Bipolar Disorder and ASD

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7.1 Introduction

Autism spectrum disorder (ASD) is the label given in *DSM-5* to a variety of neurodevelopmental conditions grouped in by impairment in social communication and restricted, repetitive, and stereotyped interests and behavior [1]. This is the so-called umbrella diagnosis including very heterogeneous early onset neurodevelopmental syndromes. Heterogeneity is expressed at genetic, neuroanatomical, neurobiological, and clinical levels. The complexity of individuals with ASD and the "dimensionality" of the diagnosis can be shaped by means of clinical and severity specifiers allowing the distinction of different ASD phenotypes for both clinical and research purposes. From a practical perspective, the distinction between high- and low-functioning ASD is relevant: high functioning autisms (HFA) is defined by "less marked general impairment" only "requiring support" (level 1), including for example Asperger syndrome and pervasive developmental disorder not otherwise specified of *DSM-IV-TR* [2]. Low-functioning autism (LFA) with co-occurring intellectual

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disability (ID) and language impairment is the form "requiring very substantial support" (level 3). The two subcategories may have different diagnostic and management issues regarding eventual co-occurring psychiatric disorders in adults.

Although in the past early diagnosis was reserved only to children with severe autistic symptoms and developmental delay, in the last few years the reconceptualization of ASD and the broadening of diagnostic boundaries increased the attention to the ASD "soft" signs, with a consistent growth of the diagnoses during childhood [3, 4]. In spite of this, the first recognition of ASD in adults seeking treatment for superimposed mental issues is still very common, a phenomenon defined by Lai and Baron-Cohen as the "identification of the lost generation of adults with autism spectrum conditions" [4].

In subjects without a childhood diagnosis of ASD, the diagnostic difficulties are mainly derived by the poor acquaintance of adult clinicians about ASD, lack of reliable developmental information, and the peculiarities of psychiatric manifestations. For example, the comorbidity of bipolar disorder (BD) and HFA often produces atypical and bizarre clinical presentations, easily misdiagnosed as schizophrenia, with relevant consequences for the treatment choice and management [5, 6].

LFA with co-occurring psychiatric disorders is exactly the opposite. Subjects are diagnosed as ASD since the childhood, but the restricted repertoire of communication skills and behaviors may impact the presentation of the comorbid disorder so considerably that psychiatric manifestations may be neglected or misconceived as symptoms proper to the basic neurodevelopmental disorder. The phenomenon is known as "diagnostic overshadowing" [7]. When challenging behaviors dominate the clinical picture and an intervention is required, usually the approach is based on the problem instead of the diagnostic precision.

BD is a common psychiatric comorbidity in both HFA and LFA and may be a significant cause of further distress and impairment [8]. The purpose of this chapter is to examine epidemiological, clinical, and therapeutic implications of comorbid BD in ASD, considering different issues on the basis of the level of functioning.

7.2 Epidemiology

Depressive symptoms and episodes of manic-depressive illness have been reported since the first descriptions of ASD [9]. Current literature is not exhaustive regarding the co-occurrence of ASD and BD in adults, and the results are mixed: this can be attributable to the heterogeneity of psychiatric presentations in ASD and methodological differences across studies [10]. Moreover, a large part of the data are related to childhood and adolescence, and it is not possible to fully generalize the results to adults: in clinical samples of very young subjects, depressive and other psychiatric symptoms may be more represented than hypomanic and manic symptoms, which could become manifest later in life [7, 11]. This is confirmed by a 2011 study of the Interactive Autism Network (IAN): the rates of BD in children and adolescents aged between 5 and 18 increased with growing age from 2.3% to 10.4% [12]. On the other hand, in the last years epidemiological research has

included mainly HFA, while in LFA the detection of co-occurring BD has been complicated by atypical clinical presentations with high rates of under-recognition and mistreatment.

Few research accounts for the differential prevalence of BD in ASD according to ID level. In the IAN study, Rosenberg and colleagues estimated that in 4343 ASD children and adolescents, BD was more common in Asperger syndrome than in pervasive developmental disorder not otherwise specified and autism (8.6% vs. 5.6% and 3.0%, respectively). However, the authors suggested caution in the interpretation of the data, given the inadequacy of "classical" criteria for psychiatric disorders to depict the comorbidity in lower functioning ASD [12]. The prevalence of overall mental disorders increases from 8–13% in intellectually disabled persons to 16–30.4% when an ASD is also present, similar to the prevalence rates in HFA [13]. These studies suggest that the co-occurrence of ASD add further vulnerability to the development of another psychiatric disorder.

