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Clinical Interplay Between Autism Spectrum Disorder and Bipolar Disorder: A Narrative Review

Running Head: **Interplay Between Autism and Bipolar Disorder**

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ABSTRACT

Introduction: Autism Spectrum Disorder (ASD) and Bipolar Disorder (BD) present significant challenges in diagnosis due to their complex nature. This review aims to examine the interface and overlapping features of these conditions.

Methods. We conducted a narrative review to examine clinical overlap, common psychiatric comorbidities, and shared neurobiological bases between ASD and BD.

Results. There is a notable convergence of symptoms in ASD and BD, including mood instability and emotional dysregulation; irritability, impulsivity, and aggressive behavior; deficits in social skills and social cognition; impairments in executive functions; sleep disturbances; problematic sexual behaviors; and sensory sensitivities. Common psychiatric comorbidities and shared neurobiological basis further underscore this potential interplay.

Conclusion: Despite distinct clinical trajectories and diagnostic criteria, our findings indicate a significant overlap in symptoms and clinical presentations between ASD and BD. This complexity makes it challenging to identify the co-occurrence of ASD and BD, which can lead to difficulties in accurately diagnosing and managing both conditions simultaneously.

Keywords: Autism Spectrum Disorder, Bipolar Disorder, Comorbidity, Overlapping Symptoms.

1. Introduction

Autism Spectrum Disorder (ASD) is characterized by early-onset difficulties in social communication and markedly restricted, repetitive behaviors and interests. It affects individuals across the lifespan, with symptoms typically emerging in early childhood. Early diagnosis is often more readily made in individuals with severe symptoms and obvious neurodevelopmental delays[1]. However, ASD may remain

undiagnosed until adulthood in some cases, despite significant clinical impairment[2]. The prevalence of ASD has been steadily increasing, with recent estimates indicating approximately 1 in 36 children in the United States[3], and around 1% globally[4]. These prevalence rates underscore the importance of ASD as a major public health issue and highlight the need for accurate and timely diagnosis.

Bipolar Disorder (BD), characterized by fluctuating mood episodes, is also a prevalent psychiatric condition affecting approximately 2% of the global population[5]. Individuals typically experience their first manic episode in late adolescence or early adulthood. Diagnosis of BD involves a thorough clinical assessment, focusing on the presence, duration, and impact of mood episodes, and may also consider associated functional, social, and occupational impairments [6,7].

ASD in adults (without a previous diagnosis) and BD are complex conditions that present significant challenges for diagnosis and treatment. Diagnostic overshadowing in ASD occurs when co-existing conditions or preconceived notions about ASD stereotypes obscure the recognition of ASD symptoms, leading to delayed or inaccurate diagnoses. Compounding this issue, both disorders share overlapping symptoms, such as like emotional dysregulation, impulsivity, and deficits in social skills. This overlap can result in misdiagnoses, particularly when an individual may have both ASD and BD[7]. The challenge is to differentiate, on a case-by-case basis, whether these overlapping symptoms represent a single disorder with a broad presentation, the co-occurrence of both ASD and BD or another condition altogether.

The primary aim of this narrative review is to explore the clinical interplay between BD and ASD, with a particular emphasis on Level 1 ASD. This review will elucidate the overlap in symptoms, highlight the unique diagnostic complexities encountered by clinicians, and emphasize the need for potential solutions to improve diagnostic accuracy. Additionally, it examines common comorbidities and shared neurobiological bases among ASD and BD.

2. Methods

We conducted a narrative literature review using Medline (PubMed) with the search terms “Autism”, “Autism Spectrum Disorder”, “ASD”, and “Bipolar Disorder”. This review aimed to explore relevant clinical and preclinical studies, as well as

observational and interventional trials, published up to April 2024. Articles were selected based on their relevance to the topic, without predefined inclusion or exclusion criteria, as this was not a systematic review.

