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Review

Autism spectrum disorders and psychiatric comorbidities: a narrative review

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SUMMARY

Background.

Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders characterized by persistent difficulties in social communication, restricted interests, and repetitive behaviors. Diagnosis can be difficult because of the heterogeneity of clinical and subclinical expression of symptoms among individuals. ASD rarely presents in its pure form, and individuals with ASD are more likely to have comorbid psychiatric disorders than the general population. Symptoms related to psychiatric comorbidities can worsen the clinical course of ASD, and distinguishing psychopathological symptoms from the main or atypical symptoms of ASD can be difficult for clinicians. The aim of this narrative review is to make an overview of psychiatric comorbidities of ASD, updating prevalence, highlighting symptoms and available diagnostic tools, and finally defining possible treatment strategies.

Methods.

This narrative review was conducted first by defining the objective, followed by a research of the scientific literature and data evaluation, and finally by presenting results. Search terms were entered into ERIC, MEDLINE, PsycARTICLES, PsycINFO, Scopus, and PubMed. Only studies published in English were included. Only studies that analyzed autistic traits in severe mental disorders and studies of patients with ASD and severe mental disorders in comorbidity were included. Studies on children, adolescents, and adults were included. Given the breadth and specificity of the topic, studies on psychosis, schizophrenia, gender dysphoria, trauma and post-traumatic stress disorder, substance use disorders, and suicidal behavior were not included in the search terms and are not discussed in this review. The terms and databases were combined using the Boolean search technique to make the search more restrictive and detailed. Tables were then constructed and results were sorted by prevalence, symptoms, diagnostic tools and treatment, and finally discussed in a narrative way.

Results.

The included studies were divided into eight categories based on psychiatric comorbidity in ASD: attention deficit hyperactivity disorders; anxiety disorders; personality disorder; repetitive behaviors and obsessive compulsive disorders; sleep disorders; mood disorders; Tourette syndrome and tic disorder studies; feeding and eating disorder studies.

Discussion.

ADHD has the highest prevalence among psychiatric comorbidities in ASDs, followed by anxiety disorders. The clinical presentation of all the disorders considered is often overlapping with core symptomatology of ASD, although some peculiarities may help clinicians to recognize the presence of a comorbidity. With the exception of few scales adapted for ASD patients, assessment tools available for the diagnosis of psychiatric disorders in the context of ASD are often not adjusted for individuals on the autism spectrum. The co-occurrence of these disorders is usually associated to a worsening of the clinical presentation and to a resistance to conventional treatments, especially pharmacological. Among non-pharmacological treatments, behavioral interventions, and specifically cognitive behavioral therapy, seem to be effective in almost all the psychiatric disorders evaluated in this study.

Conclusions.

Prospective studies with homogeneous samples are needed to develop specific diagnostic tools and dedicated treatments for psychiatric comorbidities in the context of ASD.

Key words: autism spectrum disorders, psychiatric comorbidities, diagnostic features

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Introduction

Autism spectrum disorders (ASDs) are a group of neurodevelopmental disabilities characterized by persistent difficulties in social communication, restricted interests, and repetitive behaviors [1]. With millions of people affected and a global prevalence estimated of about 0,6% percent [2], ASDs account for more than 58 daily adjusted life years (DALYs) per 100,000 population while other ASDs for 53 DALYs per 100,000 [3]. The concept of autism spectrum was introduced in the DSM-5, overcoming the definition present in the DSM-4 of "Pervasive Developmental Disorders" (PDD) which included five separate diagnoses [4]. A mental spectrum disorder includes a number of interrelated conditions, symptoms and traits that are in a continuum and are thought to arise from the same underlying mechanism [5,6]. ASDs are characterized by significant social, communication and behavioral impairment [1]. The DSM-5-TR indicates that diagnosis of an ASD requires: "persistent deficits in social communication and social interaction across multiple contexts, as manifested by all of the following" [7]. Therefore, in order to diagnose a disorder in the autism spectrum, a child must present persistent deficits in all of the three areas of communication and social interaction, as well as at least two of the four types of restricted and repetitive behaviors, the severity of each defining three different levels of support [8]. However, the diagnosis of ASD is often complex in light of the heterogeneity of clinical and subclinical expressions across individuals [9] In fact, ASD rarely presents in its pure form, and DSM-5 supplementary diagnoses, among those with ASD, are no longer precluded [10]. Many people with ASD require lifelong support and an integrated, interdisciplinary, medical approach. Apart from medical comorbidities, like gastrointestinal disorders and seizures [11], individuals on the autism spectrum present an increased risk of developing a comorbid psychiatric disorder, when compared to the general population [10]. Several studies highlighted the epidemiological burden of psychiatric disorders in subjects with ASD, among which the most common are mood disorders, depressive disorders, bipolar disorders, attention deficit hyperactivity disorder (ADHD), disruptive behavior disorders, anxiety disorders, feeding and eating disorders, obsessive-compulsive and related disorders, tic disorders and Tourette syndrome, and personality disorders [12 13 14]. Nearly 70% of people with ASD, experience, during the course of their life, one comorbid psychiatric disorder, and almost 40% two or more [15]. Moreover, symptoms related to psychiatric comorbidities might worsen the clinical presentation, thus contributing to reduced quality of life and increased mortality due to suicide [16 17 18]. Furthermore, distinguishing psychopathological symptoms from core or atypical features of ASDs may be challenging for clinicians [19]. Furthermore, the psychopathological dimension of comorbid conditions can hide the dimension of ASD, blurring the line between ASD and the psychiatric disorder. Another critical issue regards the diagnostic tools available, as they are essential to integrate the clinician's judgment with a standardized method for diagnosing comorbidities [20]. Finally, treatment, whether pharmacological or non-pharmacological, must also consider the peculiarities of the ASD dimension and the individual psychiatric comorbidities [21]. In light of these evidence, symptom recognition, appropriate diagnosis, and treatment of ASD comorbidities are a priority. Therefore, in this narrative review we aim to present an overview of psychiatric comorbidities of the autism spectrum disorder, focusing on prevalence, symptoms, diagnostic tools available, and possible treatment strategies.

Methods

This narrative review was conducted first defining a goal, then searching literature and evaluating data evaluation, and finally with the presentation of the results. The search terms "autism", "autism spectrum disorder", "ASD", "autistic", "autistic disorder", "asperger", "pervasive developmental", "mental disorders", "mental illness", "common mental disorders", "psychiatric", "psychiatric disorders", "psychiatric illness", "severe mental disorder", "comorbidity", "depression", "depressive disorders", "bipolar disorder", "mood disorder", "affective disorders", "attention deficit hyperactivity disorder", "catatonia", "ADHD", "disruptive behavior", "obsessive compulsive behavior", "obsessive compulsive disorder", "OCD", "repetitive behavior", "tic disorder", "tourette syndrome", "feeding disorders", "eating disorders", "panic", "anxiety disorder", "social phobia", "sleep disorder", "sleep-wake disorders", "parasomnia", "insomnia", "schizoid personality disorders", "paranoid personality disorder", "schizotypal personality disorder", "borderline personality disorder", "narcissistic personality disorder", "histrionic personality disorder", "antisocial personality disorder", "obsessive compulsive personality disorder", "dependent personality disorder", "avoidant personality disorder", were entered in ERIC, MEDLINE, PsycARTICLES, PsycINFO, Scopus and PubMed. Terms and databases were combined using the Boolean search technique, to make search more restrictive and detailed. Only studies published in English have been included. Only studies that analyzed autistic traits in severe mental disorders and studies of patients with ASD and severe mental disorders in comorbidity were included. Studies on children, adolescents, and adults were included. Given the breadth and specificity of the topic, studies on psychosis, schizophrenia, gender dysphoria, trauma and post-traumatic

stress disorder, substance use disorders and suicide behavior were not included in the search terms and were not discussed in this review. Tables were then constructed, and the main findings were sorted by prevalence, symptoms, diagnostic tools and treatment. Main results were then discussed in a narrative way.