Rates of BD in ASD range from 1.7% to 31% in pediatric samples [14] with most studies reporting percentages around 5–8% [12, 15–17]. In samples of adults, sometimes including also adolescents, prevalence rates of BD are higher, with the lowest rate at 0.74% in adults with autistic spectrum conditions regardless the IQ level [18], and the highest at 66% in a study recruiting persons with Asperger syndrome [19]. Generally, the prevalence range was 6–40% [20, 21], with variability depending on sampling, sensitivity of diagnostic criteria, and other methodological differences, whether or not data are collected in vocational, third-level, clinical settings or the general population.

On the contrary, the prevalence of ASD in children and adolescents with bipolar spectrum conditions, including BD type I, type II, and softer BD forms, ranged from 7.3% [22] to 56.9% [23], with the majority of the studies going beyond the prevalence of 15% [14, 24–26]. Such high rates are not surprising given that early onset BD could be considered a neurodevelopmental disorder and is associated to a variety of psychiatric comorbidities. Indeed, the familial correlates and the phenotypic expression were similar in BD patients, irrespective of the association with ASD [14]. There are very few studies exploring the co-occurrence of ASD in samples of BD adults. In a recent large population-based report performed matching different Swedish national registers, including data of 54,723 BD individuals, ASD was found to co-occur in the 1.4% of BD cases vs. 0.1% of the controls from the general population, and genetics accounted for 2/3 of the correlation between the two diagnoses [27]. In a screening of autistic traits by means of the autism quotient (AQ) assessment in a sample of adults with BD type I, 36.1% of BD patients scored at or above the cut-off of clinical significance. As expected, autistic traits resulted significantly more prominent in male probands than in females (50.75% vs. 21%) [28]. Data regarding the gender distribution are actually not conclusive, but it is possible that, as in the general population, some differences might rise on the basis of the bipolar illness course and subtype. For example, in a Swedish sample of 54 HFA adult outpatients, an additional diagnosis of BD type II was made in the 9% of the cases with a slight preponderance in the female gender (11% vs. 8%) [29].

The association between ASD and BD is confirmed by familial studies [30–32]. Asperger himself was convinced that the syndromic picture he described had "by nature an important load of inheritance" [33].

Among ASD patients, a positive family history for affective disorders can be found in the 17% and 13% of the family members of autistic and Asperger subjects, respectively [34]. Several studies reported higher prevalence of depression and BD among ASD patients' relatives compared to family members of children with other types of disabilities [30, 35, 36]. Some authors suggested that familiarity for mood disorders could represent a determinant for subtyping different phenotypes or distinct classes of patients. DeLong hypothesized the existence of two "taxa" of ASDs, one constituted by high-functioning subjects, with prominent anxiety, obsessive symptoms, mood imbalance, and positive family history for major psychiatric disorders, specifically mood disorders. The other class would be made up of subjects with language and learning disorders associated to the lack of family history for mood disorders [37]. In a 1988 study DeLong and Dwyer [38] found higher rates of BD in families with an AS history compared to other ASDs (6.1% vs. 3.3%). A 1994 study showed that, in ASD children, the absence of a defined neurological disease correlated with autistic syndrome was associated with family history for affective disorders [39]. The majority of the studies on psychiatric morbidity of ASD patients' parents show that the mood disorder onset usually precedes the birth of the ASD offspring. This observation seems to suggest the prevalence of biological and genetic underpinnings in mood disorders among relatives of ASD patients, particularly HFA; on the contrary, a reactive component linked to the stress of care-giving a disabled child might have less pathogenetic weight [30, 40].

In 2005 Ghaziuddin analyzed the family history of 58 AS patients aged from 7 to 20 years and recruited from the community services. The 60.3% of first-, second-, and third-degree family members of probands reported a history of depression and other mental disorders [41]. The author noted that the lack of a specific correlation with BD might be attributable to the use of different diagnostic criteria comparing to previous studies.

Another study pertinent to the IAN project considered 988 couples of mother and child and examined the potential association between maternal history of mental disorders and high-functioning phenotypes of ASD [42]. This study found a significantly higher prevalence of both depression (47.1% vs. 39.1%) and BD (10.1% vs. 6.2%) in mothers of HFA probands than in the mothers of autistic children. Women with a mood disorder, particularly those with BD, showed higher rates of depressive recurrences; moreover, the majority of mothers affected by depression and BD reported the onset as preceding the first pregnancy. On the other hand, the history of bipolar illness in this population was associated with significantly higher risk of bearing an HFA than an autistic child (OR 2.11, CI 1.20–3.69). Similar results have been obtained in a case–control study considering four different samples. A diagnosis of bipolar illness in parents increases of 1.5 to 1.9-fold the risk of ASD in offspring. The odds ratio (OR) is near to that of general population (1.1) when ID co-occurs, whereas it is 1.7 for people with average IQ. The risk of ASD is further higher (OR 2.5) in siblings of bipolar patients [43].