3. Results and Discussion

3.1. Clinical overlap between ASD and BD

Below, we discuss the overlapping symptoms of ASD and BD. **Figure 1** offers an overview of the primary similarities and differences between the two disorders.

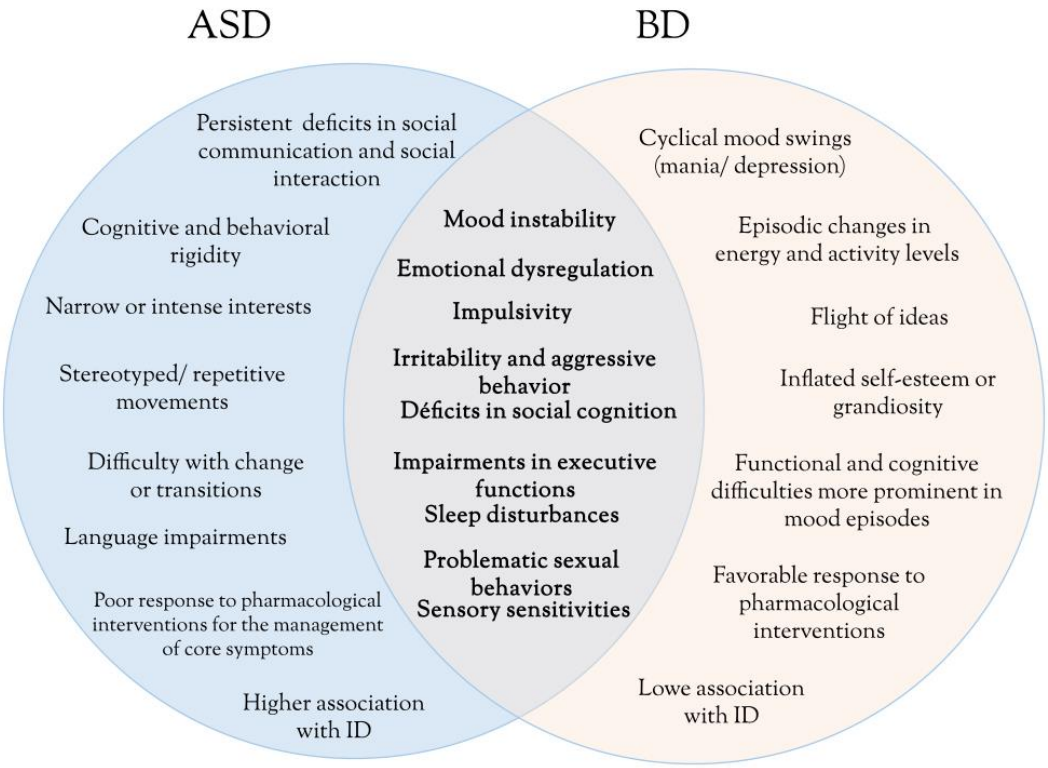

Figure 1. Overlap and Differentiation of Symptomatology in Autism Spectrum Disorder (ASD) and Bipolar Disorder (BD).

The Venn diagram highlights the overlapping (central pathway) and different characteristics observed in individuals with ASD and BD. **Persistent deficits in social communication and social interaction** are a core feature of ASD, while **deficits in social cognition** can also be present in BD. **Cognitive and behavioral rigidity, narrow or intense interest, stereotyped or repetitive movements, difficulty with change or transitions, and language impairments** are more specific symptons of ASD, considering the DSM-5-TR diagnostic criteria. **Poor response to pharmacological interventions for the management of core symptoms in ASD and higher association with ID** are also contributed to distinguishing between ASD and BD.

Mood instability and emotional dysregulation, impulsivity, irritability and aggressive behavior are commonly observed is ASD and BD. **Impairments in executive functions** deficits are also observed in ASD and BD, characterizing common difficulties in planning and decision-making. **Problematic sexual behaviors, sleep disturbances,** and **sensory sensitivities** introduce additional layer of complexity to the overlapping symptoms of these conditions. **Cyclical mood swings, episodical changes in energy and activity levels, flight of ideas, inflated self-esteem or grandiosity, and functional and cognitive difficulties more prominent in mood episodes** are more specifics symptons of BD, considering DSM-5-TR.

