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Multimorbidity in autism spectrum disorder: A comprehensive review

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Abstract

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition defined by persistent differences in social communication and interaction, together with restricted and repetitive patterns of behavior and interests. Autism Spectrum Disorder rarely occurs in isolation; a substantial proportion of autistic individuals experience co-occurring psychiatric, developmental, neurological, gastrointestinal, sleep, feeding, motor and immune-related conditions that shape the clinical presentation, complicate diagnosis and influence long-term outcomes. This review synthesizes the major comorbidities associated with autism spectrum disorder and examines their impact on assessment and management across the lifespan. The evidence shows that anxiety, attention-deficit/hyperactivity disorder (ADHD), mood disorders, obsessive-compulsive disorder (OCD), intellectual disability (ID), epilepsy, gastrointestinal disturbances, sleep disorders and feeding and eating difficulties are especially common in ASD. These conditions often overlap with core autistic traits, contributing to diagnostic overshadowing, delayed recognition and delayed interventions. They may also intensify social withdrawal, irritability, repetitive behaviours and functional impairment, thereby increasing the burden on families and health-care systems. Biologically, comorbidities appear to arise from interacting genetic, neurobiological, environmental and immune-related pathways. Recognizing comorbidities is therefore essential not only for accurate diagnosis but also for individualized intervention. Effective care requires systematic screening, multidisciplinary assessment and targeted treatment that addresses both core autism spectrum disorder features and associated conditions. Early identification and integrated management can improve adaptive functioning, reduce symptom burden and enhance the quality of life.

Keywords: Autism spectrum disorder; Mood disorder; obsessive-compulsive disorder; Intellectual disability; Epilepsy and Anxiety

1. Introduction

The concept of autism spectrum disorder (ASD) was first clearly defined in the 1940s, when a group of children showing extreme social withdrawal and lack of responsiveness to their surroundings was studied by the American psychiatrist Leo Kanner [1]. Around the same time, Austrian child psychologist Hans Asperger detected a similar condition in children with relatively higher cognitive functioning, later known as Asperger's syndrome [2]. Together, these early observations laid the foundation for our modern understanding of ASD. In the initial decades, ASD was considered extremely rare and was often mistaken for a symptom of schizophrenia. Due to limited knowledge, diagnostic criteria were not well defined and treatment mainly focused on behavioral approaches and psychotherapy. Over time, growing research into the genetic and neurobiological aspects of ASD helped build a more comprehensive understanding of this condition. Since the 1990s, diagnoses of ASD have increased significantly, largely due to improved diagnostic criteria and greater public awareness. This period has also witnessed the importance of early diagnosis and intervention,

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leading to better outcomes and improved quality of life for many individuals with ASD [3]. In contrast to several other neurodevelopmental disorders, ASD is characterized less by uniformity than by marked diversity. Clinical expression ranges from individuals who need high levels of day-to-day support to those who live independently yet continue to face difficulties in social reciprocity, communication and adaptive functioning. This wide variation in presentation has contributed to ASD being conceptualized as a spectrum condition rather than a single, uniform disorder [4]. Although individuals with ASD are very different from one another, the disorder is defined by two behavioral domains: persistent social communication differences and restricted, repetitive sensory–motor patterns of behavior, interests or activities (RRBs), with onset in early development and clinically significant functional impact, irrespective of culture, race, ethnicity or socioeconomic group [5]. Autism spectrum disorder (ASD) is a serious developmental disorder that is usually diagnosed between 0 and 3 years. Although the severity of its symptoms varies from patient to patient, the ability to communicate with others is affected significantly in all its forms [6]. Children also manifest non-specific symptoms such as unusual sensory perception skills and experiences, motor clumsiness and insomnia. Associated phenomena include repetitive, stereotyped behaviours often accompanied by cognitive impairment, seizures or epilepsy, gastrointestinal complaints, disturbed sleep and other problems [7].

2. Methods

The present study was conducted as a comprehensive narrative review aimed at critically examining the major comorbidities associated with autism spectrum disorder (ASD) and evaluating their impact on diagnosis, treatment and long-term outcomes. The review synthesizes evidence from psychiatric, neurological, medical and behavioral research to provide an integrated understanding of the multidimensional nature of ASD comorbidities. A narrative review design was selected because it allows broad exploration and critical interpretation of diverse literature originating from multiple disciplines, including psychiatry, neurology, pediatrics, psychology, neuroscience and developmental medicine. This approach was particularly appropriate due to the heterogeneity of ASD and the wide range of associated comorbid conditions. A comprehensive literature search was conducted using multiple internationally recognized scientific databases and academic search platforms to ensure inclusion of high-quality and up-to-date evidence viz., PubMed, Google Scholar, Wiley, Taylor and Francis online library. Additionally, official reports and diagnostic manuals published by major organizations were also consulted, including World Health Organization (WHO), American Psychiatric Association (APA), Centers for Disease Control and Prevention (CDC) and National Institute of Mental Health (NIMH).

3. Medical Comorbidities in Autism Spectrum Disorder

3.1. Core diagnostic domains

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition marked by persistent difficulties in social communication and social interaction, along with restricted and repetitive patterns of behavior, interests or activities. It typically manifests in early childhood and persists throughout life, with varying levels of severity and functional impact [8].

3.1.1. Difficulties in social interaction

Autistic individuals often face significant challenges in social interactions. They may find it hard to understand others' feelings and intentions, struggle with maintaining eye contact or appropriate facial expressions and have difficulty adjusting to social norms and expectations. Forming and sustaining friendships can also be challenging, as they might not fully grasp the two-way nature of social communication or may feel uncomfortable sharing their interests and activities with others [9].