In summary, epidemiological and clinical studies showed a bidirectional relationship between ASD and BD both at personal and at familial level, with rates of co-occurrence higher than in the general population. In the perspective of hereditariness, the link between ASD and BD seems to be stronger in high-functioning subtypes, suggesting larger contribution of commonly shared genetic underpinnings. However, from the clinical side, the comorbidity with BD shows similar rates in both HFA and LFA with comparable implications.

7.3 Clinical Features of Bipolar Disorder in Autism Spectrum Disorder

Consistently with our experience, Skeppar et al. [6] observed that comorbid affective disorders in adults with ASD, especially in HFA, are often diagnosed as Schizophrenia spectrum conditions. When the atypical presentation of mood symptoms together with the peculiar, sometimes odd, adaptive, and behavioral functioning of autistic persons are combined, the clinical picture considered in a cross-sectional perspective may strongly resemble what we are used to call schizophrenia. Even the premorbid functioning of HFA may be confused with a variety of cluster A and C personality disorders, corroborating the misdiagnosis [4].

Manic episodes in adult with ASD seem to be frequently characterized by irritable, instable, and dysphoric mood and hostility more than classic euphoric mood, elation, and jocularity. Other important symptoms are restlessness, anxiety, perplexity, aggression, violent behavior, and insomnia [5, 6, 11, 14, 44, 45]. To our knowledge, frequencies of mixed versus classic manic features were not systematically studied in adults with ASD.

Psychotic symptoms may be an important feature of the manic: in many cases, hallucinations, psychotic interpretations, and delusional ideas (mostly with persecutory, reference and grandiose content) may be prominent and dominate the clinical presentation [5, 6, 44, 45]. Bizarre thought contents are not rare but they have to be distinguished from odd thinking, bizarre ideas, and idiosyncratic views or feelings, which are really common among ASD subjects also during euthymia [19, 45–47]. It has been suggested that during manic episodes the peculiar way of thinking of ASD subjects becomes more prominent or that they become more prone to share their thoughts with others [6, 46]. Making a differential diagnosis should be considered a crucial point. Indeed, persons without ID and language impairment and with good adaptive skills may remain undiagnosed till a comorbidity onset. The differentiation of bizarre, “different,” and concrete thinking and perceptual anomalies of autistic persons by psychotic symptoms is based on comprehending whether those symptoms are autistic core features or reactive behaviors with understandable link to the experience and specific cognitive deficits of these persons [48]. For example, there are clear differences in the peculiar pedantic and accurate language of some HFA persons from the formal disturbances in thought and language found in schizophrenic patients with prominently negative symptoms, mostly incoherence, vagueness, and circumstantiality [49]. Similarly, paranoid ideas might be dragged by

difficulty in the theory of mind and social reciprocity associated with repeated negative social experiences. Concretism may also lead to misinterpretation of medical questions during the psychiatric exam.

The presence of other behavioral features typical for ASD such as rigid adherence to routines, sensory issues, and early-onset stereotypies can support the diagnostic process. As a rule, although odd thinking may become more intense during acute affective phases, it is stable and long-lasting, and in the majority of the cases, it is present since childhood without the classical rift of thinking and functioning as they are described in other psychotic conditions. In addition, "psychotic" thoughts are less interfering with daily functioning and less emotionally engrossing in ASD than in schizophrenia [46, 50]. In ASD patients with ID and language impairment, the excitatory phase may be described more appropriately by the disruption of neurovegetative patterns such as appetite, sleep, sexual activity, and the variation of psychomotricity.

The detection of hypomania in BD type II and other soft bipolar spectrum conditions is usually more difficult. Irritability, excessive mood reactivity, increase of energy and activity, psychomotor activation, and diminished need for sleep may be labile and often labeled as "simple reactions" to environmental conditions in persons which are more vulnerable to changes. Such symptoms may actually be elicited by difficulties in the modulation of arousal, for example, when routines change or during the exposition to new and/or social situations [51–53] but, when a set of recurring wax-and-waning symptoms are identified, clearly different from the usual and interfering with baseline functioning, the diagnosis has to be considered. Beyond an accurate clinical interview, the systematic use of specific assessment instruments for mood symptoms is recommended [7, 11, 54, 55]. The presence of positive familial history for BD, special abilities, early onset anxiety, and/or multiple psychiatric comorbidities and comorbid Tourette's syndrome are other important risk factors for bipolarity in ASD [12, 30, 32, 37, 56–59].

