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MOOD DISORDERS (E BACA-GARCIA, SECTION EDITOR)

A Review on the General Stability of Mood Disorder Diagnoses Along the Lifetime

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Abstract

Purpose of Review The purpose of this review is to review the most recent literature regarding diagnostic stability of mood disorders, focusing on epidemiological, clinical-psychopathological, and neurobiological data for unipolar and bipolar affective disorders.

Recent Findings Unipolar depression follows a chronic course in at least half of all cases and presents a considerable diagnostic stability across all age ranges. Studies using latent class analysis are allowing improved profiling of depressive subtypes and assessment of their prevalence. Advances have been made in our understanding of the neurobiological underpinnings of depression, with data highlighting the roles of amyloid deposits, the ApoE4 allele, and atrophy of the anterior hippocampus or frontal cortex. The diagnostic instability of bipolar disorder is manifest in the early years, seen in both the extent of diagnostic delay and the high rate of diagnostic conversion from unipolar depression. Regarding disruptive mood dysregulation disorder, we have little data to date, but those which exist indicate a high rate of comorbidity and minimal diagnostic stability for this disorder.

Summary Diagnostic stability varies substantially among mood disorders, which would be related to the validity of current diagnostic categories and our diagnostic accuracy.

Keywords Diagnosis stability · Mood disorders · Bipolar disorder · Depressive disorder · Latent class analysis · Disruptive mood dysregulation disorder · Dementia

Introduction

The diagnostic classification of mood disorders, particularly major depressive disorder and bipolar disorder, is a dynamic process. In a recent meta-analysis, Ratheesh et al. found that at least one quarter of patients diagnosed with a major depressive episode will be subsequently diagnosed with bipolar disorder [1••]. Bipolar disorder may carry a diagnostic delay of up to 10 years, usually following an original diagnosis of major depressive disorder [2]. As such, great effort has been made to differentiate unipolar depression from bipolar (references) and facilitate prompt identification [3–6]. A similar process occurs between major depressive disorder and dementia, two diseases which have been a focus of diagnostic stability studies due to their overlapping presentations (either concurrent or sequential) and their similar neurobiological underpinnings. In the present article, we will review the most recent literature regarding diagnostic stability of mood disorders, focusing on epidemiological, clinical-psychopathological, and neurobiological data for unipolar and bipolar affective disorders.

This article is part of the Topical Collection on *Mood Disorders*

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Materials and Methods

We conducted a PubMed search of articles related to diagnostic stability of mood disorders, with particular focus on those published since 2014. Examples of queries include the following: ((“Mood Disorders”[Mesh]) OR (“Bipolar Disorder”[Mesh] OR “Bipolar and Related Disorders”[Mesh]) OR (“Depression”[Mesh] OR “Depressive Disorder”[Mesh]))

AND Course, AND diagnos*, AND diagnosis stability, AND longitudinal course, AND ((“follow-up”) or (“prospective study”) or (“course”) or (“longitudinal analysis”)), AND Congruence of diagnoses, ((“Mood Disorders”[Mesh]) OR (“Depression”[Mesh] OR “Depressive Disorder”[Mesh])) AND latent class analysis, Disruptive Mood Dysregulation Disorder, (“Dementia”[Mesh]) AND (“Depression”[Mesh] OR “Depressive Disorder”[Mesh]). We have also included pertinent bibliographic references from those articles reviewed. We present a narrative overview on all eligible publications.

Results and Discussion

Table 1 summarizes the results from reviewed literature of mood disorders.

Unipolar Depression

Depressive disorders follow a chronic course in at least half of all cases [7–9], with symptom patterns that usually remain stable over time [10••]. According to an 11-year follow-up study of adults diagnosed with major depressive disorder (MDD) ($n = 392$), dysthymia ($n = 94$), or both ($n = 53$), 34% of those with MDD and 43% with dysthymia had their diagnoses switched to other forms of depression, anxiety, or alcohol use disorder [11, 12].

Studies with Latent Class Analysis

In recent years, numerous studies with latent class analysis (LCA) have shown evidence supporting the typology of depression based on symptom categories (typical/melancholic/cognitive vs. atypical/psychosomatic depression) and on severity (mild vs. severe depression) [13].

