# Advances in Differential Diagnosis of Bipolar II Disorder and Depressive Disorder in Primary Care: Postprint

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## Abstract

Bipolar II disorder and depressive disorder exhibit overlapping clinical manifestations, posing a significant challenge for their differentiation in primary care settings. Early and accurate diagnosis is crucial for improving patient prognosis, and general practitioners, as first-contact physicians in the primary care system, play a vital role in early screening, identification, and initial treatment planning. However, general practitioners currently still encounter difficulties in accurately distinguishing bipolar II disorder from depressive disorder. This article summarizes recent research advances in the differential diagnosis of bipolar II disorder and depressive disorder, elaborating on differential approaches for the two conditions in primary care from the perspectives of clinical features, application of screening tools, and follow-up strategies, and discusses the advantages and limitations of existing screening instruments. Furthermore, the article also prospects the potential applications of tools such as artificial intelligence, biomarkers, and remote monitoring in enhancing the accuracy of differential diagnosis, aiming to provide references for future research and clinical practice.

## Full Text

## Preamble

**Focus on Hot Topics**
**Research Advances in Distinguishing Bipolar II Disorder from Depressive Disorder in Primary Care**

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**Abstract** The overlapping clinical presentations of bipolar II disorder (BD-II) and depressive disorder (DD) pose significant challenges for differential diagnosis in primary care. Early and accurate diagnosis is critical for improving patient prognosis, and general practitioners (GPs), as the first point of contact in primary care systems, play a pivotal role in early screening, identification, and initial treatment planning. However, GPs currently face difficulties in accurately distinguishing BD-II from DD. This article summarizes recent research advances in the differential diagnosis of BD-II and DD, focusing on clinical features, application of screening tools, and follow-up strategies to elucidate differentiation methods in primary care settings, and discusses the advantages and limitations of existing screening instruments. Furthermore, the article explores the prospective applications of artificial intelligence, biomarkers, and remote monitoring technologies in enhancing diagnostic accuracy, aiming to provide valuable insights for future research and clinical practice.

[**Key words**] Primary care; General practitioners; Bipolar II disorder; Depressive disorder; Diagnosis, differential

Distinguishing bipolar II disorder (BD-II) from depressive disorder (DD) represents a critical challenge in primary care. BD-II is characterized by alternating episodes of depression and hypomania[1], whereas DD primarily manifests as persistent low mood, loss of interest, and decreased energy[2]. The high degree of symptom overlap during initial episodes substantially increases misdiagnosis risk. International studies indicate that up to 40% of bipolar disorder cases are misdiagnosed, with the majority initially mistaken for depression[3]. In urban China, the rising prevalence of bipolar disorder, combined with BD-II' s closer clinical resemblance to DD, further complicates differentiation[4].

Misdiagnosis not only delays mood stabilizer treatment for BD-II patients but may also precipitate manic or hypomanic episodes through inappropriate antidepressant use, exacerbating disease complexity and suicide risk[1],[3],[5]. It also compromises long-term disease management, leading to prolonged illness duration and reduced quality of life[6–8]. Therefore, improving early diagnostic accuracy is essential for optimizing patient outcomes and enhancing primary care service quality[9]. As frontline providers, GPs play a crucial role in early screening, identification, and intervention for BD-II and DD[10], yet face substantial clinical challenges. Hypomanic symptoms are often insidious—such as increased energy or social activity—and may be misinterpreted as normal mood fluctuations[11], complicating differentiation, particularly during initial consul-

tations[1],[12–13]. Additionally, patients typically focus on depressive symptoms, and recurrent depressive episodes in BD-II may obscure hypomanic manifestations[14–15]. Furthermore, the primary care context—characterized by multimorbidity and time constraints—adds complexity to the diagnostic process[10].