In individuals with ASD, depression may be barely recognizable, because it is frequently characterized by mild severity and long-lasting, often chronic, course. Depressive symptoms have to be specifically investigated as a clear-cut variation in personal, adaptive, and social functioning in comparison with a baseline reference point: some of the core autistic dimensions, such as blunt affect and social withdrawal, can be simply amplified during depression, and the depressive dimension remains neglected [6]. Moreover, difficulties in social communication and introspection, idiosyncratic thinking, and feelings might add difficulties in investigating or correctly interpreting the "inner" dimension of depression [6, 12]. Non-verbal typical expressions of depression may also lack [4]. To improve the capacity of detecting depression in clinical settings, the systematic utilization of specific assessment instruments, both self- and hetero-administered rating scales (e.g. MADRS, BDI), could be useful. As in the case of mania and hypomania, variations in psychomotricity and neurovegetative functioning are the best depressive diagnostic parameters (from hypersomnia to insomnia, loss of appetite) [12, 55, 60, 61]. The loss of energy may reflect in the reduction of the number and involvement in usual interests and activities. Anhedonia, apathy, feelings of

worthlessness or guilt, low self-esteem, recurrent thought of death, diminished concentration, and indecisiveness are common as in other depressive patients [7, 53, 55, 56]. Stressful events preceding the onset of depression are not uncommon, especially in higher functioning subjects with problems in social adjustment but high social motivation with decrease of self-esteem and experience of personal failure [62]. Mood instability, atypical, violent and sudden affective changes, from lability to irritability, aggression, self-injuring, and agitation are not uncommon [7, 63–65]. It has to be considered that such behavioral features of depression are particularly common in persons with co-occurring ID in which psychopathology may manifest itself via challenging behaviors and the increase of core symptoms of the basic neurodevelopmental disorder, for example, stereotypies. In LFA a deterioration in cognitive performance, behavior, or activities with cyclic pattern ("alternation of good and bad times"), even in the absence of other clear mood symptoms, may be indicative of the co-occurrence of bipolarity [11]. Suicidality in ASD is not infrequent becoming a primary challenge. Any suicidal behavior including suicidal ideation, planning, suicide attempt, and completed suicide ranged from 11% to 50% in different populations, much higher than suicidal rates in schizophrenic patients (7–10%) [66, 67]. In such a case, the implications of a misdiagnosis might be severe. Suicidal ideation may be facilitated by some cognitive peculiarities of HFA such as the impairment of the capacity to understand mental and emotional states, difficulties in realizing what suicide means for their relatives, reduced flexibility, and dichotomous thinking: suicidal thoughts may become an obsession, and the person may spend lot of time searching information and planning [4].

Consistent with our experience, movement disorders and catatonia have also been frequently reported in adults with ASD [68–70]. Catatonia can be identified in the 12–17% of clinical samples of ASD adolescents and young adults [71, 72]. Catatonia seems to be equally distributed in HFA and LFA [71]. Catatonia in ASD subjects seems to be often associated with repetitive self-injuries, posturing, and negativism [69]. In those cases, while lorazepam has demonstrated a certain efficacy, electroconvulsive therapy seems to be the most and persistently successful treatment [73]. *DSM-5* recognized that both BD and ASD are independently associated with catatonia which is no more considered a sign of psychosis [1] and, in persons with ASD and BD, might be precipitated or worsened by antipsychotics [74].

7.4 Treatment

Recent studies have shown that some ASD manifestations might be partially modified by appropriate pharmacological treatments, leading to improvement in socialization, language, adaptive skills, and mood [75, 76].

Current literature on pharmacological options in comorbid ASD and BD consists of case reports or case series, and all the available treatments are not adequately studied in systematic or controlled studies.

7.4.1 Mood Stabilizers

Controlled studies regarding the use of lithium and other mood stabilizers in comorbid ASD and BD are substantially lacking, but their use is supported by numerous case reports and case-series, indicating their efficacy for mood instability and cyclicity in ASD subjects, both in childhood and in adulthood, as in neurotypical persons [77–80]. Lithium is recommended as first choice for the treatment of manic symptoms in ASD-BD patients with BD among relatives [81–83]. Positive family history [36], severe hyperactivity unresponsive to stimulants, cyclical pattern of behavioral changes, irritability, enduring outbursts of laughter, subjective dizziness, and the presence of at least some BD diagnostic criteria [84] are predictors of favorable lithium response. Lithium seems to be effective in controlling aggression and hyperactivity in some cases, even in LFA, as well as in reducing manic symptoms and mood swings [85].