Mood instability and emotional dysregulation. BD is primarily characterized by distinct periods of abnormal mood, alternating between depressive and manic episodes. Although ASD is defined by lifelong persistent symptoms, individuals with ASD often exhibit heightened sensitivity to environmental stimuli and changes in routine, as long as disruptive behavior when frustrated[8,9]. In all these situations, they may frequently experience mood swings, which can mimic or complicate the recognition of a comorbid affective disorder[10,11]. On the other hand, mood instability in BD also can be influenced by environmental factors, including stress, life events, frustrations and disruptions in sleep patterns[12], further complicating the differentiation or identification of the simultaneous presence of these two conditions.

Emotional dysregulation, characterized by difficulties in managing and responding to emotional experiences, is commonly observed in both ASD and BD, although the underlying mechanisms and triggers may differ. Individuals with ASD may exhibit emotional lability due to difficulties in recognizing, labeling, and expressing emotions, which can lead to sudden and intense emotional responses[10]. When individuals with ASD experience disruptions in their routines, they may exhibit symptoms that resemble manic or hypomanic episodes, such as psychomotor agitation, irritability, and distractibility[11]. Some individuals with ASD may also experience abrupt mood fluctuations without an apparent cause.

Similarly, individuals with BD may show inadequate emotional reactivity or intense emotional expression, with emotional dysregulation occurring more frequently, but not only during mood swings[12,14]. Additionally, there is evidence suggesting that emotional instability may be a predictor of a future BD diagnosis[15]). The presence of emotional dysregulation in both ASD and BD further complicates the differential diagnosis process and underscore the importance of assessing the context and temporal patterns of mood disturbances. Individuals with comorbid ASD and BD may encounter additional challenges due to the interaction between mood dysregulation and social communication difficulties inherent in ASD.

Irritability, impulsivity and aggressive behavior. Irritability, impulsivity, and aggressive behaviors are common manifestations in both ASD and BD. Individuals with ASD may exhibit heightened irritability, which can be triggered by sensory overload, changes in routine, or difficulties in communication and social interactions[16]. Adults with ASD might also show periods of increased social intrusiveness, restlessness, and verbal aggression[7], traits that overlap with those observed in manic episodes. Likewise, individuals with BD frequently experience irritability, particularly during manic, depressive, or mixed episodes, often accompanied by impulsive and aggressive behaviors[17]. Moreover, a recent systematic review indicated that impulsive behavior in BD can persist even during periods of euthymia, suggesting that impulsivity may be a trait feature of the disorder rather than solely a mood state.

Deficits in social cognition and social skills. Social cognition is a complex psychological domain crucial for successful social interactions, as it supports adaptive social behaviors[18]. Impaired social communication and interaction are well-established core features of ASD[6]. Individuals with ASD often struggle with nonverbal cues, reciprocity, and maintaining peer relationships, and frequently exhibit problematic behaviors such as irritability and emotional reactivity[7,9]. They commonly face difficulties in understanding social cues and engaging at a level of social maturity comparable to their peers, which significantly impacts their ability to navigate social interactions and form meaningful connections[19]. Furthermore, deficits in the Theory of Mind domain consequently affect interpersonal effectiveness, which is the ability to convey emotions and needs, as well as interact with others and build relationships based on reciprocal empathy[8]. Patients with ASD may also use camouflage—a strategy to behave as though they are non-impaired—which can lead to depression and further obscure the underlying impairments in social cognition[20].