To address these challenges, numerous screening and assessment tools with good clinical utility have been developed in recent years[16]. As understanding of diagnostic differences between these conditions deepens, more training programs and auxiliary diagnostic tools are being implemented in primary care. This review systematically examines research advances over the past five years, focusing on three key aspects: clinical features, screening tool application, and follow-up strategies. In November 2024, we searched PubMed, Web of Science, and other databases using terms including "bipolar II disorder,""Depressive Disorder,""Primary Care," and "Differential Diagnosis." We included clinical studies, reviews, and guidelines related to BD-II and DD differentiation, excluding case reports, animal studies, and low-quality or inaccessible articles, yielding 87 eligible publications. This article also explores the potential value of emerging technologies such as artificial intelligence, biomarkers, and remote monitoring in improving diagnostic accuracy, aiming to provide GPs with effective strategies to reduce misdiagnosis and improve patient management.

## 1. Differentiating Clinical Features in Primary Care

BD-II and DD share numerous overlapping symptoms, particularly during depressive episodes. Careful examination of differences in medical history, symptom characteristics, and treatment response can help GPs make accurate diagnoses. We analyze these differences across five key dimensions.

### 1.1 Identification of Hypomanic Symptoms

The key to distinguishing BD-II from DD in primary care lies in recognizing hypomanic episodes. BD-II patients often exhibit prodromal or brief hypomanic symptoms during depressive phases, including pressured speech, racing thoughts, impulsive behavior, and increased social activity[17]. These differ markedly from typical DD symptoms, which primarily involve persistent low mood, anhedonia, fatigue, helplessness, and self-deprecation[18–19]. These hypomanic features are frequently overlooked initially, as they may be masked by depressive symptoms, leading to misdiagnosis or diagnostic delays[6].

### 1.2 Cognitive Impairment and Associated Features

GPs should assess cognitive dysfunction, particularly during depressive episodes. Recurrent BD-II patients often exhibit more severe cognitive deficits, including impaired attention, memory decline, and reduced decision-making capacity[20]. While DD patients may also experience cognitive impairment, their difficulties are typically more closely linked to low mood and negative self-evaluation[18],[21],

whereas cognitive problems in BD-II tend to be more pervasive and persistent[22–23]. Additionally, BD-II patients frequently display impulsive behavior and social dysfunction, while DD patients show emotional self-deprecation and pessimistic future outlook[17–18],[24]. GPs should carefully evaluate these features in conjunction with medical history for accurate differentiation[1].

### 1.3 Course Characteristics and Atypical Symptoms

BD-II typically manifests as cyclical mood fluctuations, with recurrent hypomanic episodes following depressive periods—a stark contrast to the persistent low mood without cyclical variation seen in unipolar DD[25]. GPs should pay particular attention to the regularity and periodicity of mood fluctuations, which are crucial for early diagnosis and treatment adjustment. Age of onset is also important, as early-onset depression before age 25 may signal BD-II[2],[26]. Furthermore, BD-II may present with atypical symptoms such as increased appetite, weight gain, and hypersomnia[27], and even during depressive phases may show hypomanic features like excess energy and decreased sleep[28]. In contrast, DD typically presents with classic symptoms of appetite loss, weight reduction, and insomnia[29]. GPs must closely monitor these atypical features, especially during initial consultations, to avoid misdiagnosing BD-II as unipolar DD[30].

### 1.4 Differences in Treatment Response

Treatment response differences provide important diagnostic clues. DD patients generally respond well to antidepressants, whereas BD-II patients may experience treatment-emergent manic or hypomanic episodes[1],[31]. This is particularly critical for GPs, as many patients present with depressive symptoms alone during initial visits[32]. Failure to recognize emerging manic symptoms during antidepressant treatment may lead to misdiagnosis of BD-II as unipolar DD[1]. Therefore, GPs must exercise caution when prescribing antidepressants, particularly for patients with mood fluctuations or family histories of affective disorders, and closely monitor treatment response to avoid precipitating manic episodes[31],[33].

### 1.5 Family History and Past Experiences

Family history plays an important role in differentiation. BD-II shows strong genetic susceptibility, with many patients having first-degree relatives with affective disorders[34–36]. For GPs, knowledge of family history is crucial, as a family history of bipolar disorder indicates elevated risk. While DD also has genetic predisposition, its familial aggregation is relatively weaker[37]. Additionally, inquiry about past emotional trauma is necessary, as severe childhood emotional trauma may increase bipolar disorder risk[38]. As GPs are often the first clinicians to encounter these patients, asking about family history of bipolar disorder and past emotional trauma facilitates early differentiation and prevents misdiagnosis.