An anticonvulsant may be a better choice than lithium when the patient is epileptic or significant EEG alterations have been found. Some antiepileptic drugs may also be useful when other psychopathological dimensions dominate the clinical picture (e.g., severe anxiety, impulsivity, and aggression) or the clinical psychopathological picture is particularly polymorphic with a mix of variable symptoms going from psychosis to derealization/depersonalization, depression, anxiety, and somatizations, suggesting a possible etiologic correlation with forced normalization of EEG abnormalities [86]. Valproate is the anticonvulsant with the largest number of observations in comorbid ASD and BD. Some reports suggest the effective use of valproate in adults with ASD with the reduction of non-convulsive symptoms such as hyper-arousal, irritability, dysphoria, and anxiety [87]. Valproate has been found to have promising effects when in LFA with typical and atypical forms of manic depressive illness including rapid cycling [88]. Another retrospective small study including 14 patients with HFA found valproate to be effective on affective instability, impulsivity, and aggression, independently from the presence of seizures and EEG abnormalities [89]. There are two large studies regarding persons with ID, including ASD patients, one perspective and the other retrospective: they both evidenced the efficacy of valproate in the 70% of the cases on hyperactivity, impulsivity, and stereotypies but even more on aggressiveness and self-injury [90, 91], all considered possible behavioral equivalents of mood symptoms if contextualized in a syndromic and recurrent pattern.

Like valproate carbamazepine is used in persons with intellectual and relational disabilities as anticonvulsants when epilepsy co-occurs, and it has the general indication as mood stabilizer for the treatment and prophylaxis of BD even in the case of raid cycling [92, 93]. Other targets of carbamazepine may be aggressiveness and self-mutilations especially in persons with ID in which these challenging behaviors are related to epilepsy or mood disorders [94, 95]. Few observations indicated that oxcarbazepine may be useful in combination with low doses of second-generation antipsychotic HFA adults with BD [5].

Although lamotrigine has the indication for the prophylaxis of depressive recurrences in BD in neurotypical subjects, the few available data on its use in ASD do not allow conclusive remarks [96].

7.4.2 Antipsychotics

The use of antipsychotics in ASD has been extensively studied although most studies regarded small samples of children and adolescents, and the focus of the treatment was irritability. Clinical trials may have considerable selection and referral biases mostly recruiting individuals with severe problem behavior, without a clear distinction among specific clinical phenotypes, ID presence, and severity and presence of psychiatric comorbidity. As a consequence, the results are only partially generalizable to all persons with ASD.

First-generation antipsychotics (FGA) in the past were the most prescribed drugs [97, 98]. In the 1970s, haloperidol and pimozide were extensively used given their efficacy in the decrease of stereotypies, hyperactivity, emotional outbursts, and temper tantrums [99–103]. However, their used became later not recommended because of the high rate extrapyramidal side effects and dyskinesias (5–15%) [104, 105], with the exception of co-occurring tic disorders and Tourette's syndrome. As a consequence, second-generation antipsychotics (SGA) replaced FGA in the last few decades. However, it has to be kept in mind that certain FGA, mostly chlorpromazine which have a complex pharmacodynamic profile including 5-HT2a antagonism, may represent a valid treatment option in acute manic and mixed phases to rapidly reach the remission of excitatory symptoms. Risperidone and aripiprazole are the most frequently studied and used: they are the only medications with a FDA-specific indication for the treatment of irritability in ASD children [75]. The vast amount of data on the use of risperidone in children and adolescents with ASD showed it is effective for repetitive, aggressive, and impulsive behaviors; some studies also suggested it would improve at some degree social impairment [106–109]. It has to be taken into account that it is possible that the improvement of core autistic dimensions is dragged by the improvement of co-occurring mood symptoms, reactivity, and hyperactivity more than a true "curative" effect on these dimensions. The severity of irritability and also aggressive behavior are reliable predictors of response to risperidone [110]. In spite of initial enthusiasm, risperidone prolonged or high-dosage use can often produce extrapyramidal symptoms (EPS) and tardive dyskinesia, although to lesser extent than haloperidol. Moreover, risperidone often induces weight gain, drowsiness, and hyperprolactinemia and, in many cases, would require drug discontinuation [111–115]. Some data suggested paliperidone to have similar efficay as risperidone, also in its long-acting formulation [116]. Risperidone in the 70% of HFA children and youngsters (6–12 years old) treated produced a significant reduction in negative symptoms [117]. Risperidone is widely used, in childhood as well as in adulthood, for the treatment of manic symptoms and related behavioral problems in BD [118]. In a case-series of adults with BD and HFA, low doses of

risperidone associated with anticonvulsants have shown a good efficacy [5]. In children, adolescents, and adults with ID, risperidone halves the intensity of challenging behaviors (aggressiveness, rage outbursts, and self-injury in the 50% of the persons treated) [119]. The effectiveness on challenging behaviors in LFA seems to be dose-related [120] and increases by the association to rehabilitative-educational interventions, for example, parent training [121].