Results

Included studies have been divided in eight categories according to psychiatric comorbidity:
studies on mood disorders (e.g. major depressive disorder, bipolar disorder) in people with ASD; studies on ADHD in people with ASD; studies on OCD and repetitive behavior in people with ASD; studies on Tourette syndrome and tic disorder in people with ASD; studies on anxiety disorders in people with ASD; studies on sleep disorders in people with ASD; studies on eating disorders in people with ASD; studies on personality disorders (e.g. schizoid personality disorders, paranoid personality disorder, schizotypal personality disorder, borderline personality disorder, narcissistic personality disorder, histrionic personality disorder, antisocial personality disorder, obsessive compulsive personality disorder, dependent personality disorder, avoidant personality disorder) in people with ASD. Main findings of the included studies have been summarized in Table I.

Narrative overview

Autism Spectrum Disorders and Attention Deficit and Hyperactivity Disorders

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [8], Attention-Deficit/Hyperactivity Disorder is characterized by a persistent and impairing pattern of inattention and/or hyperactivity/impulsivity. It is the most common neurodevelopmental disorder [22]. ADHD is often comorbid with other psychiatric conditions (e.g., sleep disturbances, specific learning disorders, oppositional defiant disorder/conduct disorder, mood, and anxiety disorders) [23 24]. In recent years, the association between ADHD symptoms and ASD has been widely investigated [25], and it was an important novelty if thought that in DSM-IV-TR the presence of a pervasive developmental disorder is considered an exclusion criterion for ADHD diagnosis (criterion E) [26]. Nevertheless, individuals with a diagnosis of ASD frequently meet the criteria for a diagnosis of ADHD, and co-occurrence of ASD and ADHD is associated with more severe impairments in adaptive and executive functioning and health-related quality of life [27-29]. As reported by Shoaib et al. ADHD is the most common comorbidity in ASD [30].
A systematic review led by Catalá-López et al. analyzed the risk of mortality among children, adolescents, and adults with ASD or ADHD and their first-degree relatives. The study showed that ASD and ADHD tend to run in families and may have a significant negative impact on health and longevity of both those with the disorder and their first-degree relatives [31].
In a meta-analysis by Hossain et al. the prevalence of co-occurring ADHD in individuals with ASD ranged from 25.7% to 65% [12]. Moreover, meta-analyses conducted by Lai et al., found overall pooled prevalence estimates of 28% for attention-deficit hyperactivity disorder [14].
Referring to symptoms in common between these two disorders, according to a review from Antshel et al., social communication skills/deficits appear to impact social perception similarly, although social impairment is clearly implicated in both diagnoses [25]. Executive functions (EF) are more impaired in ADHD than in ASD. Studies examining the shared EF profiles of co-occurring ADHD and ASD have found that those with an ASD and ASD and comorbid ADHD both have cognitive flexibility and planning impairments, while those with ADHD and ASD with comorbid ADHD have response inhibition difficulties [32].
Neuroimaging and genetic studies showed an interesting overlap in the two conditions. A study by Dougherty et al. reported an overlap in neuroimaging at the level of the corpus callosum and cerebellum (lower volume in aMRI and decreased FA in DTI) and superior longitudinal fasciculus (reduced FA) [33]. A twin study suggested a phenotypic correlation between ASD and ADHD symptoms [32], and concluded that in young adults, a substantial proportion of the genetic influences on self-reported ASD and ADHD symptoms may be shared between the two disorders. A study by Nijmeijer and colleagues suggested that 15q quantitative trait locus (QTL) has possible pleiotropic effects for ADHD and ASD [34]. Gold standard diagnostic measures include the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule - 2nd edition for ASD and the use of standardized ADHD rating scales, structured interviews such as the KSADS-PL, global impairment measures, and behavioral observations for ADHD [35]. Psychotropic drugs are widely used [36] to treat ASD associated conditions such as ADHD, behavioral problems, anxiety, depression, and seizures. Psychostimulants are the most prescribed (32.6%), followed by anxiolytics and mood stabilizers (22.8%) and, finally, antidepressants (17.9%). Furthermore, combination therapy is frequently used (30.3%) [31]. A study by Reichow and colleagues highlighted the reduction in tolerability and efficacy of psychostimulants when used in patients with ADHD with comorbid ASD [37]. The British Association for Psychopharmacology recommended the use of methylphenidate, atomoxetine, and guanfacine (in that order)

for ADHD management in individuals with ASD [38]. Non-pharmacological interventions are based on behavioral techniques (e.g., stimulus-based procedures, instruction-based procedures, extinction-based procedures, reinforcement-based procedures, punishment-based procedures, and systems change procedures). Moreover, early use of behavioral intervention leads to reduction of problematic behavior by 80-90% [39].

Autism Spectrum Disorders and Anxiety Disorders

Research suggests that maladaptive and interfering anxiety is a common symptom in the population affected by ASD [40]. Reported prevalence of anxiety in ASD has varied widely [41]. The most common DSM-5 anxiety disorders are social anxiety disorder (SAD), generalized anxiety disorder (GAD), and specific phobia (SP) [42]. Meta-analytic pooling of the estimates yielded the prevalence of any current anxiety disorder as 20%, and the most frequent anxiety disorders in ASD appear to be specific phobias, with a lifetime prevalence of 31% and generalized anxiety disorder (prevalence of 18% and life-time prevalence of 26%) [43,14]. GAD shows a prevalence of 18% and lifetime prevalence of 26% and Panic/agoraphobia an estimated current and lifetime prevalence of 15% and 18%, respectively [43]. Separation anxiety was only reported by few studies, with an estimated prevalence of 3% of the sample [44].

Several research studies, including structural [45] and functional neuroimaging [14], underlined the presence, in both anxiety disorders and ASDs, of alterations regarding different brain areas, such as the amygdala, ventromedial prefrontal cortex, hippocampus, and insula. Inconsistencies exist with respect to the nature of such amygdala abnormalities [46]. A 2019 systematic review demonstrated that preliminary evidence on the neurobiology of anxiety in autism is inconclusive [47].

From a strictly clinical point of view, ASD and anxiety symptoms frequently overlap, although individuals with ASD might present with peculiar anxiety symptoms, like unusual specific phobias (e.g., vacuum cleaners, toilets) and fears of change/novelty [48 49]. However, it is unclear whether such symptoms are manifestations of anxiety or reflect aspects of the core symptoms of ASD. Moreover, since ASD presents a wide range of intellectual, verbal and adaptive functioning, it is challenging to determine the presence and the rate of anxiety in adults with ASD [43]. Moreover, impairments in the communication skills, difficulties in interoception (the sense of one's own physiological state) as well as in verbal expression of emotional states, one aspect of alexithymia (present in 40-65 % of individuals with ASD) may be also accountable for a struggle in expressing distress or discomfort verbally [50].

The aforementioned factors are also implicated in the complexity of the diagnosis of anxiety disorders in people with ASD, therefore it is vital a multi-method analysis of anxiety in ASD, including parental, caregiver, and/or teacher report and direct observation. Only a handful of measures of anxiety have received comprehensive psychometric evaluation using autism samples [51], so clinical interviews are nowadays regarded as more robust than questionnaires [52]. Therefore, self-reports from the individual affected, behavioral monitoring and, where possible, direct observation is hardly recommended [53]. Recently a research team developed a preliminary self-report anxiety measure (ASA-A) as the first self-report anxiety questionnaire specifically developed and validated for autistic adults. Preliminary evaluation of the measurement properties indicates that the scale will be a useful tool in research and clinical contexts [54].

Non-Medical treatments for anxiety disorders in ASD are mostly rooted in cognitive behavioral therapy (CBT). The Coping Cat series of interventions for children, adolescents, and adults is recommended for social anxiety disorder (SAD), generalized anxiety disorder, separation anxiety (SA), and specific phobias (SP), with disorder-specific approaches generally favored in treatment of anxiety disorders in adults [55]. CBT studies have been conducted in group, individual [56], and mixed group/individual modalities [57]. CBT adapted for ASD (the Behavioral Interventions for Anxiety in Children with Autism [BIACA] program) to address social-communication symptoms is important, given the synergy between social-communication challenges and anxiety in children with and without ASD [58]. ASD can benefit also from Mindfulness-based therapy (MBT-AS) training [59].

Pharmacological intervention includes the use of selective serotonin reuptake inhibitors (SSRIs) and the serotonin and noradrenaline reuptake inhibitors (SNRIs) for individuals with ASD and anxiety disorders, due to relatively good efficacy and relatively low incidence of adverse effects [60], although limited evidence of the effectiveness of SSRIs in adults is yet available [61].