Lamers et al. identified three subtypes of depression: moderate, severe typical (or melancholic), and severe atypical. Seventy-six percent of patients maintained the same subtype over the 2 years studied. The most common change from moderate was to severe typical (19%), from severe typical was to moderate (24%), and from severe atypical to severe typical (8%) [10••]. Similar results were obtained by Rodgers et al., who additionally found that among those age 29 to 50 years, diagnostic stability was greater in men than women, which they attributed to the influence of perimenstrual hormonal fluctuations [14].

In a study of 13,745 subjects ages 40–59 followed over 4 years, four different trajectories of depressive symptomatology were identified: minimal symptoms (35.1% of men vs. 36.3% of women), mild persistent (47.4 vs. 50%), moderate persistent (14.4 vs. 12.3%), and severe persistent (3 vs. 1.5%) [15].

In a study of 11,640 subjects ages 18–48 with primary diagnosis of MDD, four trajectories of healthcare engagement were identified: brief contact (77% with low probability of contact after 2 years post diagnosis), prolonged initial contact (12.8% defined by decreasing contact with a specialist in the 5 years following an episode), later reentry (7.1% with moderate probability of contact after 5 to 10 years), and persistent contact (3.1% with minimal loss of contact) [16].

LCA has been employed in specific populations of depressed patients. Among those with multiple sclerosis, it was used to demonstrate a distribution of 10% severe, 26.2% moderate, and 63.8% mild [17]. Among patients with postpartum depression, LCA has been used to identify specific risk factors including symptom severity, symptom onset during pregnancy, perinatal complications, and history of mood disorder or suicidal ideation [18].

Regarding those with subclinical depression, around 80% do not go on to develop MDD in the subsequent 6 months, and those who did often had a history of previous depressive disorders. [19•].

Infancy and Childhood

Agerup et al. analyzed a sample of 242 adolescents between 15 and 20 years of age, then followed them for 5 years. Among those who were not diagnosed with MDD at age 15, 70% were still not diagnosed at age 20, while 10% had developed minor depression and 19% had MDD. Of those already diagnosed with minor depression by age 15, 54% achieved complete remission by age 20, while 5% retained the same diagnosis and 42% progressed to MDD. Among those already diagnosed with MDD by age 15, 27% achieved complete remission by age 20, while 11% transitioned to minor depression and 62% retained the same MDD diagnosis [20].

Longer follow-up studies have found the presence of depressive symptoms in infancy to be an important risk factor for the development of MDD in adulthood [21, 22].

Old Age

There is a lower prevalence of depressive disorders among the elderly, despite an increased rate of subclinical depressive symptoms [23]. In those presenting with a depressive disorder, the majority follow a chronic course [24]. The most important negative prognostic features include recurrent depressive episodes, poor overall health, and the presence of dementia [25].

Mixed Anxiety-Depressive Disorder

Mixed anxiety-depressive disorder (MADD) is a category which has disappeared from the recent diagnostic classification of DSM-5, and which showed very little diagnostic stability. In a 17-month follow-up, only 23% of patients maintained their diagnosis of MADD, with 47% achieving