3.1.2. Communication difficulties

Communication difficulties are another core feature of ASD. These may appear as delays in language development, such as speaking first words or forming simple sentences later than expected. Some individuals may not use language to communicate at all. Even those with typical language skills may struggle to use language effectively in conversations to express their needs, feelings or thoughts. Additionally, nonverbal communication such as understanding and using body language and facial expressions can also be affected [10].

3.2. Epidemiology and global prevalence trends

Autism is also referred to as autism spectrum disorder (ASD) as it constitutes a diverse group of conditions related to development of the brain. About 1 in 127 persons had autism in 2021 globally [11]. ASD affects approximately 2.3% of

children aged 8 years in the US and approximately 2.2% of adults [12]. ASD affects all regional, racial and socioeconomic groups. The global prevalence of ASD in 2023 was approximately 1 in 100 children (WHO), with higher prevalence estimates from high-income countries [13]. ASD prevalence varies globally due to several reasons, which includes variation in awareness in different countries, the absence of diagnostic tools that are culture sensitive and cultural variation in interpreting the behavior of children [6].

The reported prevalence of ASD in the MENA (Middle East and North Africa) region tends to be lower than in Western European countries. This could be due to underestimation of ASD prevalence due to social stigma, limited access to diagnostic resources and poor screening programs in some MENA countries. Epidemiological studies worldwide indicate an increasing trend in ASD prevalence. This rise reflects not only a genuine increase in cases but also heightened awareness, improved research methodologies and evolving diagnostic criteria [12].

3.3. Concept of comorbidity in neurodevelopmental disorders

Comorbidity is most often defined in relation to a specific index condition, as in the seminal definition of Feinstein: “Any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study” [14,15]. Co-occurring conditions or disorders, such as anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), depression, intellectual disability and seizures are common among individuals with ASD, with one study (112 ten-to twelve-year-old autistic individuals) showing that over 70% of individuals with ASD have at least one co-occurring psychiatric condition and more than 40% have two or more [16, 17].

3.3.1. Relevance and clinical importance of understanding comorbidities in ASD

Since ASD is a lifelong disorder and comorbidity needing treatment or interventions can be present during various phases of life, the diagnostic procedure needs to continue even after ASD has been diagnosed [18]. Diagnostic complexity and overshadowing occur in autism because comorbid conditions can mask, mimic or amplify autistic traits, clinicians who attribute all change to “autism” risk missing treatable medical or psychiatric problems; therefore, systematic screening for comorbidities is essential [19]. Comorbid disorders often present with atypical signs in autistic individuals (e.g., internalized anxiety expressed as increased repetitive behavior or aggression), so standard diagnostic checklists may miss them.

3.4. Diagnostic criteria

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition established during early fetal development and childhood. The diagnostic framework has evolved from the narrow "pervasive developmental disorder" of the DSM-3 (Diagnostic and Statistical Manual of Mental Disorders) to the current DSM-5 (2013) and ICD-11 (International Classification of Diseases), which conceptualize autism as a single, multidimensional spectrum. According to modern diagnostic frameworks such as the DSM-5, ASD encompasses a wide range of conditions previously categorized separately (e.g., autistic disorder, Asperger’s syndrome), reflecting its spectrum nature [5].

3.5. Diagnostic criteria according to DSM-5 or ICD-11.

According to the DSM-5, a diagnosis requires persistent deficits in reciprocal social communication and interaction across multiple contexts, alongside restricted, repetitive patterns of behavior, interests or activities. These symptoms must be present in the early developmental period, cause clinically significant impairment and are not better explained by intellectual disability. While the DSM-5 relies heavily on observable behavioral manifestations, the ICD-11 moves toward a social model that considers the "inner experience" of the individual, allowing for a higher variety of symptom combinations.

3.6. Overview of the spectrum and why it's important in understanding comorbidities.

The spectral nature of ASD is critical for understanding comorbidities because "pure" autism is extremely rare, rather, symptoms almost never occur in isolation [20]. The spectrum encompasses a vast range of clinical heterogeneity, where neuroanatomical, metabolic and immunological pathways overlap with other conditions [4]. This spectral view allows clinicians to use specifiers such as level of intellectual impairment, language impairment and association with known medical or genetic factors to capture the diverse needs of the individual.

3.7. Classification of comorbidities in ASD: Their types and prevalence

Individuals with ASD experience a significantly higher burden of medical and psychiatric conditions than the general population, with studies estimating that 74% of the autistic population present with at least one comorbidity [21]. The major comorbidities occurring in autism spectrum disorder are discussed.

4. Mental health disorders

Previous studies have shown that psychiatric comorbidity in ASD significantly increases the difficulties in adaptive responses and affects the daily activities, decreases the quality of living and accentuates problems like restlessness, passivity, social isolation, aggressiveness, irritability or self-injury. Individuals with ASD are likely to experience a higher prevalence of common mental disorders compared to the typically developed individuals [22]. Moreover, children with ASD have been found to have a higher burden of psychiatric comorbidity than children with intellectual disability. Many core or attendant ASD behaviours (e.g., inattention, repetitiveness, social withdrawal, ritualized behavior) overlap with features of ADHD, anxiety, OCD and mood disorders, making differential diagnosis difficult [23]. As many as 70% of children and adults with ASD are estimated to meet diagnostic criteria for at least one co-occurring psychiatric disorder, such as anxiety disorders, depressive and bipolar mood disorders and schizophrenia spectrum conditions. Psychiatric conditions are the most frequently reported comorbidities in ASD. Anxiety disorders are ubiquitous, affecting up to 84% of individuals and include specific phobias, obsessive-compulsive disorder and social anxiety [24].