## 2. Advantages, Limitations, and Selection of Screening Tools in Primary Care

Screening tools play a vital role in improving diagnostic accuracy during BD-II and DD differentiation. In primary care, these instruments help GPs identify conditions amid symptom overlap and enable timely referral or intervention. We examine their advantages, limitations, and selection strategies.

### 2.1 Advantages of Screening Tools

Screening tools offer multiple advantages in primary care, particularly for early BD-II and DD identification. Validated instruments such as the Mood Disorder Questionnaire (MDQ)[39], Bipolar Spectrum Questionnaire (BSQ)[40], and 32-item Hypomania Checklist (HCL-32)[16] assist GPs in differentiation. MDQ is a simple, rapid tool that effectively screens for bipolar disorder risk, providing preliminary diagnostic clues[39]. SAYYAH et al.[41] found MDQ sensitivity of approximately 71% and specificity of 77% for bipolar disorder screening. The 33-item Hypomania Checklist-External Assessment (HCL-33-EA) helps GPs identify hypomanic or mixed symptoms by assessing depressive symptoms and mood fluctuations[6].

The clinical utility of screening tools also lies in their operational convenience and standardized features, which are particularly valuable in time- and resource-limited primary care settings. HCL-32 can be completed quickly, offering high time efficiency and good clinical practicality[42]. Studies show that HCL-32 achieves 87% sensitivity, 69% specificity, and an area under the ROC curve (AUC) of 83.3% (95%CI=74.5%~92.1%) in distinguishing BD from DD[43]. Additionally, self-report-based data collection reduces clinician assessment bias and provides more objective evidence.

### 2.2 Limitations of Screening Tools

Despite their advantages, screening tools have limitations. Research indicates that MDQ demonstrates high specificity but relatively low sensitivity for hypomanic symptom identification, potentially yielding false-negative results that compromise clinical decision-making[41]. HCL-32' s self-report format is vulnerable to retrospective memory bias and subjective cognitive distortions, which may reduce diagnostic sensitivity and increase false-negative rates when hypomanic symptoms are atypical or patients have limited symptom awareness[16]. Although the Mini International Neuropsychiatric Interview (MINI) shows good reliability and validity for identifying manic episodes and core bipolar symptoms, its requirement for specialized training limits its suitability for rapid screening in primary care, restricting its broader implementation[44].

### 2.3 Selection of Screening Tools

In selecting screening tools, primary care institutions must integrate evidence-based medicine with patient phenotypic characteristics and resource availability. For adolescent patients with suspected bipolar disorder, HCL-32 and HCL-33-EA demonstrate good clinical value due to their favorable time-efficiency ratio and strong hypomanic/manic symptom identification capabilities[14],[16]. MDQ serves as an important reference for differentiating bipolar disorder from DD, though its diagnostic accuracy may be influenced by sociocultural and demographic factors[45]. Similarly, HCL-32 validation results vary across cultural contexts; a study in Taiwan showed different factor structures from European samples and differential performance in distinguishing DD from BD-II[46].

The Bipolar Index (BI) shows high sensitivity (0.82) and specificity (0.73), offering advantages in BD-II versus DD differentiation[41]. Although MINI is difficult to popularize in primary care, GPs with standardized training and clinical experience can use it as an assessment tool for affective disorders in older adults, providing more comprehensive diagnostic information[47].

When selecting assessment tools, GPs should systematically integrate clinical symptoms, disease evolution, and family history, using screening results as one component of diagnostic decision-making. Tool selection should consider not only sensitivity and specificity but also clinical feasibility and time-effectiveness ratios. Therefore, GPs should employ screening tools based on evidence-based medicine, considering each instrument' s strengths and limitations (Table 2 ). Individualized assessment protocols should be developed based on symptom characteristics, disease course, and resource availability. In practice, GPs can combine multiple screening tools to improve diagnostic accuracy and establish standardized referral pathways to ensure at-risk patients receive timely specialist evaluation and intervention.

