic systems and clinical trials are undertaken.

The progression classification studies carried out so far have not been fully clarified yet, and this article aims to bring a new perspective to the field.

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