One novel approach to the treatment is internet-based CBT program for children with comorbid High Functioning Autism Spectrum Disorder and anxiety, for instance online CBT program for anxiety disorders (BRAVE-ONLINE) [62]. The use of biofeedback devices to increase emotional awareness and support development in interoception in this population, have shown some positive effects, particularly when multiple channels of biofeedback are used [63 64].

Research on the effectiveness of and comprehensive intervention and specific strategies to improve anxiety symptoms in individuals with ASD, especially those with associated learning impairments, is still at its infancy.

Autism Spectrum Disorders and Personality Disorders

A personality disorder (PD) is an enduring pattern of inner experience and behavior that deviates markedly

from the norms and expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment [65]. PD patients often display impairment of social and emotion regulation, which are also a core characteristic of ASD [66].

A review from Gillet et al. identifies preliminary evidence of an increased prevalence of ASD diagnosis and traits among individuals diagnosed with borderline personality disorder (BPD), schizotypal personality disorder (STPD), Obsessive-Compulsive Personality Disorder (OCPD) and unspecified PD diagnoses [67]. PDs show a pooled prevalence of 12.6% in ASD [12], where Cluster A and Cluster C personality disorders (PD) are the most frequent co-occurring PD in ASD patients [68]. This could be related to early difficulties and less interest in social interaction in ASD, limiting the effects of poor parenting and inconsistent parent-child interaction on the developing personality [66].

The essential feature of obsessive-compulsive personality disorder is a preoccupation with orderliness, perfectionism, and mental and interpersonal control, at the expense of flexibility, openness, and efficiency [65]. The results of Gadelkarim et al. suggest that the presence of OCPD, and, in particular, those OCPD traits that were most significantly over-represented in individuals with an estimate diagnosis of ASD (need for control, overconscientiousness, workaholism, preoccupation with detail, perfectionism and rigidity) should alert the clinician to the possible co-occurrence of ASD [69]. The study identified particularly strong correlations between specific ASD domains and OCPD scores, including problems in attention-switching, representing a measure of cognitive rigidity [70], which may reflect similar attentional set-shift changes as previously reported in OCPD using the intra-extradimensional set-shift task [71].

Schizoid personality disorder is defined by DSM-V as a pervasive pattern of detachment from social relationships and a restricted range of expression of emotions in interpersonal settings [65]. The study of Cook et al. [72] identified a close correlation between schizoid personality disorder and ASD. In this sample of participants with ASD, the entire distribution of schizoid PD diagnostic symptoms was pathologically shifted, strongly indicating that the condition of ASD is associated with a distinct increase in schizoid PD symptom burden in adolescence. The stability of traits in this sample fully reflected the marked stability of traits that has been observed over time in prior research [73].

Borderline Personality Disorder is a pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity that begins by early adulthood and is present in a variety of contexts [65]. Two studies reported the prevalence of ASD diagnosis in borderline personality disorder [74,75]. Rydén et al. al found a prevalence of ASD around 14.6% of the total sample [74], while a retrospective case-control study from Shen et al. assessed the prevalence of psychiatric comorbidity across a 3-year period prior to BPD diagnosis. Self-harm and non-suicidal self-injury (NSSI) are commonly observed in both ASD and BPD, and in both cases are aimed to reduce tension and anxiety states [76].

Antisocial Personality Disorder (ASPD) is a pervasive pattern of disregard for, and violation of, the rights of others that begins in childhood or early adolescence and continues into adulthood. This pattern has also been referred to as psychopathy, sociopathy, or dyssocial personality disorder. Narcissistic Personality Disorder (NPD) on the other hand is defined as a pattern of grandiosity, need for admiration, and lack of empathy [65]. Deficits in affective resonance, are commonly associated with antisocial personality disorder and narcissistic personality disorder [77]. On the other hand, in ASD, lack of empathy is considered to be related to reduced levels of cognitive empathy (Theory Of Mind), rather than affective empathy [78]. It was once hypothesized that there may be a common neurodevelopmental basis for ASDs and childhood antisocial behavior, with shared genetic and environmental factors linking ASDs with conduct disorder and oppositional defiant disorder [77].

Finally, it has been observed how other personality disorders that may be found in comorbidity with ASD are Paranoid, Schizotypal and Avoidant Personality Disorders. Some studies [79] [80] revealed a superimposition of symptoms between Schizotypal PD and ASD, especially in communication, social skills, and attention domains. Personality assessment could help in confirming the diagnosis but has to be used carefully by an expert clinician who knows the ASD cognitive style in order to avoid misunderstandings [81].

Personality assessment with dedicated diagnostic tools as the Structured Clinical Interview for DSM IV Axis II (SCID-II) could help in confirming the diagnosis but has to be used carefully by an expert clinician who knows the ASD cognitive style in order to avoid misunderstandings [81]. The Personality Assessment Inventory (PAI) was administered to assess overall personality and emotional functioning in ASD sample [82]. Although there is only a paucity of randomized controlled studies on the effect of psychotherapy in PD, the few studies published suggest that it should be the core treatment, leading to individual benefit and a reduction in care costs [83].

Several effective psychotherapeutic programs and manuals for treating PDs are available for adults. For adolescents, these therapies (with the exception of DBT-A) have not yet been fully evaluated [66].

Pharmacological interventions for ASD and PDs are only symptomatic and supportive. The main target symp-

toms are aggressive behavior/temper tantrums, depression, sleep problems, and ADHD [84]. Neuroleptics are widely used to decrease intrapersonal stress levels, enabling a distancing from environmental stressors and a reduction of impulsivity and reactive aggressive behavior [84]. Although widely used, neuroleptic treatment shows poor evidence of efficacy on Personality Disorders and Autism Spectrum Disorder as large RCTs are lacking, especially for second-generation antipsychotics. Anticonvulsants – aside from their use in epilepsy and bipolar disorder – are commonly used to reduce impulsivity and aggressive behavior. The evidence of such treatment is, however, poor [84]. Antidepressants are generally less effective in ASD and PD [61].

Autism Spectrum Disorders Repetitive Behaviors and Obsessive-Compulsive Disorders

Obsessive-Compulsive Disorder is defined by the DSM V by the presence of "obsessions and/or compulsions. Obsessions are recurrent and persistent thoughts, urges, or images that are experienced as intrusive and unwanted, whereas compulsions are repetitive behaviors or mental acts that an individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly". The presence of restricted, repetitive patterns of behavior, interests or activities are also central characteristics of ASD [65]. Repetitive behaviors are defined as a set of behaviors that are performed repetitively and are considered to be inappropriate or odd. In OCD, obsessions are intrusive, recurrent thoughts that cause marked anxiety. Compulsions are typically performed in response to these intrusive thoughts and used to relieve anxiety. For individuals with OCD, these repetitive behaviors are unwanted and bothersome. In ASD, repetitive behaviors vary in type and severity and include stereotyped motor behaviors (flapping, rocking, shaking fingers in front of the eyes and more complex behaviors, such as insistence on following the same routine in everyday life, lining up objects). Notably, some repetitive behaviors in ASD may not cause distress, as in the case of OCD, but can be time-consuming and may cause burst of anger when the individual is interrupted or asked to stop the behavior [85]. Therefore, establishing whether individuals with ASD present features suggestive of a separate diagnosis of OCD is challenging for clinicians. Measurement and assessment of OCD in autism can be complicated by the social impairing characteristics of ASD [65].

Studies investigating types of repetitive behaviors in individuals with ASD and OCD found that individuals with OCD show higher levels of obsession and compulsions and greater symptom severity, when compared to individuals with ASD [86 87]. These two clinical populations can be distinguished based on the content of their repetitive thoughts and behaviors. For instance, people with ASD seem to be less likely to experience thoughts with aggressive, contaminations, sexual, religious content than people with OCD [86]. Similarly [88], found that OCD individuals reported higher frequencies of contamination and aggressive obsessions, and checking compulsions compared to ASD individuals who, on the other hand, displayed slightly higher frequencies of hoarding obsessions.

Measurement and assessment of OCD in autism can be complicated by the social impairment characteristic of ASD, such as deficits in communication, insight, ability to recognize emotions, or a co-occurring intellectual disability. Many of the currently available measures to evaluate OCD were initially developed and standardized for typically developing children. The Children's Yale-Brown Obsessive-Compulsive Scales for ASD (CY-BOCS-ASD) has been shown to be a reliable measure to evaluate repetitive behaviors [89]. Other tools to evaluate repetitive behaviors in ASD include the Autism Diagnostic Interview-Revised (ADI-R), the Repetitive Behaviour Questionnaire (RBQ), the Repetitive Behaviour Interview (RBI), and the Repetitive Behaviour Scale-Revised (RRB-R) [90 91].