## 3. The Role of Follow-up in Differentiating BD-II from DD in Primary Care

BD-II and DD often present with highly similar clinical manifestations during early disease stages, particularly during depressive episodes, posing challenges for initial differential diagnosis[48]. However, systematic follow-up data reveal that disease dynamics and progression provide crucial decision-making information[49]. Short-term follow-up observes temporal symptom fluctuation patterns, while long-term follow-up reveals cyclical changes and natural disease course—features that play important roles in differentiation. Through standardized follow-up protocols, GPs can systematically evaluate emotional symptom changes and treatment responses, improving diagnostic accuracy for BD-II versus unipolar DD.

### 3.1 Short-term Follow-up Provides Symptom Change Clues

Short-term follow-up is valuable for monitoring symptom fluctuations during early disease stages. Studies show that BD-II patients may exhibit characteristic hypomanic symptoms during brief follow-up periods, while DD patients show relatively stable depressive symptom clusters (core, psychological, and somatic symptoms) without hypomanic features[32],[50]. Through short-term follow-up, GPs can identify these dynamic symptom patterns to enhance early BD-II recognition.

Short-term follow-up also aids differentiation by assessing treatment response. BD-II patients may develop manic switch or symptom exacerbation during antidepressant treatment, whereas unipolar DD patients typically show stable or improved responses[51–52]. Systematic observation of treatment reactions thus provides clinical evidence for distinguishing the two conditions.

### 3.2 Long-term Follow-up Reveals Characteristic BD-II Course

Long-term follow-up is instrumental for BD-II versus DD differentiation. BD-II patients typically show alternating depressive and hypomanic episodes, with this cyclical mood fluctuation pattern becoming more apparent over extended follow-up[1],[32]. As follow-up duration increases, characteristic patterns in symptom evolution and mood fluctuations emerge, providing important diagnostic evidence. In contrast, DD course is characterized by persistent depressive symptoms without cyclical variation[29].

Through systematic long-term follow-up, GPs can better understand BD-II' s typical course features, such as recurrent depressive episodes, mood fluctuations, seasonal patterns, or other trigger factors. Long-term follow-up not only reveals BD-II' s course characteristics but also provides valuable clinical evidence for early diagnosis and treatment optimization. Systematic course observation and standardized assessment are clinically significant for improving BD-II diagnostic accuracy and developing individualized treatment plans.

### 3.3 Challenges and Recommendations in Follow-up Implementation

Despite its importance, follow-up implementation faces challenges. First, BD-II hypomanic symptoms are often insidious and may be subtle or overlooked by patients during early disease stages[25]. Second, depressive symptom clusters may persist for extended periods, making short-term BD-II identification difficult[18]. These realities demand enhanced health management capabilities from GPs, requiring particular attention to potential hypomanic manifestations—such as elevated mood, excess energy, or impulsive behavior—to avoid missed diagnoses.

To improve follow-up effectiveness, GPs should dynamically adjust management strategies based on symptom fluctuations, mood changes, and treatment responses, combining screening tools (e.g., MDQ, HCL-32) to enhance diagnostic

accuracy. Follow-up should emphasize individualized patient characteristics to develop targeted follow-up plans ensuring comprehensive course assessment.

In summary, follow-up plays an irreplaceable role in BD-II and DD differentiation (Table 3 ). Through follow-up, GPs can identify manic or hypomanic symptoms and understand the cyclical mood fluctuation patterns characteristic of each disorder, providing crucial diagnostic evidence. Enhanced dynamic symptom monitoring, combined with screening tools and flexible follow-up strategies, is key to improving diagnostic accuracy. GPs should focus on disease evolution during follow-up, identify potential risks early, and implement appropriate interventions to ensure timely and effective patient care.