4.1. Attention-Deficit/Hyperactivity Disorder (ADHD)

Attention-Deficit/Hyperactivity Disorder (ADHD) is also highly prevalent, with estimates ranging from 31% to 84%, often leading to significant academic and social dysfunction. The identification and assessment of ADHD and ASD is complex due to shared etiologies, overlapping symptoms and shared characteristics [25]. Children with both ASD and ADHD often show more pronounced social and cognitive difficulties and are at a greater risk of anxiety, mood disorders and academic challenges [26]. Both clinically elevated ADHD and anxiety symptoms were documented at high rates in the ASD group and ASD participants with ADHD symptoms showed more severe autism impairments. When ADHD and anxiety symptoms co-occur with ASD, they are associated with greater impairments in socialization and daily living skills, emphasizing how overlapping symptom profiles can affect adaptive functioning and quality of life [27].

4.2. Anxiety

ASD and anxiety symptoms frequently overlap, although individuals with ASD might present with peculiar anxiety symptoms (e.g., unusual specific phobias and fears of change) that may be difficult to distinguish from core autism features [23]. When ADHD and anxiety symptoms co-occur with ASD, they are associated with greater impairments in socialization and daily living skills, underscoring how overlapping symptom profiles can affect adaptive functioning and quality of life [27].

4.3. Obsessive compulsive disorder (OCD)

A disorder that frequently co-occurs is, obsessive–compulsive disorder (OCD), defined by intrusive, repetitive thoughts (obsessions) and time-consuming, repetitive behaviours (compulsions) that lead to clinically significant distress and/or marked functional impairment [28].

4.4. Mood disorders

A large proportion of autistic individuals experience at least one co-occurring mood disorder, most commonly Major Depressive Disorder (MDD) and bipolar disorder (BD). According to the DSM-5 criteria, MDD is characterized by a persistent sad, empty or irritable mood, along with somatic and cognitive changes that significantly impair daily functioning while bipolar disorder (BD), is defined by the occurrence of hypomanic or manic episodes [22, 29]. Studies have reported varying prevalence rates, with approximately 11% for MDD and around 5% for BD figures notably higher than those observed in the general population (about 7% for MDD and < 1% for BD) [30]. These differences may be influenced by several factors. For instance, mood disorders are reported in about 5-10% of autistic individuals who also have an Intellectual disability (ID) whereas, much higher rates, reaching up to 53% have been observed in individuals with ASD but without an ID. Age and sex also appear to play a role. During early adolescence, males tend to report higher rates of depression compared to females, although this difference seems to diminish by early adulthood. In the case of BD, manic symptoms in individuals with ASD are more likely to become evident later, typically emerging in adulthood. Patients with autism have been reported to be at increased risk of depression (prevalence of about 2% of all autism-spectrum disorders), particularly those who are more cognitively able [31].

4.5. Feeding and eating disorders (FEDs)

Empirical evidence indicates that atypical patterns of eating behavior occur with greater frequency in children diagnosed with ASD compared to their typically developing peers. Over recent decades, growing scholarly focus has been directed toward the relationship between feeding and eating disorders (FED) and autism spectrum disorders

(ASD) given that atypical feeding practices, ranging from mild irregularities to severe food selectivity are frequently documented in children with ASD, with reported prevalence rates varying widely from 13% to 87% [32, 33]. However, it remains unclear whether this substantial variability reflects the presence of shared comorbidities or overlapping clinical characteristics between the two conditions. One study estimated the prevalence of co-occurring FEDs and ASD to range between 1.4% and 7.9%; among the FED subtypes examined, anorexia nervosa (AN) demonstrated the highest rate of comorbidity (6.7%), followed by bulimia nervosa (2.7%) and binge-eating disorder (1.4%) [34].

The most frequently reported feeding-related difficulties in individuals with ASD include atypical eating behaviours such as picky eating, food selectivity (often linked to aversion toward specific textures or colours), restricted dietary variety and gastrointestinal (GI) disturbances including abdominal pain, diarrhoea, constipation and gastrointestinal reflux. Children presenting with both ASD and GI-related symptoms are more likely to exhibit higher levels of irritability, hyperactivity, agitation, social withdrawal and lethargy compared to those without GI involvement. In view of this evidence, routine follow-up visits should incorporate a comprehensive clinical evaluation, including screening for body mass index (BMI), abdominal discomfort, mealtime challenges and gastrointestinal alterations [35]. Multiple studies emphasize on the importance of early detection of atypical eating behaviours in children with ASD, as delayed recognition may negatively influence therapeutic outcomes. This concern is particularly significant because, despite limited evidence regarding treatment efficacy for co-occurring ASD and FEDs, the presence of ASD has been proposed as a factor contributing to reduced responsiveness to conventional therapies. In early intervention contexts, educators and school psychologists may play a pivotal role by supporting children with ASD in navigating the social context of eating within school environments and by reducing associated stressors [36]. Key assessment tools that aid in the identification of feeding and eating disorders include food diaries, self-reported questionnaires, such as the Eating Disorder Inventory-3 (EDI-3) or the Food Frequency Questionnaire (FFQ), as well as parent-reported measures like the Brief Autism Mealtime Behavior Inventory (BAMBI) [37]. A recent observational investigation by Folta identified a variety of coping mechanisms employed in social context, leading the authors to recommend that intervention strategies adopt a responsive framework that incorporates the individual's existing adaptive skills for managing eating in social contexts [38]. A thorough understanding of the factors surrounding feeding difficulties may facilitate the selection of targeted treatment components, such as psychoeducation and enhancement of the parent–child feeding relationship [36]. While mild food selectivity may not necessitate immediate clinical intervention, moderate to severe forms can progress to meet diagnostic criteria for an eating disorder and may place the child at risk for nutritional deficiencies and subsequent medical complications. Behavioral interventions, including Cognitive Remediation Therapy (CRT) and Parent Training (PT), have demonstrated particular effectiveness in the management of FEDs in children with ASD [39]. In conclusion, it is essential to systematically examine the etiology, therapeutic requirements and prognosis when addressing the co-occurrence of ASD and FEDs. Additional longitudinal research is essential to address existing gaps in knowledge and to inform evidence-based clinical practice.