Table 1 Summary of main results of the studies about stability of mood disorders

Author/year	Study type	Sample size	Initial diagnose	Age (mean, median, range)	Follow-up time	Variable examined	Results
Markkula (2011)	Cohort study using a nationally representative sample	5.806	MDD = 392, dysthymia = 94	Aged 30 and above	11 years	Diagnosis stability	34% of those with MDD and 43% with dysthymia changed their diagnoses to other forms of depression, anxiety or alcohol use disorder
Lamers (2012)	Cohort study using LCA	488	Moderate subtype (39%), severe typical subtype (30%), severe atypical subtype (31%)	Aged 18–65	2 years	Diagnosis stability	76% stability, greatest stability in the severe atypical class (79%)
Kim (2015)	Retrospective cohort study using a four-latent class growth trajectory model	13.745	MMD	40–59 years	Median follow-up 4.0 years	Four trajectories of depressive symptoms	Minimal (35.1%, $n = 2374$), persistent-mild (47.4%, $n = 4545$), persistent-moderate (14.4%, $n = 987$), persistent-severe (3.0%, $n = 207$)
Musliner (2016)	Cohort study	11.640	MDD	18–48 years	10 years	Four trajectory classes	Brief contact (77.0%), prolonged initial contact (12.8%); later reentry (7.1%); and persistent contact (3.1%)
Davidson (2015)	Longitudinal cohort study of primary care patients	250	Subthreshold depression	Mena age 50.3 years	Six-month follow-up	Presence of MDD during the following	45 (18.0%) met the criteria for MDD at least once over the following 6 months
Agerup (2014)	Longitudinal cohort study	242	No depression = 134, minor depression = 45, MDD = 63	Followed from age 15 to age 20	5 years	Stability and change in depression diagnosis	The proportion without depression practically unchanged. The prevalence of major and minor depression did not increase significantly ($p = 0.24$).
Hettema (2015)	Population-based survey study using LCA	7500	MADD	Mean age 29.3	17 months (two waves)	Classification results in the second wave of the subjects identified as MADD during the first wave.	47% were in remission, 23% had persistent MADD, and 30% developed syndromal anxiety or depressive disorder.
Ostergaard (2014)	Population-based, historical prospective cohort study	8588	UPD	Mean age 55.2	12 years follow-up	Diagnostic conversion from UPD to BD	609 (7.1%) developed BD during follow-up
Salvatore (2013)	Prospective naturalistic study	107	First lifetime psychotic MDD episode	Mean age 34.6, range 10–82 years	Over 2 years or more	Diagnostic stability	70.1% sustained the diagnosis, 29.9% changed their diagnosis to BD (18.7%) or schizoaffective disorder (11.2%)
Ratheesh (2017)	Meta-analysis	56 studies included	MDD	Studies with pediatric, adolescent, and adult samples up to the age of 65 years	Followed up for a mean length of 12–18 years	Diagnostic conversion from MDD to BD	22.5% of adults and adolescents developed BD
Nakamura (2014)	Retrospective chart review of patient medical records	89	Severe depression with and without psychotic symptoms	Mean age = 55.6	Mean follow-up time was 74.8 ± 37.7 months	Diagnostic conversion from severe depression to BD	11(12.4%) patients had developed BD.

Table 1 (continued)

Author/year	Study type	Sample size	Initial diagnose	Age (mean, median, range)	Follow-up time	Variable examined	Results
					(range 15–137 months)		
Liu (2017)	Register-based cohort study	122.622 women	Parous women without psychiatric history who received antidepressants	35.2 years	Up to 16 years of follow-up	Diagnostic conversion from postpartum depression to BD (compared to women who started antidepressants who had not recently given birth)	HR = 1.66
Carballo (2011)	Naturalistic prospective cohort study	582	Depressive disorders	Between 6 and 17 years	Up to 21 years of follow-up	Diagnostic conversion from depressive disorder to BD in adulthood	8.2% changed to BD.
Kessing (2015)	Register-based cohort study	354	Psychoactive substance use 2.9%, schizophrenia 22.9%, affective disorder 22.9%, neurot, stress-rel. and somatof. 19.5, personality disorders 1%, pervasive developmental disorders 7.1%, behavioral and emotional disorders 10.9%	Median age 17.4 years, follow-up of the sample up to 19 years	Median follow-up 1.31 years	Moment that they received the diagnosis of mania/BD	59.3% received the diagnosis in the follow-up
Heslin (2015)	Population based cohort study	403	First episode psychosis	Median age 27 years	10 years	Diagnostic change to other psychotic disorders	76% maintained the initial diagnosis of BD, 3.95% received the diagnosis from other psychotic disorders
Consoli (2014)	Cohort study	80	Manic or mixed episode	Mean age 15.82	8 years	Diagnostic stability of the BD diagnosis	63.6% maintained the diagnosis
Poon (2017)	Retrospective follow-up study based on review of medical records	87	ATPD	Mean age 31.5	20 years	Diagnostic stability of the ATPD diagnose	27.6% changed to BD
Dougherty (2016)	Cohort study	36	DMDD	Assessed at ages six and nine	3 years	Diagnostic stability of the DMDD	5 (13.9%) maintained the diagnosed

MDD major depressive disorder, *LCA* latent class analysis, *MADD* mixed anxiety and depressive disorder, *UPD* unipolar psychotic depression, *BD* bipolar depression, *HR* hazard ratio, *ATPD* acute and transient psychotic disorder, *DMDD* disruptive mood dysregulation

remission and 30% reclassified with alternative diagnoses of anxiety or depression [26].