## 4. Summary and Outlook

Currently, BD-II and DD differentiation relies primarily on comprehensive clinical experience-based assessment. GPs make preliminary judgments about BD-II through patient interaction, integrating clinical features and family history with screening tools like MDQ and BSQ[53–54]. However, GPs often lack sufficient psychiatric knowledge and clinical experience in history-taking and symptom differentiation, while time and resource constraints in primary care limit comprehensive screening tool application during initial consultations[55]. GPs thus face considerable challenges in differentiation, highlighting the urgent need for enhanced psychiatric diagnostic capacity through systematic training and continuing education to improve recognition and differentiation skills. Studies show that basic psychiatric training can improve GPs' diagnostic accuracy for mental disorders[56]. Through systematic training, physicians can better master core symptoms, differentiation points, and screening tool application, effectively reducing misdiagnosis and missed diagnosis rates. In cases with substantial symptom overlap, GPs should flexibly employ multiple diagnostic tools, such as screening algorithms and metabolic profiles, for auxiliary confirmation[14],[57].

With technological innovation meeting primary care needs, BD-II and DD differentiation will become increasingly precise and intelligent. GPs must learn to appropriately utilize artificial intelligence (AI) for differential diagnosis. AI technology has demonstrated substantial potential in mental health fields, including diagnosis, differentiation, prognosis assessment, and treatment optimization for DD and other conditions[58–60]. FAURHOLT-JEPSEN et al.[61] collected voice data and applied random forest algorithms to achieve high specificity (0.84) in distinguishing BD from DD based on voice features. Digital phenotyping technology also shows promise in differentiating BD from unipolar disorder, serving as a supplementary assessment tool for physicians[62]. Future AI models based on machine learning and deep learning algorithms could extract key diagnostic information from clinical data—including clinical manifestations and family history—to provide early screening and diagnostic prediction support for GPs[63]. For instance, by integrating data on affective disorder family history, recurrent DD features, and symptom fluctuations, AI could help GPs more accurately identify potential BD-II patients, improving diagnostic accuracy and efficiency.

Similarly, diagnostic tool innovation holds promise for future differentiation. While existing scales like MDQ and HCL-32 are used in primary care, their sensitivity and specificity require improvement. Future diagnostic tools incorporating biomarkers, neuroimaging, and multimodal data are expected to enter clinical practice[64–67]. JIANG et al.[68] demonstrated that amygdala-based functional connectivity features may serve as potential biomarkers for distinguishing BD from major depressive disorder, offering new perspectives for early accurate diagnosis. SALVETAT et al.[69] found that RNA editing-based biomarkers combined with machine learning could differentiate BD from DD, reducing misdiagnosis and enabling early appropriate treatment. In the future, GPs may combine blood biomarkers, brain imaging data, and other objective measures for earlier and more accurate BD-II versus DD differentiation, moving beyond sole reliance on clinical symptoms and traditional scales.

Furthermore, remote monitoring technology will play an important role in BD-II and DD differentiation. FAURHOLT-JEPSEN et al.[70] remotely collected mood and activity data from BD and DD patients, calculating instability indices that revealed significantly lower activity levels in BD patients across stable and depressive states compared to DD patients. With the development of electronic health records and remote health monitoring platforms, GPs can track patient conditions in real-time, adjust treatment plans promptly, and further achieve individualized and precision treatment[71–73]. For patients in remote or resource-limited areas, telemedicine applications will improve accessibility and accuracy of mental health services for BD-II, DD, and other psychiatric conditions[74].

In conclusion, systematically integrating clinical symptoms and medical history, rationally selecting and applying effective screening tools, employing evidence-based medicine, and strengthening specialized psychiatric training are effective strategies for improving BD-II and DD differential diagnostic accuracy, reducing misdiagnosis, and improving patient outcomes.

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**Conflicts of Interest:** None declared.

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**Tables**

**Table 1** Distinguishing Clinical Features of BD-II and DD in Primary Care

**Table 2** Advantages and Limitations of Common Screening Tools for BD-II and DD in Primary Care

**Table 3** The Role of Follow-up in Differentiating BD-II from DD in Primary Care

*Note: MDQ = Mood Disorder Questionnaire, HCL-32 = 32-item Hypomania Checklist, HCL-33-EA = 33-item Hypomania Checklist-External Assessment, BSQ = Bipolar Spectrum Questionnaire, MINI = Mini International Neuropsychiatric Interview, BI = Bipolar Index.*

*Note: Figure translations are in progress. See original paper for figures.*