Deficits in social cognition are also evident in BD, affecting individuals not only during symptomatic states but also during periods of euthymia[21]. Individuals with BD show moderate impairments in Theory of Mind including difficulties in social perception and deficits in face emotion recognition[21-23]. These persistent deficits can result to clinical presentations that may be mistaken for the enduring deficit in social skills observed in ASD, thereby complicating the identification of potential overlap between these two disorders.

Deficits in executive functions. Executive functioning refers to a set of cognitive processes crucial for goal-directed behavior, attentional control, and self-regulation[24]. Both ASD and BD are associated with deficits in executive functioning, including impaired performance in planning, organizing, decision-making, inhibitory control, set-shifting, verbal fluency, working memory, and problem-solving[25,26]. These shared cognitive impairments may contribute to difficulties in decision-making, impulse control, and adaptive functioning observed in both conditions[25,26].

Problematic and harmful sexual behavior. Individuals with ASD often encounter challenges related to sexuality[27]. Some individuals with ASD adopt strategies to gain acceptance or inclusion within their social groups by engaging in sexual behaviors, which can also lead to periods of intensified sexual activity[28]. Patients with ASD often have underdeveloped social skills and exhibit repetitive and restrictive behavior patterns[29]. Consequently, both groups may experience feelings of exploitation or abuse in their sexual encounters, underscoring the distinct challenges each group faces in navigating aspects of sexual functionality.

In BD, mood swings significantly impact sexual functioning. Depressive episodes often lead to a decreased interest in sexual activity, while manic states can result in heightened sexual arousal[30]. Mania or hypomania may lead to hypersexuality and risky sexual behaviors, including engaging in unsafe practices, increasing the number of sexual partners, and disrupting daily routines[31]. As individuals transition back to euthymia, they may experience emotions like feelings of exploitation or abuse, as they become aware of the potential risks associated with their actions during manic or hypomanic states. Additionally, the disorder's significant implications can persist even during euthymic phases, affecting individuals throughout their lives[32].

Sleep disturbances. Sleep disturbances are frequently reported in both ASD and BD and can significantly impact mood regulation. Individuals with ASD often experience difficulties with sleep initiation and maintenance, which can exacerbate emotional dysregulation[33]. Similarly, insomnia or hypersomnia are common symptoms of BD, occurring not only during depressive and manic episodes, but also during periods of euthymia[34]. A multicenter longitudinal study involving 556 euthymic BD patients found that disrupted sleep is not uncommon during intervals between mood episodes and may be associated with a more severe course of illness[34]. Addressing sleep problems is crucial in managing mood dysregulation in both conditions.

Sensory sensitivities: Heightened or atypical sensory sensitivities are observed in both ASD and BD, and they can manifest during symptomatic episodes of BD. Individuals with ASD frequently experience sensory sensitivities to light, sound, touch,

or taste[35]. Likewise, individuals with BD may exhibit hypersensitivity to sensory stimuli during manic or depressive episodes[36].

3.2. Common psychiatric comorbidities in ASD and BD

When discussing the common interface between ASD and BD, it is essential to consider the high rates of comorbidity between these two disorders, as well as the presence of comorbid conditions observed in both. The association between these conditions was initially highlighted in family-based studies that have identified clinical evidence supporting a link. It has been observed that relatives of individuals diagnosed with ASD frequently exhibit a heightened prevalence of affective disorders[37]. Additionally, previous cohort studies have consistently identified the presence of BD in first-degree relatives as a significant risk factor for ASD[38].

Some studies suggests that the prevalence of BD in individuals with ASD ranges from 3-27%[39]. Whereas these data are greatly variable, it is also significantly higher than the prevalence of BD in the general population (2%)[5,40]. In a cohort study from Minnesota, for instance, individuals with ASD by 30 years of age showed cumulative incidence of BD 7.3%, while controls showed 0.9%[41]. Selten (2015) performed a population-based study and demonstrated that individuals with ASD have a heightened risk of developing non-affective psychotic disorders, schizophrenia, and BD compared to age- and sex-matched individuals without ASD from the general population (OR 8.5% for BD before age 28years)[42]. Importantly, the increased risk for these disorders was also significantly higher among individuals with ASD compared to their siblings who do not have ASD[42]. The sibling analyses conducted in the study suggest that shared familial factors do not fully account for this association, implying that ASD may play an important role in the development of BD[42].