Co-occurring OCD has been found in 9 to 22% of individuals with ASD. This wide range of estimates is attributable to differences in the source and size of the sample as well as the assessment method used[92,43,14 93,12]. Moreover, Lai and colleagues reported that OCD show a pooled prevalence of 9% in ASD [14].

Studies using genetically engineered nonhuman primates shed light on how alterations in the MECP2 gene may relate to functional brain changes associated with ASD and OCD [94]. Carlisi and colleagues found similar deficits at the level of the dorsomedial prefrontal cortex in both ASD and OCD individuals. Furthermore, differences in a network of neurons regulating the basal ganglia were identified among ASD and OCD [95].

While the appearance of ASD and OCD may be similar on the surface, the processes that drive these behaviors are quite different, and each requires a different kind of treatment. Using typical OCD treatment interventions with individuals with OCD comorbid with ASD will not be effective and vice versa [96]. Basic social skills training is essential for successful cognitive therapy and should be used to treat both OCD and ASD. Anger management, social skills, and mindfulness training followed by gradual introduction of Exposure Response Prevention (ERP) and Cognitive-Behavioral Therapy (CBT) may be considered in dealing with intense and sudden bursts of anger and frustration presented by both the conditions [96].

As for pharmacological treatment, no definitive research exists to detail an effective pharmacologic strategy for the occurrence of both mental disorders in a patient.

Nonetheless, the use of antidepressants, especially SSRI, to treat the comorbid ASD and OCD has become prevalent. Fluvoxamine and fluoxetine showed superiority to placebo in reducing repetitive behavior [86 97]. Studies investigated the use of N-acetylcysteine (NAC) as a potential drug for both these conditions, particularly, a study by Lee and colleagues reported that NAC is safe and tolerable, reduces hyperactivity and irritability and enhances social awareness in people with autism spectrum disorder. However, NAC did not show a role in reducing repetitive behavior [98]. Furthermore, the usage of Deep Brain Stimulations (DBS) in patients with treatment-refractory OCD and comorbid ASD was analyzed. Graat et al reported DBS as a viable treatment option for OCD in patients with comorbid ASD [99].

Autism Spectrum Disorders and Sleep Disorders

Sleep disorder (SDs) include problems regarding quality, timing and total amount of sleep that could result in impaired level of function and daytime distress [65]. Studies indicate that most children with ASD (with a range of percentage between 50 and 80%) have experienced SDs [100]. SDs in ASD show a pooled prevalence of 13% versus 3.7% in Typically Developed (TD) and tend to be more persistent in ASD [14 101]. ASDs are associated with different sleep alterations, in particular, sleep discontinuity and shorter duration of REM sleep [102]. Differently from TD children, in which the SD usually regresses overtime, SDs in children with ASD are more likely to worsen or change as the child ages, it has been observed that bedtime resistance improves, while sleep anxiety worsens.

The etiology is supposedly multifactorial, including potential disruption in circadian rhythms of cortisol [103] and melatonin, together with poor sleep hygiene practices [104 105]. These abnormalities in sleep patterns observed in ASD are considered to be related to mutations in melatonin production pathways and CLOCK genes polymorphisms. Animal studies have shown that REM sleep has multifaceted functions in brain development, including learning and memory consolidation, thus suggesting that SDs play an important role in the pathophysiology of ASDs, increasing the individual's vulnerability to develop symptoms of ASD by altering the sleep regulation [106-113]. Furthermore, children with ASD showed strong night-to-night variability and stronger response to sleep environments [114]. 25% of ASD's SD start from birth and are early indicators of neurological impairment in ASD [115]. It has been demonstrated that bedtime access to bright screens is associated with reduced sleep in ASD children, when compared to TD, as bright screens hamper melatonin release and dysregulates circadian rhythms [116].

Psychiatric and neurologic comorbidities, mainly epilepsy, worsen SDs in ASD. Depression and anxiety disorders are major co-occurring problems in ASD**.** Anxiety disorders in particular disorganized sleep, causing sleep initial and central insomnia [117]. The most common SD in children is chronic insomnia (defined as sleep onset problems associated to multiple night awakenings, symptoms should last for at least three months), followed by secondary insomnia [118]. SDs are also associated with worsening of internalizing (social withdrawal, anxiety, and depression) and externalizing symptoms (hyperactivity, aggression, and irritability), core symptoms of ASD, executive and adapting functioning [119,120 121]**,** mainly the worsening of daytime functioning, which may impair the quality of life of both patients and caregivers. Children with concurrent ASD and SD may experience an exacerbation of the symptomatology [122]**,** especially poorer growth, increased behavioral and learning problems, marked social impairment, as well as more frequent occurrence of repetitive behaviors, affective problems, and inattention-hyperactivity [123]. A diagnostic algorithm to assess sleep problems exists in children with ASD [115]: sleep diaries, together with actigraphic recording (at least 1 week) could confirm the diagnosis and assess the sleep-wake behavior. Actigraphy provides useful information about sleep in the natural sleep environment, collecting data representing body movement over time, painting a picture of daily sleep-wake cycles [124 125]. When major SD are suspected and actigraphy is not diagnostic, a video polysomnographic recording with EEG is warranted, being the gold standard for the pediatric diagnosis of nocturnal epilepsy, SD breathing and sleep movement disorders [126,127]. In ASD, prolonged EEG recording showed increased prevalence of interictal epileptiform discharges (IEDs) in up to 60% of cases [128]. Treatment of underlying neurological or psychiatric conditions should be part of the multidisciplinary approach to the therapy, in particular treatments of SDs in ASD are represented by both pharmacological and non-pharmacological interventions [129]. Sleep hygiene and behavioral treatment are effective [129]. Basic sleep hygiene includes an appropriate bedtime, a positive bedtime routine, and reduction of media exposure [116]. ASD children show more sensitivity to tactile stimuli: wrapping a child in weighted blankets might help [130]. Those procedures need to be performed with a more gradual pattern in ASD [131]. It is important to note that most of the studies on the effectiveness of behavioral therapy in insomnia were conducted in children with special neurological needs, not just in ASD [132,133]. The effectiveness of behavioral therapy has been established, however, samples considered were not ASD-group specific. A growing body of evidence suggests a link between sleep-wake cycles and melatonin secretion [134]. Melatonin treatment in ASD improves sleep duration, sleep onset latency, but not nighttime awakenings

[135,136]. An international consensus established a series of recommendations on the use of melatonin in children/adolescents [137]: 1-3 mg should be administered 30 min before bedtime. Not all sleep problems improve with behavior and melatonin. In those cases, sleep history should be obtained to ensure that other SDs, such as breathing ones are not present [138]**.** Clonidine has been shown to slightly improve sleep in children with ASD, as well as ASD behaviors [138], but mild-moderate collateral effects are associated with such drug, therefore it should only be considered in extreme cases, in which other protocols failed.

Compared to TD, ASD are particularly vulnerable to the repercussions of lockdown on sleep, given their difficulty to tolerate extreme changes in routine [139 140 141]: COVID-related lockdown increased SDs of ASD children [142]**.** More accurate protocols are needed for SDs treatment in subjects with ASD, achieving a better comprehension on the pathophysiology of both phenomena and intensifying melatonin-based studies: Melatonin treatment still remains the most adequate treatment, if combined with behavioral therapy, nowadays [143 144]. It is also important, since most studies comprehend ASD, but are not exclusively ASD-oriented, to promote analysis that are purely ASD-group specific.