Depression with Psychotic Features

In a prospective study of 8588 patients diagnosed with psychotic depression, 7.1% eventually received the diagnosis of bipolar disorder (BD). Risk factors most associated with this diagnosis conversion include early age of onset, recurrences, living alone, receiving disability benefits, and having a high level of education [27]. In a study of 107 patients (average age 34.6 years) diagnosed with a first episode of psychotic depression then followed over 4 years, 70.1% retained the diagnosis while 18.7% were alternatively diagnosed with BD and 11.2% with schizoaffective disorder. Risk factors for conversion to BD include history of impulsivity (RR = 2.10), initial mixed state (RR = 5.43), and history of hypomanic symptoms (RR = 10.9) [28].

Relationship Between Depression and Dementia

Depression has been proposed as a risk factor for the development of dementia (including Alzheimer's disease, vascular dementia, and other forms) [29–31, 32••]. Alternatively, depression may be a prodromal symptom of dementia rather than an independent risk factor [33].

Beta Amyloid

Beta amyloid plaques in the plasma may represent a marker of the prodromal stages of Alzheimer's disease, especially if seen together with the ApoE4 allele [32••].

PET studies have demonstrated that half of elderly patients with depression have amyloid buildup in the cortical areas associated with the early stages of Alzheimer's, with similar levels of beta amyloid seen in subjects with depression and those with Alzheimer's disease [34]. However, other authors highlight the lack of correlation between depressive symptoms and beta amyloid deposits in patients with cognitive impairment and Alzheimer's disease [35]. It has been suggested that carriers of the ApoE4 allele who suffer a depressive episode early in life may later be vulnerable to developing dementia [36]. In contrast, the presence of depressive symptomatology during the onset of dementia does not seem to be affected by the allele and therefore would not impose additional risk [37].

Neuroimaging and Neuroanatomy

The presence of chronic depressive symptoms in patients with mild cognitive impairment has been associated with progressive atrophy of the frontal region (though not temporal regions), which may represent another risk factor for the development of Alzheimer's disease [38, 39]. Alzheimer's disease patients show atrophy throughout the hippocampus, while those with MDD show milder atrophy of only the anterior hippocampus [40]. Regarding left hippocampal volumes, no difference was found between depressed patients with mild cognitive impairment and those without cognitive changes, which may suggest that depression on its own is not sufficient to accelerate progression to dementia [41].

Use of Antidepressive and Risk of Dementia

The prolonged use of antidepressants has been associated with a decrease in the risk of dementia [30], which may be explained by their influence on the metabolism of the amyloid precursor protein. Still the relationship remains unclear. Certain data support the relationship between the use of antidepressants not selective for serotonin reuptake (such as MAOIs and SNRIs) and a greater risk of developing depression than is seen with use of SSRIs or tricyclics [42•].

Bipolar Disorder

BD and MDD

A meta-analysis found that 22.55% of MDD patients followed for 12–18 years were later diagnosed with bipolar disorder (BD), most often within the first 5 years of follow-up [1••]. Estimated rates of conversion from unipolar to bipolar depression range from 0.37% per year to 3.95% per year [43]. Predictably, the proportion of diagnostic conversions typically increases with the duration of follow-up: between 8.6 and 14% by 5 years [43, 44], 17% by 10 years [45], and in certain studies as much as 45% by 15 years [46] or 20% by 30 years [47]. The rate of conversion from MDD to BD also increases with age, occurring in 2.21% from ages 10 to 14 as compared to 7.06% from ages 30 to 34 [48]. Although patients who receive a stable diagnosis of BD have previously received other psychiatric diagnoses, once they receive a stable diagnosis of BD they do not switch to any diagnostic [49].

Known risk factors for the conversion of unipolar to bipolar depression include early age of onset and the presence of psychotic or hypomanic symptoms. However, no association has been found between conversion risk and the presence of suicidal behavior or the use of antidepressants [1••]. In a 75-month follow-up of 89 patients hospitalized for severe depression, 12.4% were later diagnosed with BD (of whom 82% were diagnosed in the first year of follow-up). This suggests that severe depression could represent a risk factor for conversion to BD [50].