Both ASD and BD are also associated with an increased risk of developing other psychiatric disorders, including a higher vulnerability to suicidal ideation or behaviors[43,44]. Individuals with ASD frequently experience elevated levels of symptoms and psychological distress throughout adulthood; in one sample, up to 79% of individuals met criteria for at least one psychiatric disorder during their lifetime[45]. Meng-Chuan Lai et al. (2019) examined in their comprehensive meta-analysis the prevalence of co-occurring mental health diagnoses among individuals with ASD[2]. The

study reported the following prevalence rates: 28% for Attention-Deficit/Hyperactivity Disorder, 20% for anxiety disorders, 13% for sleep-wake disorders, 11% for depressive disorders, 9% for obsessive-compulsive disorder, and 5% for BD. On the other hand, individuals diagnosed with BD frequently exhibit one or more comorbid psychiatric diagnoses, such as ADHD, anxiety disorders, OCD, substance use disorder (SUD), and ADHD[5,46,47].

Specifically, individuals with ASD may have a higher prevalence of Intellectual Disability (ID), which can make the diagnosis and management of comorbid BD more challenging[48,49]. Population-based studies have shown that BD is diagnosed four times more frequently in autistic individuals without intellectual disability (ID) than in those with ID[42]. The reason for this difference in incidence remains unclear; however, a possible explanation is that while individuals with ASD are at a high risk of developing additional psychiatric disorders throughout their lifetime, the diagnosis is often missed due to their difficulty in expressing emotions and reporting symptoms—challenges that are even more pronounced in patients with ID as a comorbidity[50].

Substance Use Disorder (SUD) can also co-occur in ASD and BD, potentially exacerbating mood dysregulation, impulsive behaviors, and social functioning difficulties[48,49]. On the other hand, SUD can mask symptoms, making it difficult to correctly diagnose the prevalence in individuals with comorbid ASD and BD. Furthermore, certain behaviors associated with ASD and BD can be misinterpreted as, or coexist with, personality disorders[6]. The reviewed literature highlighted that individuals with borderline personality disorder typically score higher on assessments measuring autistic traits compared to non-clinical populations[51]. Additionally, adults diagnosed with level 1 ASD may exhibit comorbidities or behaviors resembling schizotypal, schizoid, or narcissistic traits. Similarly, individuals with type I BD frequently present with comorbid personality disorders, particularly schizotypal and borderline personalities[6].

The presence of psychiatric comorbidities may be influenced by the severity of symptoms, the level of functional impairment, and specific subtypes within the ASD and BD spectra[7,48]. Comorbidities between ASD and BD can contribute to a range of psychosocial challenges, such as difficulties in educational settings, occupational functioning, and social relationships[52,53]. These findings underscore the need for

tailored mental health care and emphasize the importance of adequate treatment for individuals with ASD and BD.

3.3. Shared neurobiological basis between ASD and BD

Understanding the biological origins of ASD and BD may shed light on the commonalities and complexities observed in these conditions. The relationship between ASD and BD is likely due to shared genetic factors, which has been previously shown in whole-genome studies with large samples[54]. Recent research supports this by identifying genetic variants and chromosomal regions associated with both conditions, suggesting overlapping genetic mechanisms[55,56].

The etiologies of ASD and BD remain incompletely understood; however, the role of genetics in these conditions has been progressively established. Recent meta-analyses of twin studies on ASD have yielded a substantial heritability estimate of 64–91% with no significant contribution from shared environmental contribution[57]. BD, on the other hand, is also highly heritable, and show genetic overlap with other psychiatric diseases[58,59,60].