Autism Spectrum Disorders and Mood Disorders

Most people with ASD, experience one comorbid mood disorder, mostly major depressive disorder (MDD), defined by the DSM V as "the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function"[65], and bipolar disorder (BD), which on the other hand is defined by the presence of hypomanic or manic episodes[65,15]. Different studies on ASD co-occurrence and mood disorders reported varying levels of prevalence, 11% for MDD and 5% for BD [14], much higher than general population (7% and < 1%) [145]. Such variations may depend on several factors: it has been observed that 5-10% of ASD people with a concomitant intellectual disability (ID) have a mood disorder, while, higher percentages (up to 53%) have been observed in individuals with an ASD but without an ID [146]. Age and sex should also be taken into consideration, as males reported higher depression rates than females during early adolescence, although no differences are reported in early adulthood [147]. Regarding BD, manic episodes in the context of ASD become apparent only in adulthood [148]. A genetic association between ASD and mood disorders has been proposed. By means of ConsensusPathDB and GeneGO pathway maps, a study carried out by Ragunath et al. has showed common pathways involved in ASD and BD: the synaptic transmission pathway, the neuroactive ligand receptor pathway, the circadian rhythm pathway, and the catecholamine biosynthesis one [149]. In addition, genomic analysis of psychiatric disorders revealed an overlap between genetic risk for ASD with schizophrenia and BD, but no significant overlap between ASD and MDD [150]. Another important element is 5-HT, whose role in the development of depression in ASD has been hypothesizes by analyzing the effectiveness of antidepressants [151]. In ASD, the most evident alteration observed is hyperserotonemia [152]. Moreover, it seems that pregnant women suffering from depression, treated with SSRIs, and with high levels of cortisol, would have a higher percentage of giving birth to a child affected by ASD [153]. Indeed, high levels of cortisol increase the expression of the serotonin trasporter (SERT), thus modifying prenatal neural development in children [154].Common ASD symptoms can hide symptoms of psychiatric comorbidities [43].Depression may manifest with symptoms such as crying, self-injury, apathy, anhedonia, feelings of guilt, low self-esteem, thought of death [148].neurovegetative symptoms (changes in appetite, weight or sleep disturbance), but also with more ASD-specific symptoms, like irritability, a change in stereotyped behavior, or an increase in compulsive behaviors [147]. In individuals with low-functioning autism (LFA) depression might even manifest with loss of language, social withdrawal, loss of eye contact, moodiness, fearfulness, obsessiveness, hyperactivity, and occasionally self-injurious behaviors [155]. High-functioning autism (HFA) subjects seems to be more prone to the development of feelings of low self-esteem may derive from the awareness of difficulties in social functioning [13].

On the other hand, BD may manifest with manic and hypomanic symptom, such as irritable or dysphoric mood, excessive reactivity, hyperarousal, agitation, flight of ideas, pressured speech, increase distractibility, poor judgment, intrusiveness, laughing, aggressivity, and noncompliance [148]. However, manic symptoms can be expressions of deficits in social understanding, rather than clinical signs of concurrent mood disorder [19]. Cognitive capacity is an important expression factor of depression in ASD [156]. Mood disorders might present also with catatonia, with a prevalence of 10,4% [157]. Several studies explored this comorbidity leading to different hypotheses: it might be related to abnormalities in GABAergic functioning in neural circuitry, in the cerebellum, or to mutations present at the level of chromosome 15 [158-160]. Catatonia may also be an exacerbation of pre-existing mood symptoms [161]. However, since mood symptoms may be difficult to recognize in patients with ASD, the presence of catatonic symptoms, such as mutism, repetitive behaviors, echolalia, posturing, mannerisms, purposeless agitation, and rigidity, may be an easier tool of identification. In addition, catatonia, in the context of ASD, usually onsets in early preschool years, earlier than in other psychiatric condition, where it is usually observable from late ado-

lescence [157], There are different tools for assessing the presence of concomitant ASD and a mood disorder. For instance, the Psychopathology in Autism Checklist (PAC), which discriminates between autism and psychosis, depression, anxiety, and obsessive-compulsive disorder (OCD) [162], can be a useful tool. The treatment of mood disorders in ASD individuals, includes different approaches, behavioral and pharmacological. Among the behavioral treatment option, two have been specifically highlighted: cognitive behavioral therapy (CBT) and metacognitive behavioral therapy (MBT) [163]. CBT is useful to treat ASD-specific symptoms (aggression, altered social skills, theory of mind, or improvement of emotion recognition and regulation) without a specific focus on mood symptoms [164,165]. On the other hand, MBT can be used to relieve depression in ASD populations, since in individuals with mental and communication deficit, an accepting, present-focused approach, is encouraged [166]. Pharmacological treatments, normally employed in cases that did not respond to non-medical interventions, include primarily the use of risperidone and aripiprazole, as those are the only two medications approved for irritability in ASD associated to a mood disorder [167 168]. Literature shows inconsistent results on the effectiveness of quetiapine, olanzapine and ziprasidone [169], as well as of tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitor (SSRIs) [14]. Lithium can be used to treat manic symptoms [170] while sodium divalproex is effective in the treatment of aggression in ASD patients [168]. Considering that mood disorders in co-morbidity with ASD is a negative prognostic factor for a good outcome [171], the need for appropriate screening tools, as well as the study of the mechanisms underlying, are a priority for the future.

Autism Spectrum Disorders Tic Disorders and Tourette Syndrome

Tourette Syndrome (TS) is characterized by the presence of motor and vocal tics, with a waxing and waning course, often accompanied by compulsive behaviour [172]. Tics are defined as sudden, rapid, recurrent, nonrhythmic movements, and vocalizations, can be simple or complex [173]. Although "movement disorders" can be common in ASD, and may resemble tics, they are phenomenologically different entities, called stereotypies. Stereotypies are repetitive, seemingly driven, and apparently purposeless motor behaviours, postures, or utterances. Motor stereotypies are categorized as simple or complex [174]. On the other hand, even if ASD and TS are apparently different disorders, these two conditions share some epidemiological, phenomenological, and neurobiological features [175].

Recent studies highlighted how ASD is overrepresented in TS population, co-occurring in about 4-5 % of cases [176 177]. Burd et al. show that a diagnosis of TS seems to increase the risk of ASD of about 13-fold. Another review by Hossain and colleagues reported the prevalence of Tourette syndrome or tic disorders between 2.6% and 36%, among study participants with ASD [12]. Moreover, a study by Kadesio et al. found that about 17 % of patients with TS presented concomitantly three or more ASD-specific symptoms, and 65 % had deficits related to the autism spectrum [178]. In 2010, the Center for Disease Control and Prevention (CDC) Developmental Disabilities Monitoring Network Surveillance found that male gender is more prone to present a comorbidity of ASD and TS, with an age of onset ranging between 4.7 to 6.0 years. Capuano et al. in "Psychiatric Symptoms and Comorbidities in Autism Spectrum Disorder" [179] highlighted that several studies have identified a positive family history of TS and/or ASD in individuals presenting with both disorders. A positive family history for tic disorders was reported in 59.5 % of patients presenting with ASD and comorbid TS. Burd et al investigated in a family study the association between neuropsychiatric symptoms (including TS and ASD) and a deletion involving exons 4, 5, and 6 of the gene neuroligin 4 (NLGN4) [176]. Gene mapping within rare gene copy number variants (CNVs) in TS subjects showed significant overlap with CNVs previously identified in individuals with ASD [180].

Furthermore, in a study of Kern et al. [181] a wide range of neuropsychological similarities have been observed between TS, ASD, and ADHD, thus suggesting that these disorders may be part of a broader neurodevelopmental illness spectrum (defined as abnormal connectivity spectrum disorder [ACSD]). ACSD may be the results of neural processes that cause long-range underconnectivity and short-range overconnectivity. These connectivity abnormalities may be related to neurotoxicity, neuroinflammation, excitotoxicity, sustained microglial activation, proinflammatory cytokines, toxic exposure, and oxidative stress. Evidences also suggest that the severity of connectivity deficits is associated with symptom severity in TS, ASD, and ADHD. Collectively, these data support the hypothesis that these disorders, though separate, may share common risk factors or possibly etiology [179].