5. Neurological disorders

5.1. Epilepsy

Epilepsy is a neurological disorder marked by episodic, unpredictable alterations in mental status, typically presenting as seizures or convulsions. Similar to autism, epilepsy is now increasingly viewed as a spectrum. Research indicates that up to 60% of children with autism show abnormal electroencephalogram (EEG) findings, compared to approximately 6%–7% in typically developing children. Additionally, around 10% to 30% of children with autism are diagnosed with epilepsy, while nearly 8% of children with epilepsy meet criteria for ASD [40]. The bidirectional overlap between Autism and Epilepsy has led to the recognition of autism as a comorbidity of epilepsy and vice versa, with both conditions often co-occurring. The prevalence of epilepsy in individuals with ASD is highest among those with co-occurring intellectual disability, particularly during the second decade of life and the risk of developing epilepsy persists into adulthood. Age is a key factor strongly linked to the onset of seizures in individuals with ASD. Evidence from multiple studies suggests a bimodal pattern of epilepsy occurrence, with one peak in early childhood and a second during adolescence. In contrast, several large cross-sectional studies report a steady increase in epilepsy risk with age, reaching its highest point in early adolescence [41]. Among children diagnosed with ASD in the first decade of life, the majority of seizures tend to develop after the age of 10, with the likelihood of epilepsy continuing to rise into the third decade [42]. There is clear and consistent evidence indicating that ASD, intellectual disability and epilepsy co-occur. Research has shown that epilepsy may either precede or follow the diagnosis of neurodevelopmental conditions such as intellectual disability or ASD, highlighting a complex and bidirectional relationship among these disorders.

Seizures, disrupted neuroplasticity and autism-like behaviours frequently occur together during the early stages of brain development, suggesting a possible link among these factors [43]. The likelihood of epilepsy in children with ASD is higher in the presence of intellectual disability and is also reported to be greater in females. Children diagnosed with

autism should be assessed for seizure activity, ideally through prolonged EEG monitoring of 24 hours or more under the supervision of a pediatric neurologist. The use of video EEG is strongly recommended in cases where autism co-occurs with significant intellectual disability where nearly 50% may develop epilepsy or when autism is associated with genetic or neurological conditions such as Angelman syndrome, Down syndrome (DS) or tuberous sclerosis. It is essential for parents, caregivers, therapists and others involved in the child's care to recognize seizure manifestations, including warning signs and potential triggers. Awareness is critical, as seizures can be life-threatening in some cases. When seizure activity is confirmed, appropriate treatment of the seizure disorder becomes necessary [44].

5.2. Sleep disorders

Sleep disorders (SDs) include problems regarding quality, timing and total amount of sleep that could result in impaired level of function and daytime distress [29]. Sleep disorders are one of the most commonly reported comorbid conditions in individuals with ASD. Although prevalence estimates vary by study design and measurement methods, research indicates that 40% to 80% of children with ASD experience significant sleep difficulties which is substantially higher than that observed in their typically developing peers [45]. The etiology is considered to be multifactorial, involving potential disruption in circadian rhythms of cortisol and melatonin, along with poor sleep hygiene practices. Approximately 25% of sleep disturbances (SD) in individuals with ASD begin at birth and are early indicators of neurological dysfunction in ASD [46]. Additionally, research has shown that bedtime access to bright screens is linked to reduced sleep in ASD children, when compared to typically developing (TD) peers, likely because bright screens hamper melatonin release and disrupts normal circadian rhythms [47]. Sleep problems can cause difficulty falling asleep, inability to sleep in a flat position, night-time reawakenings, sleepwalking, learning problems, hyperactivity, inattention, anxiety, aggression and various health problems alongside insomnia, delayed sleep onset, night wakings, shortened sleep duration, parasomnias (such as night terrors and night walking) and circadian rhythm disturbances. It could be due to hormonal imbalances, GI disorders, seizure activity, poor sleep environment, sleep apnea or as a side effect of some medications commonly used to treat autistic symptoms. A narrative review further reports that insomnia alone affects between 60% and 86% of children with ASD and is often associated with harmful consequences like aggression, irritability, inattention and hyperactivity [48].

The sleep community has identified autism as a priority population for targeted interventions for sleep disorders [49]. Poor sleep affects the health of the individual and daily functioning, as well as the integrity of the family. Sleep disorders are highly treatable. Therefore, evidence-based standards of care for monitoring, assessing and treating sleep disorders in children with ASDs are of great importance. The implementation of non-pharmacotherapeutic interventions such as bedtime routines and sleep-appropriate approaches is the mainstay of behavioral management. Treatment strategies along with limited regulated pharmacotherapy can help improve the quality of life of children with ASD and have a positive effect on the family [40].