Postpartum depression may also be a risk factor for conversion to BD. A Danish study followed 122,622 women with no prior psychiatric history who received postpartum antidepressant treatment. Compared to women started on

antidepressants who had not recently given birth, postpartum patients had higher rates of conversion to BD, with a hazard ratio of 1.66 [51].

It has also been found that roughly two thirds of patients experiencing bipolar depressive episodes experience subclinical hypomanic symptoms [52], a feature which could be useful in more accurately diagnosing an initial depressive episode.

Regarding age of diagnostic conversion, a cohort study of patients diagnosed with MDD between the ages of 6 and 17 found that 8.2% were diagnosed with BD in adulthood [22]. Another study of 354 youths diagnosed with mania or BD by age 19 found that 59.3% received the diagnosis at follow-up rather than their initial visit with a specialist [53•]. The most common previous diagnoses were schizophrenia and related disorders (22.9%), other affective disorder (22.9%), and diagnoses related to stress or somatization (19.5%).

Regarding the possible diagnostic category of unipolar mania, the little evidence available from prospective studies of over 10 years suggests diagnostic stability of greater than 75% [54].

BD and Borderline Personality Disorder

Approximately one fifth of subjects with BD present with comorbid borderline personality disorder (BPD) [55]. Higher rates of comorbidity are seen with BD I (29.0%) than with BD II (24.0%) [56]. This comorbidity is associated with worse prognosis in terms of both suicidality and mood [55, 56]. To differentiate the two diagnoses, bipolar disorder has been predicted by the presence of elevated mood (OR 4.02), increased goal-oriented activities (OR 3.90), and episodicity of mood symptoms (OR 3.48) [57].

BD and Attention Deficit Hyperactivity Disorder

It is estimated that 17.6% of subjects with BD meet diagnostic criteria for attention deficit hyperactivity disorder (ADHD) [58]. Furthermore, patients with MDD are more likely to be subsequently diagnosed with BD if they present with comorbid ADHD (18.9 vs. 11.2%) [59]. BD beginning in infancy or adolescence can be difficult to distinguish from ADHD due to the overlapping with prodromal symptoms of an initial bipolar episode: increased energy (68%), decreased ability to think clearly (63%), indecision (62%), pressured speech (60%), talkativeness (60%), elevated mood (58%), problems with school or work (56%), insomnia (54%), depressed mood (53%), and hyperactivity (50%) [60]. Subjects with ADHD in infancy also have increased risk of developing BD in adulthood. In a cohort of 144,920 patients diagnosed with ADHD and an equal number of controls, the ADHD group showed significantly increased risk of developing BD (2.1 vs. 0.4%) [61•]. In another study which followed 1410 adolescents with ADHD and 5640 controls over 7 months, development of BD occurred in 3.4% of those with ADHD and conduct disorder, 2.2% of those with ADHD and oppositional defiant disorder, 1.3% of those with ADHD alone, and 0.2% of controls [62].

BD and First Psychotic Episode

Heslin et al. followed 403 subjects with first psychotic episode (FEP) over 10 years, finding that 59.6% maintained this diagnosis by ICD-10 criteria and 55.3% by DSM-IV. Conversion to BD was seen in 3.95% of those diagnosed as a first schizophrenic episode, in 12% of those originally diagnosed as schizoaffective, and in 13% of those diagnosed as depression with psychotic features. Of the 55 patients who originally received a diagnosis of BD, 76% maintained this diagnosis. Among those who did not, the most common new diagnoses were schizoaffective disorder (5.4%), schizophrenia (3.6%), brief psychotic disorder (3.6%), major depression with psychotic features (3.6%), drug-induced psychosis (3.6%), and psychosis NOS (3.6%) [63••].

In a study of 80 adolescents diagnosed with BD type I when hospitalized for a first manic or mixed episode, 63.6% maintained the diagnosis over 8 years of follow-up, while 18.2% were diagnosed schizophrenic and 18.2% schizoaffective [64].

Several studies have analyzed the diagnostic stability of brief psychotic disorder, for which the most common diagnostic conversion is to BD, with rates of 14% in the first year and 21% by the second year among a sample of 56 patients [65], and 22.2% over 3 years in a sample of 45 patients [66]. Poon et al. identified 87 patients diagnosed with a first episode of brief psychotic disorder, of whom 27.6% received a diagnosis of BD in the 20 years of follow-up [67].