Currently, it is recognized that dysfunctions of basal ganglia (BG) and their circuits lead to cognitive and behavioral disorders, other than purely motor symptoms. he work of Barnhill et al. [182] highlighted how repetitive movements, stereotypies, echophenomena, self-injurious behaviours and compulsive behaviours, present in both ASD and in a subset of severe TS without autism, thus leading to the hypothesis of an overlapping frontostriatal substrate. Based on the knowledge of BG organization, it has been postulated that, in TS patients, a primary dysfunction of striatum leads to an impairment

of inhibitory control in BG [183,184]. Moreover, recent experimental and functional studies confirm the presence BG dysfunction in ASD [185], making the BG a probable anatomical and functional link between TS and ASD.
Recent studies identified five mutated genes in TS patients: IMMPL2, NRNX1, CTNNA3, NLGN4X, and CNTNAP2. The disruption of these genes seemed to be associated with comorbid conditions described in TS. In particular, NLGN4X gene mutations were also associated with ASD [186].
The diagnosis of tics and TS is based on clinical characteristics of symptoms and thought scales assessing the severity and impairment of functioning (YGTSS -Yale Global Tics Severity Scale and STSSS- Shapiro Tourette Syndrome Severity Scale). Moreover, the SCQ scale (Social Communication Questionnaire) was used to assess ASD traits and comorbidity in TS patients [187]. Regarding the treatment of TS and tics, the watch-and-wait strategy is the most indicated in many patients with tics. This strategy coupled with psychoeducation improves symptoms tolerance and supports stress reduction [188]. Guidelines from the ESSTS Group details two behavioral treatment approaches of different methodology, with most evidence pointing to the effectiveness of habit reversal training (HRT) and exposure with response prevention (ERP). Both interventions are considered first-line behavioral treatments for tics for children and adults. The choice of one or the other therapy will depend on the accessibility of the treatment and the patient's preference. The rationale behind both therapies is the notion that external and internal physiological factors influence the expression of tics and that tics thus should be regarded as semi-voluntary movements. However, a minority of patients eventually require pharmacological intervention, especially those presenting comorbidities such as ASD [189]. Based on the overmentioned guidelines, in this cases, pharmacological options include antipsychotic agents, noradrenergic agents, and miscellaneous drugs as alternatives. Haloperidol, pimozide, and risperidone show the highest level of evidence, but, in particular, haloperidol is poorly tolerated. Among new (atypical) antipsychotic agents, Aripiprazole is effective in the treatment of stereotypies in children and shows a good profile of tolerability and efficacy [179].

Autism Spectrum Disorders and Feeding and Eating Disorders

Feeding and eating disorders (FED) are defined by the DSM-V as "persistent disturbances of eating and eating-related behavior that result in the altered consumption or absorption of food and that significantly impairs health or psychosocial functioning" [8]. Different hypotheses were formulated over the history to understand the etiology of FED, from hormonal theories to psychological and social hypotheses. Currently FED are considered to arise from a multifactorial etiology, including psychosocial, personality, neurobiological and genetic factors [190].
In 1983 Gillberg first observed an overlap in the clinical presentation of autism spectrum disorders and FED along with the co-existence of ASD and FED within families, thus suggesting the presence of a common genetic predisposition [191], and leading to the formulation of the hypothesis that specific subgroups of FED and ASD may share hereditary traits [192]. Literature studies have also shown that atypical eating behavior is more prevalent in children with ASD than in typically developing children [193]. This hypothesis was also supported by findings from recent studies which explored this correlation by means of functional magnetic resonance (fMRI), demonstrating the presence of similar functional responses to food, and revealing similarities in alterations of activation of brain networks underlying theory of mind, cognitive, behavioral and central coherence shared specifically by Anorexia Nervosa (AN) and ASD [194]. In the last decades there's been increasing attention to the association between feeding and eating disorders and autism spectrum disorders [195], as atypical eating and feeding behaviors, up to severe food selectivity, are often reported in children diagnosed with ASD with a prevalence ranging from 13 to 87% [196]. Nevertheless, whether this wide range of prevalence is due to shared comorbid conditions, or to resembling clinical traits, is yet to be determined [197]. A metanalysis from Hossain et. al reported a prevalence of co-occurrence of FED and ASD ranging between 1.4% and 7.9%; among different FED considered, anorexia nervosa (AN) was the most commonly found in comorbidity (6.7%), followed by bulimia nervosa (2.7%) and binge-eating disorder (1.4%) [12]. Another observation must be made when approaching differences in rates of comorbidity in adults and children's populations. A systematic review from Boltri et al. from 2021, reported a prevalence of autistic traits in adult patients with FED ranging between 8.8% and 24.5%, while lower rates were observed among younger patients (4%-22%) [198]. Moreover, it is quite challenging to make a comorbid diagnosis of FED in the context of ASD, since FED are conditions that tend to be highly variable both among individuals and during lifetime, while ASD are early-onset, lifelong conditions [99]. A direct consequence of this issue is that the majority of eating disorders have a later onset compared to autism, therefore, individuals may present to adult psychiatrist who may not be able to make the diagnosis, especially if the developmental history is not investigated. Distinguishing restricted and repetitive behaviors, that normally recognized as core features of autism, from a more structured eating disorder can be difficult

[200]. Therefore, in order to make a differential diagnosis, or to uncover a comorbidity, it is important to keep in mind differences and similarities between the two spectra. FED patients may present a premorbid personality characterized by repetitive and rigid behaviors, therefore, in order to be distinguished from those presented by ASD patients, the clinician's attention should focus on the aim of the repetitive behavior, that usually, in FED, is related to weight control [8]. Moreover, deficits in the theory of mind, in expressing and recognizing emotions, which are normally observed in ASD, are also present in patients with FED [201]. For these reasons, collecting medical history information, along with a complete diagnostic evaluation of FEDs, including psychological, physical, and medication management investigations, should be made in children diagnosed with ASD developing feeding or eating problems [202].

Most common feeding issues in children with ASD are atypical eating behaviors, like picky eating, food selectivity (that can be due to the avoidance of specific food textures or colors), limited food variety, and gastrointestinal (GI) abnormalities, such as abdominal pain, constipation, diarrhea and gastrointestinal reflux [203]. Children with concurrent ASD and GI symptoms are more likely to be irritable, agitated, socially withdrawn, lethargic and hyperactive [204]. In light of these evidence, control visits should also include a comprehensive evaluation of the child, including screening for BMI, abdominal pain, mealtime difficulties or GI alterations [203]. Essential assessment tools useful in the recognition of FED in the context of ASD are food diaries, self-reported questionnaires, such as the Food Frequency Questionnaire (FFQ) or the Eating Disorder Inventory-3 (EDI-3), and questionnaires based on parents' reports, such as the Brief Autism Mealtime Behavior Inventory (BAMBI) [205]. Different studies underline the importance of an early recognition of abnormal eating patterns in ASD children. This issue becomes especially relevant since it may affect treatment options, since, although limited research exists on the efficacy of treatment options for co-occurring autism and FEDs, the presence of the first has been suggested to contribute to the resistance to conventional therapies. For early intervention educators and school psychologists can play an important role in assisting youth with ASD diagnosis to manage the social context of eating/feeding at school by helping mitigate related stressors [202]. In a recent observational study, Folta et al. reported a range of coping strategies in the social context, leading authors to suggest that support should involve a responsive approach that should incorporate the skills developed by the individual to navigate eating in social situations [206]. Understanding the context in which feeding or eating problems occur can help identify appropriate treatment components (e.g. psychoeducation and improving parent-child feeding relationship) [202].

Although mild food selectivity might not require immediate treatment, moderate and severe may eventually meet criteria for an ED and expose the child to nutritional inadequacies and medical sequelae [207]. Behavioral interventions, such as Cognitive Remediation Therapy (CRT) and Parent Training (PT) have been proven to be particularly effective on treatment of FED in ASD [207]. Regarding a pharmacological approach specific for this comorbidity, studies on the effectiveness of psychotropic drugs (in particular antidepressants, antipsychotics and stimulants), normally employed in the treatment of behavioral abnormalities in ASD, are still scarce, especially when approaching adolescent and adult populations [208].

In conclusion, it is of outmost importance to explore etiology, treatment needs, and prognosis when approaching the co-occurrence of ASDs and FEDs. Further longitudinal studies might be essential to fill this gap.