5.3. Motor disorders

Several recent studies have documented a high prevalence of clinically significant motor problems in those with autism spectrum disorder (ASD) diagnosis, ranging from 50% to 95% [50]. Repetitive motor movements (stereotypies), such as hand-flapping, rocking or idiosyncratic use of objects, are considered core characteristics of the ASD phenotype but can be exacerbated by co-occurring anxiety or gastrointestinal pain [51].

5.4. Medical conditions

Gastrointestinal (GI) issues are four times more frequent in the ASD population than in neurotypical peers, with a reported prevalence between 46% and 91%. Common disturbances include chronic constipation, abdominal pain and gastroesophageal reflux disease (GERD), which can often manifest behaviourally as aggression or irritability in non-verbal individuals. Immune system abnormalities, including neuroinflammation, altered cytokine profiles and increased T-cell responses, are also prevalent and may be driven by gut-brain axis dysregulation. Additionally, Intellectual Disability (ID) co-occurs in approximately 31% to 45% of children with ASD [55].

5.5. Mechanisms behind comorbidities

Epidemiological studies indicate that potential environmental prenatal factors contributing to ASD include exposure to infection during pregnancy, obesity, gestational diabetes mellitus (GDM), maternal selective serotonin reuptake inhibitor (SSRI) use, antibiotic use and prenatal exposure to toxicants [52]. These prenatal factors may alter several pathways during critical developmental periods, particularly in genetically sensitive individuals [53]. The evidence relating to the potential pathways underlying the aforementioned prenatal factors is largely preclinical and implicates immune dysregulation, mitochondrial dysfunction, oxidative stress, gut microbiome alterations and disruptions [54].

Comorbid medical and psychiatric conditions commonly co-occur with autism spectrum disorder (ASD) and both exacerbate core ASD features (social-communication deficits, restricted/repetitive behaviours) and are influenced by overlapping biological vulnerabilities; recognizing and treating comorbidities frequently yields measurable improvements in behavior and functioning [55].

5.6. ADHD

ADHD symptoms (inattention, impulsivity, executive-function deficits) frequently co-occur with ASD and tend to magnify social, cognitive and adaptive impairments; combined ASD+ADHD presentations are associated with greater functional difficulties than ASD alone and symptom overlap complicates differential diagnosis and treatment planning [56].

5.7. Anxiety disorders

Anxiety is one of the most frequent psychiatric comorbidities in ASD and often presents atypically (e.g., increased insistence on sameness, heightened sensory avoidance), such that anxiety both mimics and amplifies core autistic features (social withdrawal, ritualized behaviours), reducing responsiveness to social-skills interventions unless specifically addressed [57].

5.8. Epilepsy and epileptiform activity

Epilepsy and interictal epileptiform abnormalities are significantly more prevalent in individuals with ASD than the general population and are associated with more severe cognitive, language and behavioral impairments epilepsy can therefore both resemble and worsen core ASD manifestations, while seizure control can yield cognitive and behavioral gains. Effective seizure management may improve some aspects of functioning [58].

5.9. Sleep disorders

Sleep disturbances (insomnia, fragmented sleep, sleep-disordered breathing) exacerbate daytime inattention, irritability and repetitive behaviours in ASD and effective sleep management is associated with improvements in attention, behavior and learning capacity [59].

5.10. Gastrointestinal disorders

GI pain or dysfunction commonly presents as behavioral change (self-injury, aggression, increased stereotypies) in nonverbal or communication-impaired autistic individuals, making GI comorbidity both a contributor to behavioral burden and a driver of apparent worsening in core symptoms [55, 60].

6. Impact of comorbidities on diagnosis

6.1. Challenges in diagnosing ASD with comorbidities.

Many autistic people (especially non- or minimally verbal or those with intellectual disability) cannot describe internal states (pain, worry, depressed mood), so psychiatric or medical comorbidities are harder to detect [40]. Females with ASD more often camouflage or present less overt core symptoms but may have higher rates of certain comorbidities (e.g., internalizing disorders), which increases the risk of missed or delayed diagnosis [61]. Furthermore, the common screening tools like ADOS (Autism Diagnostic Observation Schedule), ADI-R (Autism Diagnostic Interview-Revised), or the standard anxiety/ADHD rating scales were not developed or normed for people with multiple co-occurring conditions and can have reduced sensitivity or specificity in presence of comorbidity [62].

6.2. Effect of comorbidities on individuals' lives

ASD imposes significant physical, psychological and emotional challenges on affected children and their families. Families of individuals with ASD often face significant emotional and financial challenges due to high levels of anxiety, stress and isolation associated with caregiving, as well as the extensive financial resources required [6]. Studies have also reported high levels of parental stress, depression, anxiety and physical health complications [63]. Furthermore, ASD presents a substantial economic burden on both families and national healthcare systems [64]. Additionally, social stigma, limited access to specialized healthcare services and delayed diagnosis in low-resource settings may further intensify the psychosocial burden experienced by affected individuals and their families. These challenges highlight the importance of accessible multidisciplinary care and supportive community-based interventions. Therefore, early detection and intervention are crucial for improving the intellectual and behavioral outcomes of affected children while reducing the burden on families.