Investigating the genetic associations between psychiatric disorders, a study using the *GeneAnalytics* program identified twenty-three genes shared among ASD, BD, and schizophrenia[60]. These genes are involved in nine biological superpathways, including circadian entrainment, and impact dopamine and serotonin regulation, as well as signal transduction pathways, influencing mood, behavior, and physical activity levels[59,60]. Recent evidence has pointed to a common expression patterns of risk genes associated with these mental illnesses, converging on specific cortical regions and suggesting a common vulnerability of the cortex to transcriptional dysregulation across these disorders. Additionally, epigenetic mechanisms, which control gene expression without altering DNA sequence, may also influence the overlap between ASD and BD[61-63].

3.4. Diagnostic challenges in ASD and BD

As discussed in this article, there is a significant overlap of symptoms between ASD and BD. The primary importance of recognizing this overlap lies in acknowledging the coexistence of both conditions, rather than solely focusing on differentiating them.

Individuals with this overlap may experience diagnostic overshadowing, where one condition obscures or complicates the recognition and diagnosis of the other. This can result in difficulties in accurately identifying and managing both conditions simultaneously.

There are numerous diagnostic challenges that complicate the recognition of the coexistence of these two conditions. Firstly, the age of onset and developmental stage can add complexity to the diagnostic process. While ASD is typically diagnosed before BD, prodromal symptoms of BD during childhood and adolescence can resemble those of ASD[64]. Furthermore, individuals with ASD may experience a delayed or masked onset of BD symptoms, which can lead to later diagnosis or misdiagnosis[65]. In contrast, longitudinal studies have shown that individuals with comorbid ASD and BD often exhibit mood symptoms earlier and present with additional functional impairments compared to those with BD alone[66].

Second, the clinical presentations of ASD and BD can evolve over time, further complicating the diagnostic process. Symptomatology may change or become more pronounced at different life stages or in response to environmental factors, such as stressful life events[67,68]. There is evidence suggesting that ASD level 1 might go unnoticed during childhood and may only be recognized when adolescents seek treatment for suspected depressive symptoms. In such cases, mood symptoms often serve as a key entry point for medical evaluation and the subsequent identification of a comorbid ASD diagnosis.

Despite the distinct diagnostic criteria for ASD and BD as outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) and other diagnostic classifications, which initially appear to facilitate clear differentiation, several symptoms overlap between these two conditions[10,16]. For example, symptoms such as mood swings, irritability, and social withdrawal can be present in both conditions, but may be interpreted differently depending on the clinician's focus or biases. This clinical overlap complicates the clear identification of each disorder and increases the risk of diagnostic confusion[10,16]. Social communication difficulties in ASD may lead to reduced recognition of BD symptoms, as individuals with ASD may struggle to articulate or express their mood states or internal experiences. Such difficulties in recognizing mood states or changes may potentially

conceal mood-related symptoms. Thus, differential diagnosis becomes even more challenging, as symptoms may go unnoticed, leading to potential misdiagnosis or underdiagnosis, especially when both ASD and BD coexist. Conversely, typical features of ASD, such as social withdrawal and difficulty expressing emotions, can be obscured or mistaken for depressive symptoms[10].

The importance of identifying comorbidity between ASD and BD becomes even more critical in a context where recent research highlights that clinicians often prioritize symptoms of other mental health or neurodevelopmental disorders, potentially overlooking or minimizing ASD symptoms, especially in individuals with atypical or mild presentations[8]. Stereotypes linking ASD primarily with males and specific behaviors may further contribute to missed diagnoses in females or individuals from diverse backgrounds who exhibit different symptom profiles.

4. Conclusion

In conclusion, this narrative review highlights the overlap of symptoms and clinical aspects, common comorbidities, and shared neurobiological basis between ASD and BD. The potential for overshadowing between these two disorders may delay diagnosis and appropriate treatment. Understanding these overlapping symptoms is crucial for clinicians to improve their knowledge and approach to managing these complex comorbid conditions.

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