Aripiprazole, the second most used medication, in a study regarding HFA children and adolescents reduced irritability, aggression, self-injury, and temper tantrums in the 88% of cases, with good short-term tolerability. Common side effects were weight gain, hyperprolactinemia, dose-dependent sedation, and sialorrhoea [122]. As in the case of risperidone, the long-term use is associated with high rate of EPS and tardive dyskinesia, requiring careful monitoring. The results regarding the treatment of aggressiveness, disruptive behavior, and severe challenge behaviors in persons with ID are less consistent than risperidone [123, 124]. Aripiprazole may be useful in the treatment of mania and psychosis even in LFA adults [92]. The long-term use of aripiprazole for maintenance treatment and prophylaxis of illness recurrences requires awareness of the peculiar pharmacokinetics of these medication and the special vulnerability of LFA persons to neurological and cognitive side effects.

Olanzapine, scarcely effective on core autistic symptoms, might be very effective in agitated manic and mixed ASD patients, but its use is burdened by side effects, such as sedation and weight gain [125, 126]. Quetiapine has not been extensively studied in ASD and showed some efficacy in the control of aggressive behavior and sleep disturbances, but did not seem to influence autistic symptoms [127–129]. For these reasons, olanzapine and quetiapine should not be considered first choice drugs in the treatment of ASD. In a clinical trial comparing the anti-manic short-term (8 weeks) efficacy of SGAs (risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) in 151 youth with BD, the efficacy and tolerability of SGAs were similar in patients with or without ASD. More specifically, 69% of BD patients and 65% of BD + ASD patients presented an improvement of at least 30% at the Y-MRS and 47% of BD patients compared to 44% of BD + ASD had an improvement of at least 50% [25]. However, a recent study reported less encouraging results: the treatment of BD with atypical antipsychotics, alone or in combination with mood stabilizers, showed response rates ranging from poor to modest. Authors noted that the response was low even though the rates of psychotic symptoms were higher than those found in previous studies [21]. The overall response to treatment was poor to modest.

There is a body of literature indicating that antipsychotics highly selective on the serotonin transporter (5-HTT) and the 5-HT2A receptors should be considered of first choice in ASD [130–132]. The scientific rationale is represented by those molecular and biological studies that observed in ASD some alterations involving the serotonergic system such as “hyperserotonemia” [133–136], high brain tissue 5-HT concentration, especially in the cortex [137], alteration in the brain 5-HT synthesis [138, 139], reduction of the 5-HT2A receptor binding capacity [140] (negatively related to the platelet 5-HT concentration), and reduction of the 5-HTT binding capacity, especially in the anterior and posterior cingulate cortex [141].

Asenapine is an antagonist of D2 and 5-HT2A receptors approved by FDA as adjunctive therapy with lithium or valproate for manic or mixed episodes in BD type I. Although there are not RCTs in ASD patients, its pharmacodynamic profile makes it an option to be considered in collaborative patients, also given the good tolerability of long-term flexible dose of sublingual administration [142].

Lurasidone too has 5-HT2A antagonistic properties and is indicated for the treatment of depressive episodes in adult BD type I patients. A recent study demonstrated its efficacy also in children and adolescents with a similar indication [143]. In a 2016 6-week placebo-controlled study in ASD children and adolescents requiring treatment for irritability, agitation and self-injury, lurasidone demonstrated few differences at different dosages compared to placebo in ameliorating irritability [144]. However, the potential effectiveness is suggested by a case report regarding an LFA adolescent with aggressive and impulsive behavior [145]. Lurasidone should be an option mostly because of its favorable metabolic tolerability profile when other SGAs demonstrated efficacy but caused excessive weight gain and metabolic side effects.

7.4.3 Antidepressants

The use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) is wide in daily clinical practice with young ASD patients. However, evidences of their effectiveness in ASD are poorly reliable [146, 147]. Their use with comorbid BD has not been systematically studied, but some suggestions are derived by some case reports.

SSRI antidepressants have been studied in ASDs mainly for the treatment of anxiety, obsessive-compulsive symptoms, and depression. Some evidence of efficacy has been shown for fluoxetine, citalopram, sertraline, and paroxetine [7, 148–151]. However, results are contradictory in youth and not conclusive in adulthood [147]. In the case of ineffectiveness of an SSRI, a second attempt with a different SSRI has been reported as “often unsuccessful” [152].