6.3. Impact on long-term outcomes

The long-term health outcomes associated with ASD continue to impose a high burden of care, which necessitates a scientific evaluation of how different comorbid conditions affect people with ASD [65]. In a review study by Sevaslidou (2019), almost half of the participants with ASD showed poor or very poor outcomes in adult life, whereas only approximately one-fifth had good outcomes [66]. Autistic people are at an increased risk of social isolation, academic or employment difficulties and might require psychosocial support into adulthood. The presence of multiple comorbidities has also been associated with greater dependence in adulthood, lower educational attainment, reduced employment opportunities and increased need for long-term healthcare and social support services.

6.4. Overlap of symptoms between ASD and other conditions

ASD and ADHD share several overlapping behavioral characteristics: inattention, executive dysfunction, hyperactivity and difficulties with social cognition, which often make differential diagnosis challenging and may mask one another's presence in clinical settings. These problems are difficult to identify and address, which they coexist with a complex condition like ASD. It is well documented that diagnosing ASD is a difficult task due to the unique clinical and subclinical manifestations among individuals [67].

7. Treatment and management of comorbidities

Conventional diagnostic approaches for ASD primarily depend on comprehensive evaluations of behavior and developmental history. These assessments are typically carried out by trained healthcare professionals, including pediatricians, neuropsychologists or psychiatrists. The process involves direct observation of the child, along with detailed interviews with parents or caregivers to collect information about the child's social interactions, communication abilities and behavioral patterns. While these traditional diagnostic methods are very effective in identifying ASD, they depend largely on subjective evaluations and the clinician's experience, which can result in some variability. In recent years, as understanding of ASD has expanded, newer diagnostic approaches and techniques have been developed and adopted to enhance both accuracy and efficiency [68].

Identifying and targeting underlying medical conditions, behavioral abnormalities and adverse environmental effects have the potential to significantly improve the quality of life for autistic individuals and their families.

Health conditions in children with ASD are linked to lower quality of life and increased health-related burden among parents, potentially due to spillover effects. Addressing such health concerns, particularly sleep disturbances, may lead to improvements in both quality of life and psychosocial stress experienced by parents and the family [69]. Consequently, targeted management of these issues may result in substantial improvements in the overall health and symptom profile of children with ASD. Sleep plays a critical role in overall functioning and a structured, stepwise management approach is recommended, beginning with optimization of sleep hygiene, followed by the introduction of melatonin and subsequently progressing to other pharmacological or supplemental interventions as required.

Children with co-occurring epilepsy and ASD should receive anti-epileptic medications alongside comprehensive evaluation for potential underlying genetic and metabolic disorders. In certain cases, children exhibiting epileptiform abnormalities may demonstrate symptomatic improvement following anti-epileptic treatment. Management of cerebral folate abnormalities may involve the use of leucovorin in conjunction with a milk-free diet [70, 71]. Gastrointestinal disorders in children with ASD have been addressed by an expert panel, with prebiotics and probiotics demonstrating potential therapeutic benefit.

Behavioral and psychiatric manifestations can be alleviated through multiple approaches. Irritability, for instance, may respond to parental training programs. The management of anxiety in children with ASD remains uncertain; conventional treatment with selective serotonin reuptake inhibitors yields inconsistent outcomes and may, in some cases, be detrimental, whereas cognitive behavioral therapy appears to demonstrate greater efficacy compared to standard approaches. Additionally, alternative safe medications such as propranolol and emerging techniques like transdermal electrical neuromodulation have shown promising results in addressing anxiety symptoms. The treatment of attention-deficit hyperactivity disorder is further complicated by an increased burden of adverse effects associated with standard stimulant medications in children with ASD, suggesting that alpha-adrenergic agents may represent a more suitable option [70].

Immune-related conditions are present heterogeneously, atopic disorders should be managed through allergen elimination, medication or referral to an allergist, whereas autoimmune conditions and immunodeficiencies may respond to intravenous immunoglobulin (IVIG), necessitating evaluation and treatment by an immunologist. The

treatment of nutritional deficiencies is generally straightforward; however, implementing dietary modifications may be challenging due to co-occurring behavioral difficulties. Preliminary evidence suggests that supplementation with vitamin D and/or zinc may contribute to improvements in ASD symptoms. The treatment of metabolic disorders is often complex and should be managed by specialized clinicians [70, 72].

Research highlights the need to develop and refine diagnostic tools that are sensitive to diverse presentations of ASD, including females, individuals with higher cognition and ethnic minorities. Standard screening instruments may lack sensitivity, suggesting a need for a paradigm shift in ASD screening methodologies [73]. A multidisciplinary diagnostic approach involving direct assessment, caregiver interviews and informant reports is recommended to improve accuracy. In addition, training primary care providers in ASD diagnosis has shown promise in reducing wait times and enhancing diagnostic agreement [74]. Given that women with ASD may present with subtler or internalized symptoms, diagnostic frameworks must adapt to these gender-specific manifestations and clinicians should remain vigilant against diagnostic overshadowing that can obscure ASD recognition [75,76]. Future diagnostic frameworks should also incorporate culturally sensitive and developmentally appropriate assessment strategies, particularly for underrepresented populations and low-resource settings where underdiagnosis remains common.