Discussion

The present review aims to delineate the prevalence, clinical presentation, diagnosis, and treatment of different psychiatric disorders, when found in comorbidity with ASD. Given the breadth of the topic, for selectivity reasons, the considered disorders were: mood disorders, ADHD, OCD, Tourette syndrome and tic disorders, anxiety disorders, sleep disorders, FED, and PDs. According to Lai et al., ADHD and anxiety disorders present a higher prevalence when compared to other psychiatric comorbidities, with pool prevalence estimates of 28% for the former, and of 20% for the latter [14]. Regarding the prevalence of tics and Tourette Syndrome, on the other hand, Hossein et al. reported a range between 2.6 and 36%, although data were obtained from several studies with different sample sizes, which may explain this variability [12]. Similar prevalence rates were observed when focusing on sleep (13%) and personality disorders (12.6%), among which cluster A disorders were found to be most represented. Moreover, when addressing the occurrence of concomitant mood disorders, specifically major depression and bipolar disorder, the studies considered delineated a prevalence of MD of 11%, while bipolar disorder seems to be less common (5%). Obsessive-compulsive disorder was found in comorbidity with ASD with a pooled prevalence of 9% [14]. Finally, the metanalysis from Hossein et. al reported a prevalence of co-occurrence of FED and ASD ranging between 1.4% and 7.9%; among different FED considered, anorexia nervosa (AN) was the most common (6.7%), followed by bulimia nervosa (2.7%) and binge-eating disorder (1.4%) [12].

It seems of outmost importance to explore similarities and differences in the clinical presentation that may

help clinicians in the recognition of comorbidities, in order to reach an accurate and correct diagnosis.

Individuals with a diagnosis of ASD frequently meet the criteria for a diagnosis of ADHD too, and co-occurrence of ASD and ADHD is associated with more severe impairments in adaptive and executive functioning and health-related quality of life. A review from Antshel et al., highlighted how social impairment can be observed in both diagnoses [25]. Studies examining shared executive functions profiles of patients with co-occurring ADHD and ASD demonstrated cognitive flexibility and planning impairments, along with response inhibition difficulties [32].

Clinical presentation of anxiety disorders frequently overlaps with ASD, although individuals with ASD might present peculiar symptoms, such as unusual specific phobias [48,49]. Nevertheless, it is challenging to determine whether such symptoms are manifestations of anxiety or reflect aspects belonging to ASD core symptomatology. Moreover, the broad range of intellectual, verbal and adaptive functioning of ASD individuals, which may be associated to deficits in interoception and verbal expression, may hamper the individual's ability to communicate distress verbally [50].

In ASD, the most frequent personality disorders found in comorbidity belong to clusters A and C [68], as commonalities between the two sets of disorders mostly involve difficulties and reduced interest in social interactions [66]. Moreover, OCPD traits, such as need for control, overconsciousness, rigidity or perfectionism, are common and not easily distinguishable from ASD-specific traits [69]. Social withdrawal and restriction of expression range, core features of schizoid personality disorder, are also manifestations commonly observed in patients with ASD [65]. The co-occurrence of these disorders may lead to an increased in schizoid PD symptoms burden, especially during adolescence [73]. Individuals with ASD may also display behaviors commonly associated to BPD, such as self-harm and NSSI, in both cases aimed to reduce tension and anxiety states [76]. Finally, reduced levels of cognitive empathy (TOM), often observed in ASD, may resemble affective empathy deficits observed in both antisocial PD and narcissistic PD. Other personality disorders, whose comorbidity should be assessed in individuals with ASD, are paranoid, schizotypal and avoidant PD [14].

In ASD the co-occurrence of OCD may manifest through repetitive behaviors, such as rocking, flapping or more complex behaviors and fixed routines. Differently from individuals with OCD, these conducts do not always cause distress, but they can be time consuming and may cause behavioral alterations and burst of anger [85].

It has been observed that children with ASD often present concomitant sleep disturbances [118], usually associated with worsening of the overall symptomatology [119-121].

In the context of ASD, the clinical presentation of major depression may be characterized by "typical" symptoms, such as crying, apathy or the presence of neurovegetative symptoms [148]. Nevertheless, in some cases, emotional distress may be expressed through irritability, changes in a stereotyped behavior, or an increase in compulsive behaviors, decrease or loss of verbal expression or eye contact, or low self-esteem [155], the latter being especially prominent in high-functioning autism, and probably deriving from the awareness of difficulties in social functioning [13].

Symptoms of hypomanic or manic states, which may indicate the presence of a concomitant bipolar disorder, may also derive from deficits in social understanding [19]. Stereotypies, often displayed by individuals with ASD, may resemble a tic disorder or with Tourette syndrome, but are instead phenomenologically different entities [174].

Finally, although atypical eating behaviors (picky eating, food selectivity or limited food intake) [203], found commonly in ASD, may resemble core features of FED; a fundamental difference may rely in the aim of such behavior, in ASD they may be explained as a manifestation of restrictive or repetitive behaviors, while in FED, such conducts aim to weight control [8].

Results yielded from our review underline the burden of psychiatric disorders in the autism spectrum, revealing how clinical presentation rarely allows a clear distinction between core symptoms of ASD and manifestation of one or more concurrent psychiatric comorbidity. Such difficulties become especially evident as we observed a lack of specific diagnostic tools for the assessment of symptoms of a psychiatric disorder in the context of ASD. Few assessment scales are available, as well as tools and questionnaires that have been modified and adjusted for individuals on the autism spectrum, and even less modified for the specific disorders included in such spectrum. Nevertheless, some scales and assessment tools have been in fact calibrated for neurodivergent individuals, e.g. the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule - 2nd edition for ASD, the gold-standard for diagnosing ADHD in ASD [35], the Brief Autism Mealtime Behavior Inventory (BAMBI), used for the evaluation of atypical feeding and eating behavior in ASD children [205], and the Children's Yale-Brown Obsessive-Compulsive Scales for ASD (CYBOCS-ASD), a reliable measure to evaluate repetitive behaviors [89] and the preliminary self-report anxiety measure (ASA-A) which is the first self-report anxiety questionnaire specifically developed and validated for autistic adults [54].

With the exception of the over mentioned questionnaires, in the clinical practice, the assessment of psychiatric comorbidities in the context of ASD often relies on diagnostic tools and scales, that are specific for the disorder itself

(for example SCID-II for personality disorders diagnosis) and usually not adapted to ASDs characteristics and peculiarities. In these cases, the Psychopathology in Autism Checklist (PAC) may be a useful tool to discriminate between ASD and other conditions, such as psychosis, depression, anxiety, and obsessive-compulsive disorder (OCD) [162]. On the other hand, to assess the presence of ASD traits in the context of a psychiatric disorder, other tools, such as the Autism Diagnostic Interview-Revised (ADI-R) [90], or the the SCQ scale (Social Communication Questionnaire) [187], may be employed.

The lack of dedicated diagnostic tools may lead to misdiagnosis or underdiagnoses, both when a psychiatric disorder arises in the context of ASD, as neuropsychiatrist may not be able to reliably assess the presence of a psychiatric comorbidities, but also as ASD traits may be unnoticed and difficult to recognize for psychiatrist in individuals affected by a psychiatric disorder [12].

Results from this review revealed that in most cases conventional treatment for psychiatric disorders, especially when pharmacological, seem to be less effective in patients with concomitant ASDs.

Among non-pharmacological interventions available for the treatment of these comorbidities, one of the most effective treatment seems to be behavioral interventions, especially CBT, which stands out as a reliable treatment option for all the psychiatric disorders considered in the present review [39,62,96,129,163,189,207]. Other behavioral interventions delineated in the present work are sleep hygiene for sleep disorders [129], and the involvement of school educators and psychologists in order to manage and mitigate stressors, which seems to be especially relevant in the management of atypical feeding behaviors and FED [202]. In some cases, for instance for tic disorders and Tourette Syndrome, the watch-and-wait strategy, coupled with psychoeducation, is indicated in many patients [188].

Nevertheless, pharmacological treatments available are numerous. For ADHD psychostimulants are the most used pharmacological class [30], although they seem to be less tolerated when the disorder occurs concomitantly with ASDs [37]; in such context the British Association for Psychopharmacology recommends the use of methylphenidate, atomoxetine and guanfacine [30].

SSRIs and SNRIs have proven to be an effective treatment when ASD is concomitant with anxiety disorders, especially in children [60], mood disorders, mainly major depression [148], and OCD, where fluoxetine and fluvoxamine are most commonly employed [86,97], along with Deep Brain Stimulation [99]. On the other hand, the use of antidepressants in patients with concomitant personality disorders and ASD seems to be less effective than it is on PDs alone [61].

Neuroleptics have proven to be effective in reducing impulsivity and in decreasing stress levels not only in ASD patients presenting comorbid personality disorders, along with a reduction of aggressive behaviors [84], but also in ASD concomitant with tic disorders or Tourette syndrome, although first generation antipsychotics (APs), mainly haloperidol, seem to be less tolerated, than second or third generation APs, especially aripiprazole [179].