Especially in children and adolescents, the use of these drugs should be carefully monitored; SSRIs may be related to activation syndrome, with agitation, aggression, self-injuring, insomnia, and suicidal and, in some cases, also homicidal thoughts [153, 154]; EPS have also been reported more frequently than in the general population evidencing a peculiar vulnerability as in the case of antipsychotics [155]. In a short-term chart review of 89 young ASD outpatients treated with SSRIs, although the 44.9% of the subjects were considered responders, the 54% showed activation that in the 35.4% of the cases needed the discontinuation of the medication [154].

In bipolar HFA caution needed are more as several observations and case series reported that antidepressants, especially SSRIs, can cause (hypo)manic switches and mixed symptoms [5, 44, 156, 157]. Antidepressant treatment may also negatively influence the long-term course of bipolar illness causing increased affective instability, chronic mixed states, and rapid cycling [154, 158].

For patients with ASD in general and HFA in particular seeking treatment for depressive or anxiety symptoms, a very careful personal and family medical history survey is required to exclude a bipolar diathesis. When an antidepressant is prescribed, the clinician should plan frequent controls to detect early eventual side effects and mood changes. The possible use of an antidepressant in combination with a mood stabilizer reduces but does not eliminate the possibility of mood switches and affective destabilization [158].

7.4.4 Stimulants

There are no controlled studies exploring the use of stimulants (methylphenidate [MPH], dexmethylphenidate, dextroamphetamine, mixed amphetamine salts, dextromethamphetamine, and lisdexamfetamine) in adults with ASD-BD. However, considering that the co-occurring of ASD and ADHD is not infrequent [159] and may require a pharmacologic approach, it is appropriate to mention the small literature regarding the use of stimulants in ASD-ADHD comorbidity. Indeed, such a comorbidity may represent a condition with increased risk to develop further psychiatric disorders during adulthood, namely BD. Data on this topic are lacking because the criterion E of *DSM-IV-TR* for the diagnosis of ADHD considered the presence of an ASD as an exclusion criterion [2]. This is also one of the reasons why ADHD-like symptoms in this population are often under-recognized and undertreated, although some patients with HFA refer to clinical setting for ADHD and not for mild autistic symptoms [160].

A recent systematic review [161] on the efficacy and tolerability of stimulants for ADHD-like symptoms in individuals with ASD, considering randomized-controlled, uncontrolled studies, and expert commentaries found that stimulants may be effective in ASD in the treatment of ADHD-like symptoms. The frequency of adverse events was higher than in children with ADHD without ASD. However, stimulants seem to be more effective and better tolerated in higher functioning than in other ASD individuals [162, 163]. Decreased appetite (with medium-high doses), difficulty falling asleep, stomach or abdominal discomfort, irritability and emotional outburst are common side effects [109, 164].

7.5 Conclusion

A consistent body of research evidences a significant association between BD and ASD in clinical samples, although it is difficult to estimate the actual prevalence in the general population. Up to 20% of HFA subjects referred to clinical settings report BD comorbidity [5, 165] and the prevalence reaches similar percentages in LFA [166].

The literature also strongly supports that ASD would be associated with familial load for mood disorders [30, 35, 36, 41] and that the most frequent association is reported with BD in first-degree relatives of persons with HFA [37, 38, 42]. This last

finding suggests that it is possible that high-functioning forms of ASD may represent a more homogeneous and restricted phenotype, with possible common underpinnings with BD [27]. Further research taking into account more specific phenotypes, familial history, and patterns of psychiatric versus organic comorbidity is needed.

Many of the ASD-BD adult patients are not adequately diagnosed and appropriately treated [5, 6, 46, 167]. Although epidemiological data suggest that BD is more common in HFA than in the neurotypical population, psychiatrists may neglect ASD features [168]. The presence of ASD in adults is often not correctly identified in high-functioning individuals, and the related features are interpreted as personality and/or schizophrenia spectrum disorders [6, 46, 167, 169–171].

On the contrary, in LFA, the comorbidity with BD may be underestimated, and mood symptoms are often overlooked or attributed to the neurodevelopmental condition rather than BD, in spite of the episodic or cyclic course.

In adult patients with comorbid ASD and BDs, schizophrenia is the most frequent misdiagnosis [6]. This is mainly due to the following reasons: (1) excitatory episodes are often characterized by irritability, aggression, outbursts of anger more than signs of classic mania as euphoric mood. Moreover, psychotic symptoms are common and tend to be prominent compared to other symptoms, contributing the attention of the clinician to be shifted toward the psychotic more than the affective dimension; (2) the depressive episodes are frequently chronic and attenuated by nature. Motivation, volition, and psychomotricity are mainly involved, widely overlapping with negative and residual symptoms of schizophrenia; (3) odd thinking, bizarre ideas, and idiosyncratic views can be interpreted as delusional or psychotic thoughts.