8. Discussion

8.1. Diagnostic Challenges and Clinical Complexity in ASD Comorbidities

The findings highlight the complexity that comorbid conditions add to ASD, particularly in relation to diagnosis and treatment. One key challenge is diagnostic overshadowing, where symptoms of co-occurring conditions are attributed to ASD itself. This can lead to underdiagnosis or delays in identifying conditions that are otherwise treatable [19]. The issue becomes more complicated due to the overlap in symptoms between ASD and conditions such as ADHD, anxiety disorders and OCD. For example, inattention, emotional dysregulation and repetitive behaviours may be interpreted either as manifestations of ASD or as indicators of separate psychiatric conditions, making differential diagnosis particularly challenging in clinical practice [25].

Standard diagnostic tools, although useful, may show reduced sensitivity and specificity when multiple comorbidities are present. This is especially true for individuals with intellectual disability, limited verbal abilities or atypical symptom presentations [62]. Many currently available screening instruments were originally developed for neurotypical populations and may therefore fail to adequately capture the diverse clinical presentations observed in ASD. This limitation contributes to inconsistencies in prevalence estimates across studies and may partly explain the substantial variability reported for conditions such as ADHD, anxiety disorders and gastrointestinal disturbances [35]. Gender differences also play a role. Females with ASD may present with subtler or more internalized symptoms and may engage in camouflaging behaviours, which increases the risk of under-recognition [75]. This underrepresentation of females in ASD research has historically contributed to a male-centred understanding of autism, limiting the generalizability of diagnostic frameworks and potentially delaying access to intervention and support for many females with ASD.

8.2. Neurobiological Mechanisms and the Bidirectional Nature of Comorbidities

The relationship between ASD and its comorbidities is often bidirectional. Comorbid conditions can worsen core ASD symptoms, such as social communication difficulties and restricted behaviours. At the same time, characteristics of ASD can influence how these comorbid conditions appear and are experienced [55]. For instance, sleep disturbances, epilepsy and gastrointestinal issues may present as behavioral changes, making clinical interpretation more challenging [58]. The findings also suggest that the heterogeneity of ASD extends beyond behavioral presentation and may reflect underlying neurobiological diversity. Emerging evidence involving immune dysregulation, neuroinflammation, altered gut-brain interactions, mitochondrial dysfunction and genetic susceptibility indicates that ASD and its comorbidities may share overlapping biological pathways rather than existing as entirely separate conditions [4,54]. However, despite increasing interest in these mechanisms, current evidence remains fragmented and further longitudinal and translational research is needed to clarify these complex interactions.

8.3. Implications for Diagnosis, Management and Future Treatment Approaches

Given these complexities, the findings strongly support the need for a multidisciplinary approach to diagnosis and management. A comprehensive assessment should combine clinical observation, standardized tools, caregiver input and where needed, biological or laboratory evaluations [74]. Relying only on traditional screening tools may not provide a complete understanding of the individual's condition. Integration of pediatricians, neurologists, psychiatrists, psychologists, speech therapists and behavioral specialists is therefore essential to ensure accurate assessment and holistic care.

In terms of treatment, the evidence emphasizes the importance of individualized and integrated care plans. Behavioral interventions continue to play a central role, while pharmacological treatments may be used to manage specific comorbid symptoms [70]. Emerging approaches such as precision medicine offer promising possibilities for tailoring interventions based on genetic, biological and environmental factors, although more research is needed in this area. Recent advances in precision medicine, biomarker research and artificial intelligence-assisted diagnostics may eventually contribute to earlier identification of risk profiles and more targeted therapeutic interventions. Nevertheless, these approaches remain in early developmental stages and require further large-scale clinical validation before widespread implementation. The findings of this review reinforce the idea that comorbidities should not be viewed as secondary complications of ASD, but rather as central components influencing the clinical presentation, prognosis and long-term outcomes of the disorder [65]. Overall, effectively addressing comorbidities is essential not just for managing symptoms but also for improving functional outcomes and overall quality of life in individuals with ASD [69].

8.4. Best practices in treating individuals with ASD and comorbid conditions.

The findings of this review emphasize that treatment approaches should extend beyond management of core ASD symptoms and focus equally on identifying and addressing co-occurring psychiatric, neurological and medical conditions. Early intervention is particularly important, as timely therapeutic support may improve communication skills, adaptive functioning and long-term independence [5] (Fig. 1). Behavioral interventions remain the foundation of treatment; however, evidence suggests that outcomes improve considerably when comorbid conditions such as anxiety, ADHD, sleep disturbances and gastrointestinal disorders are simultaneously addressed [57]. Effective management requires individualized treatment plans that combine behavioral therapy, psychoeducation, family support, educational accommodations and when necessary, pharmacological interventions [70].