Disruptive Mood Dysregulation Disorder

Added among the mood disorders in DSM-5, disruptive mood dysregulation disorder (DMDD) carries high rates of comorbidity [68, 69] and limited diagnostic stability [70, 71]. In a sample of 310 adolescents (ages 13–18) diagnosed with DMDD, comorbid mood disorders were seen in 58.4%, conduct or oppositional defiant disorder in 68.3%, ADHD in 31.7%, anxiety in 46.2%, and substance use disorder in 43.1% [68]. Another study of 185 subjects with DMDD (ages 6–18) found that 96% had comorbid oppositional defiant disorder, 81% ADHD, 32% depressive disorders, 25% anxiety disorders, 3% psychotic disorders, 7% cyclothymia, and less than 1% BD [69].

In a study of 36 children diagnosed with DMDD by 6 years of age, the diagnosis was maintained at 9 years of age in only five children. The most common diagnostic conversions were to ADHD (33.3%), disruptive conduct disorders (22.2%), and anxiety disorders (16.7%) [71]. In another sample of subjects age 10–16 diagnosed with DMDD then followed until age 24–26, 24.9% ended up receiving diagnoses of depressive

syndromes, 45.4% anxiety disorders, 1.7% antisocial personality disorder, 19.7% alcohol use disorder, and 29.5% cannabis use [70].

Conclusion

Diagnostic stability is a pertinent concern in psychiatry, as demonstrated by the abundance of publications from which we gleaned a selection focused on affective disorders. Despite this extensive literature, the substantial methodological differences between studies (for example in follow-up duration or period of disease timeline examined) continue to complicate direct comparison of the results.

In the case of unipolar depression, extensive data have been provided regarding the chronic nature of the symptomatology [7–9, 24]. This stands in contrast to more traditional episodic conceptualizations, at least for a significant proportion of the afflicted population. This chronicity can also be seen in the considerable diagnostic stability across all age ranges, including among adolescents [10••, 11, 12, 20]. Studies using LCA are allowing improved profiling of depressive subtypes and assessment of their prevalence, which shows an impact similar to typical and atypical depression [10••, 14]. The current diagnostic classifications have managed to achieve considerable reliability. However, there remain limitations regarding the identification of subtypes, as it becomes increasingly clear that current diagnostic categories fail to incorporate the new understanding we have acquired. For example, research into major depressive disorder has found heterogeneity that merits its division into syndromic subcategories, which can better fit the diverse clinical presentations and courses of depressive disorders.

Much progress has been made since "depressive pseudodementia" was first described, a term now in disuse thanks largely to our improved understanding of the relationship between depression and dementia. Advances have been made in our understanding of the neurobiological underpinnings of depression, with data highlighting the roles of amyloid deposits, the ApoE4 allele [34, 36], and atrophy of the anterior hippocampus [40] or frontal cortex [38, 39]. Nevertheless, other data draw these neurobiological findings into question [35, 41]. There are doubts as to the role of antidepressants in the progression of dementia [30, 42•], and it remains unclear whether the relationship between depression and dementia represents an initial manifestation or a risk factor [29–31, 32••, 33].

The diagnostic instability of bipolar disorder is manifest in the early years, seen in both the extent of diagnostic delay and the high rate of diagnostic conversion from unipolar depression [1••, 43–47]. This instability may result from the symptomatic overlap between the depressive features of bipolar disorder and unipolar depression, or between the psychotic features of affective disorders and non-affective psychosis. These difficulties notwithstanding, between 63.6 and 76% of those initially diagnosed with bipolar disorder maintain the diagnosis [63••, 64]. For those not initially diagnosed with bipolar disorder, we continue to learn more about the risk factors which indicate a higher probability of subsequent diagnosis, and great effort is being dedicated to improving the clinical differentiation.

The symptomatic overlap is also seen with other psychopathology such as borderline personality disorder (associated with a worse prognosis of comorbid bipolar disorder) [55, 56] and ADHD (whose presentation in infancy/childhood is associated with a greater risk of bipolar disorder once adult) [61•]. For both conditions, we continue to acquire clinical data which will allow for improved early differentiation from bipolar disorder [57, 60].

Regarding DMDD, we have little data to date, but those which exist indicate a high rate of comorbidity and minimal diagnostic stability for this disorder [68–71].

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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