Results from the present review unveiled how antipsychotics may be also used when a mood disorder arises in the context of ASD. In fact, when irritability or aggressiveness are manifestations of a concomitant mood disorder, the most effective drugs seem to be risperidone, aripiprazole [167,168] and sodium divalproex [168], especially for bipolar disorder, in case of which lithium remains a first-line treatment [170]. Inconsistent results were observed regarding the effectiveness of quetiapine, olanzapine and ziprasidone [169], along with SSRIs and tricyclic antidepressants [148].

Finally, in order to treat sleep disorders in individuals on the autism spectrum, suggested pharmacological treatment are melatonin, although its effectiveness seems to be restricted to children and adolescents [137], and Clonidine, which has proven to relieve also behavioral symptoms [138].

Conclusion

It is fundamental to recognize symptoms of psychiatric comorbidities occurring in the context of ASD in order to reach an accurate diagnosis and employ correct treatment options. However, the symptomatic overlap between psychiatric disorders and autism spectrum disorders, along with the lack of specific diagnostic tools, makes often difficult to reach an accurate diagnosis and to set out appropriate treatment. In conclusion, the present review underlines the need for adaptation and implementation of diagnostic tools and assessment scales, along with the development of dedicated treatment alternatives. Future studies need to take into consideration homogeneous samples of patients with ASD diagnosis or specific ASD subgroups and entities.

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Authors' contributions

The authors equally contributed

Ethical consideration

Not applicable.

TABLE I. *Main findings of the narrative review on psychiatric comorbidities in patients with autism spectrum disorders.*

Main findings of the narrative review on psychiatric comorbidities in patients with autism spectrum disorders								
Comorbidity	**Mood disorders**	**Anxiety disorders**	**Repetitive behaviors and Obsessive-Compulsive disorders**	**Feeding and Eating disorders**	**Attention Deficit and Hyperactivity disorders**	**Tics and Tourette syndrome**	**Sleep disorders**	**Personality disorders**
Prevalence	Pooled prevalence of 11% for Major Depressive Disorder and 5% for Bipolar Disorder in ASD.	Pooled prevalence of 20% for Anxiety Disorder in ASD. Across different studies prevalence ranges between 1.47% and 54%.	Pooled prevalence of 9% for OCD in ASD. Across different studies prevalence ranges between 9% and 22%	Prevalence of Feeding and Eating Disorders (FED) among individuals with ASD ranges between 1.4% and 7.9%. Anorexia nervosa is the most frequent ED, followed by bulimia nervosa and binge-eating disorder.	Pooled prevalence estimates of 28% for Attention-Deficit Hyperactivity disorder.	Prevalence of Tourette syndrome or Tic disorders ranges between 2.6% and 36% among individuals with ASD.	Pooled prevalence is 13% in SDs in ASD.	Pooled prevalence of 12.6% for Personality disorder in ASD. - Cluster A and Cluster C personality disorders (PD) are the most common PD co-occurring with ASD.
Symptoms	Peculiar depressive symptoms in ASD individuals: change in stereotyped behavior and increase in compulsive behaviors. Loss of language, social withdrawal, loss of eye contact, moodiness, fearfulness, obsessiveness, and occasionally self-injurious behaviors (in LFA). Feelings of low self-esteem (in HFA). Weight loss, appetite and sleep disturbance, decreased communication or catatonia. Mixed features with neurovegetative symptoms, seasonal or circadian variations in mood and energy. Hypomanic or Manic symptoms are often characterized by atypical presentation with irritability, hyperactivity and aggression (higher rates in LFA) or grandiosity (higher rates in HFA).	Unusual specific phobias (e.g., vacuum cleaners, toilets) and fear of change/novelty.	Higher rates of obsession and compulsions and greater symptom severity, but less likelihood to experience thoughts regarding aggression, contamination, sexual, or religious contents. Repetitive behaviors may not cause distress, but are time-consuming. Interrupting repetitive behaviors can cause sudden bursts of anger.	Atypical eating and feeding behavior (food refusal, food selectivity, obsessive routine for taking meals, preference for food color and texture) along with GI symptoms, may worsen ASD-specific symptomatology.	Severe impairments in adaptive and executive functioning: inattention, hyperactivity/impulsivity, social impairment, cognitive flexibility and planning impairments.	Motor tics, stereotypies and semi-voluntary movements may often be found in individuals with ASD, but are usually phenomenologically different entities than tics or TS.	Reduced total sleep time, longer sleep onset latency, higher time spent in stage 1 sleep, lower time of REM sleep, lower sleep efficiency and higher time awake after sleep onset. Night-time awakenings.	a) OCPD in ASD: need for control, over-conscientiousness, workaholism, preoccupation with detail, perfectionism and problems in attention-switching (cognitive rigidity). Higher neuroticism, lower extraversion, agreeableness, lower openness to experience and conscientiousness; b) Schizoid PD in ASD: Increased detachment from social relationships and stress susceptibility; c) BPD in ASD: self-harm and non-suicidal self-injury (NSSI) to reduce tension and anxiety states; d) ASPD and narcissistic PD in ASD: empathy deficits, in ASD mostly related to reduced levels of cognitive empathy (TOM), than of affective empathy.
Diagnostic tools	Psychopathology in Autism Checklist (PAC).	Preliminary self-report anxiety measure (ASA-A); Psychopathology in Autism Checklist (PAC).	Children's Yale-Brown Obsessive-Compulsive Scales for ASD (CYBOCS-ASD); Psychopathology in Autism Checklist (PAC).	Brief Autism Mealtime Behavior Inventory (BAMBI); Food Frequency Questionnaire (FFQ); Eating Disorder Inventory-3 (EDI-3).	Autism Diagnostic Observation Schedule-Second Edition (ADOS-2); Autism Diagnostic Interview-Revised (ADI-R).	Yale Global Tics Severity Scale (YGTSS); Shapiro Tourette Syndrome Severity Scale (STSSS).	N.A.	Structured Clinical Interview for DSM IV Axis II (SCID-II); Personality Assessment Inventory (PAI).
Treatment	Non-medical interventions: CBT (cognitive behavioral therapy) and MBT (metacognitive behavioral therapy). Medical interventions: -SSRIs and SNRIs for major depression -Risperidone and aripiprazole treatments for irritability. -Sodium Divalproex for aggression. -Lithium for manic symptoms.	Non-medical interventions: CBT and: -Coping Cat series of interventions for SAD, GAD, SA and SP (Social anxiety disorder, generalized anxiety disorder, and separation anxiety and specific phobias) - BIACA program - MBT-AS training - Internet-based CBT program (i.e. BRAVE-ONLINE) -Use of biofeedback devices Medical interventions: SNRIs, SSRIs (limited evidence of effectiveness in adults with ASD)	Non-medical interventions: CBT and psychoeducation (anger management, social skills) followed by gradual introduction of Exposure Response Prevention (ERP) and CBT (i.e. mindfulness training). Medical interventions: -Fluvoxamine; -Fluoxetine; -N-Acetilcysteine as nutraceutical treatment	Non-medical interventions: CBT and psychoeducation. Poor evidence on the efficacy of pharmacological treatments.	Non-medical interventions: behavioral techniques (reduction of problematic behavior by 80–90% if applied on early stages). Medical intervention: Psychotropic drugs: -Psychostimulants: a)Methylphenidate, b) Atomoxetine, c) Guanfacine -Anxiolytics and Mood stabilizers -Antidepressants -Combination therapy	Non-medical interventions: Watch-and- wait approach; behavioral treatment (Habit Reversal Training, HRT; Exposure with Response Prevention., ERP). Pharmacological Options: - Aripiprazole for stereotypies in children. -Haloperidol (poorly tolerated) -Risperidone -Pimozide	Non-medical interventions: -Sleep Behavioral interventions, parent training. Medical interventions: -Melatonin improves sleep duration, sleep onset latency, but not nighttime awakenings. Poor evidence or low efficacy for other pharmacological treatments (Anxiolytics, Clonidine).	Non-medical interventions: psychotherapeutic programs for adults with ASD (not yet evaluated for adolescents with ASD). Medical Interventions are symptomatic and supportive: - Neuroleptics to decrease intrapersonal stress levels, enabling a distancing from environmental stressors and a reduction of impulsivity and reactive aggressive behavior. Poor evidence for anticonvulsants.

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