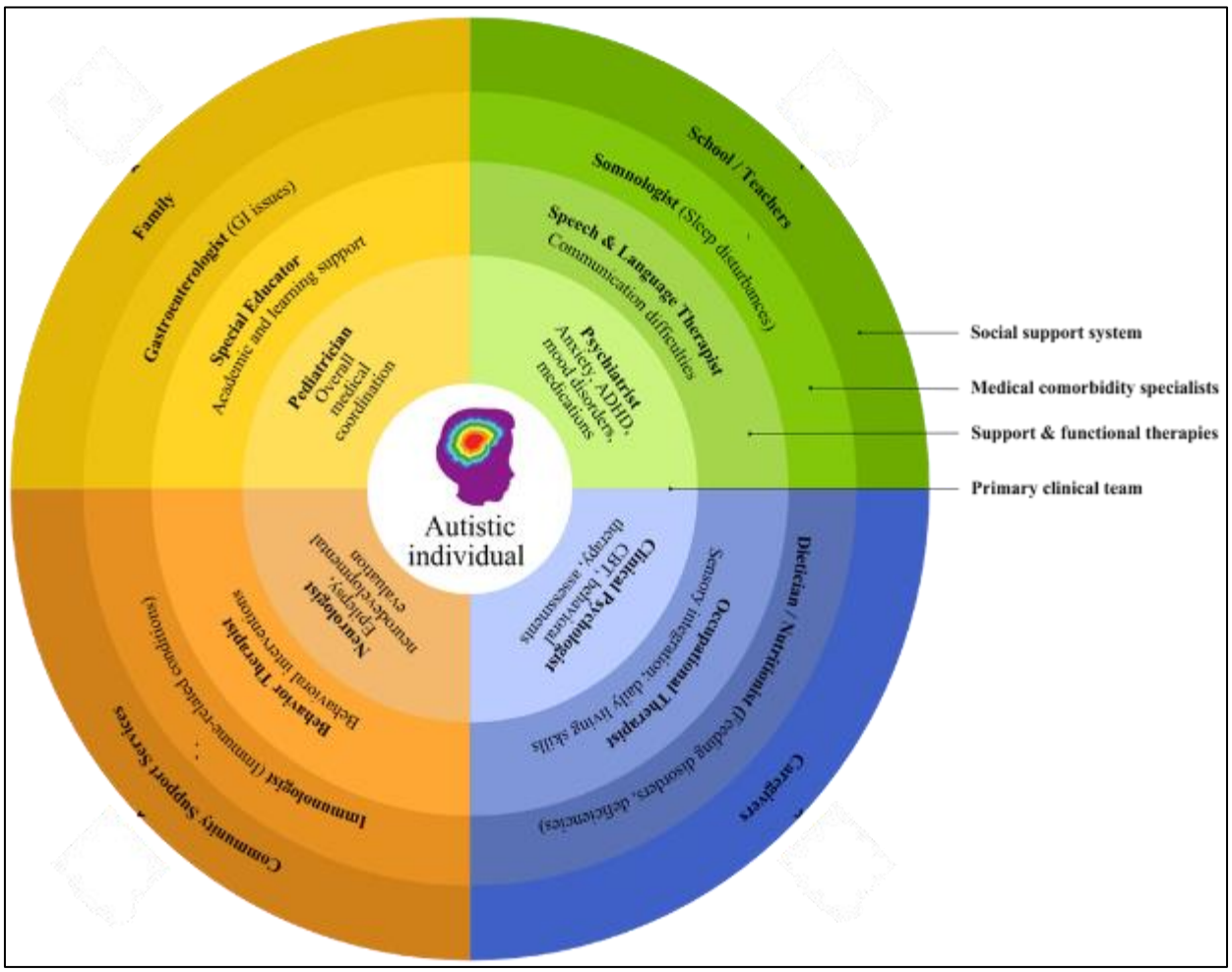

Figure 1 Multidisciplinary model for the holistic management of autism spectrum disorder integrating medical, behavioral and psychosocial care

The use of precision medicine in ASD treatment reflects a personalized approach that focuses on tailoring interventions to an individual's genetic profile, biomarkers, history of environmental exposures and lifestyle. This approach is based on the understanding that, although ASD is categorized as a spectrum (Fig. 1), each individual differs in terms of etiology, symptoms and severity, making highly individualized treatment essential. In addition, precision medicine also takes into account environmental influences and personal behaviours, ensuring that treatment options are not only scientifically effective but also suited to the individual's daily life. Although still at an early stage in the context of ASD, precision medicine holds significant promise for developing more personalized and effective treatment approaches, with the potential to greatly enhance the quality of life for an individual's lifestyle.

9. Conclusion

In conclusion, comorbidities are a pervasive and clinically significant aspect of autism spectrum disorder (ASD), profoundly influencing diagnosis, treatment, functional outcomes and overall quality of life. The presence of co-occurring psychiatric, neurological, developmental and medical conditions contributes substantially to the heterogeneity and clinical complexity of ASD across the lifespan. Among the most frequently reported comorbidities are anxiety disorders, ADHD, mood disorders, epilepsy, sleep disturbances and gastrointestinal conditions, many of which overlap with core autistic characteristics and complicate both recognition and management. As a result, failure to identify these conditions may lead to diagnostic overshadowing, delayed intervention and missed opportunities for targeted care. Early identification and comprehensive assessment of comorbidities are therefore essential for improving clinical outcomes. Effective management requires a multidisciplinary, individualized and developmentally informed approach that integrates behavioral therapies, psychosocial support, educational interventions and appropriate medical treatment. While pharmacological therapies may help alleviate specific comorbid symptoms, they do not directly address the core social communication differences associated with ASD, emphasizing the importance of balanced and holistic care. Furthermore, fostering inclusive and supportive environments that acknowledge neurodiversity is crucial for promoting wellbeing, independence and social participation among autistic individuals. Emerging evidence also suggests that ASD and its comorbidities may share interconnected genetic, neurobiological, immune-related and environmental mechanisms, reinforcing the need for continued multidisciplinary research. Future studies should focus on improving diagnostic tools, understanding long-term outcomes, addressing gender-related diagnostic disparities and advancing personalized approaches such as precision medicine. Ultimately, the findings of this review demonstrate that comorbidities should not be regarded as secondary complications of ASD, but as central components that fundamentally shape its clinical presentation, prognosis and treatment needs. Recognizing and addressing these comorbidities is therefore essential for delivering more effective, evidence-based and person-centred autism care.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have no any conflict of interest for publishing this article.

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