In LFA the diagnostic process is even more complicated by the very restricted repertoire of skills and behaviors and should require a longer term of observation. The collection of information from different caregivers may be necessary and the use of specific assessing tools might facilitate this process.

A correct diagnosis of BD in ASD individuals and vice versa has relevant implications on the choice of correct psychological, psychopharmacological, and rehabilitative treatments. Notably, data from controlled trials are limited in number and generalizability. In fact, patients with atypical and complex clinical pictures, multiple comorbidities, or organic disorders are usually excluded from clinical trials. Nevertheless, literature provides some useful suggestions for clinical practice. Mood stabilizers are preferable, either in monotherapy or in combination with other drugs. Antipsychotics should be used at the lowest effective dose and for the strictly necessary period to minimize short- and long-term neurological, cognitive, and metabolic effects and the risk of precipitating catatonia. The majority of data are relative to the use of the SGAs risperidone and aripiprazole, but other antipsychotics with 5-HT2A antagonists can be effective. Antidepressants should be used with caution and careful monitoring, in the attempt of an early detection of activation and switch phenomena and to prevent negative long-term impact on the course of the affective illness. The literature on this issue is still incomplete, and long-term controlled studies on large samples are needed to enrich the knowledge in the field.

Finally, educational and training interventions regarding ASD-BD comorbidity aimed at pediatricians, neurologists, and childhood and adulthood psychiatrists are crucial point to improve knowledge on this vast field and to ensure patients to receive appropriate diagnosis and treatment. A personalized psycho-educational and rehabilitative intervention should also be provided pursuing the goodness of fit. These interventions should also be specifically designed on the basis of ASD features and differentiated from programs commonly used in other chronic and disabled patients.

References

1. Association AP. Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5). 5th ed. Arlington: Author; 2013.
2. APA. Diagnostic and statistical manual of mental disorders. Text revision. (DSM-IV-TR). 4th-text revision ed. Washington, DC: American Psychiatric Association; 2000.
3. Mandell DS, Novak MM, Zubritsky CD. Factors associated with age of diagnosis among children with autism spectrum disorders. Pediatrics. 2005;116(6):1480–6.
4. Lai MC, Baron-Cohen S. Identifying the lost generation of adults with autism spectrum conditions. Lancet Psychiatry. 2015;2(11):1013–27.
5. Raja M, Azzoni A. Comorbidity of Asperger's syndrome and bipolar disorder. Clin Pract Epidemiol Ment Health. 2008;4:26.
6. Skeppar P, Thoor R, Sture A, Isakson A, Skeppar I, Persson B, et al. Neurodevelopmental disorders with comorbid affective disorders sometimes produce psychiatric conditions traditionally diagnosed as schizophrenia. Clin Neuropsychiatry. 2013;10(3–4):123–33.
7. Tantam D, Girgis S. Recognition and treatment of Asperger syndrome in the community. Br Med Bull. 2009;89:41–62.
8. Weissman AS, Bates ME. Increased clinical and neurocognitive impairment in children with autism spectrum disorders and comorbid bipolar disorder. Res Autism Spectr Disord. 2010;4:670–80.
9. Rutter M. Autistic children: infancy to adulthood. Semin Psychiatry. 1970;2:435–50.
10. Masi A, DeMayo MM, Glozier N, Guastella AJ. An overview of autism spectrum disorder, heterogeneity and treatment options. Neurosci Bull. 2017;33(2):183–93.
11. Frazier JA, Doyle R, Chiu S, Coyle JT. Treating a child with Asperger's disorder and comorbid bipolar disorder. Am J Psychiatry. 2002;159(1):13–21.
12. Rosenberg RE, Kaufmann WE, Law JK, Law PA. Parent report of community psychiatric comorbid diagnoses in autism spectrum disorders. Autism Res Treat. 2011;2011:405849.
13. Vannucchi G, Coli S, Scuticchio D, Bertelli M, editors. Autism spectrum disorder: a vulnerability factor for psychiatric comorbidity in adults with intellectual disability and autism? A literature review. In: WPA XVII World Congress of Psychiatry, Psychiatry of the 21st Century: Context, Controversies and Commitment. Berlin; 2017.
14. Joshi G, Biederman J, Petty C, Goldin RL, Furtak SL, Wozniak J. Examining the comorbidity of bipolar disorder and autism spectrum disorders: a large controlled analysis of phenotypic and familial correlates in a referred population of youth with bipolar I disorder with and without autism spectrum disorders. J Clin Psychiatry. 2013;74(6):578–86.
15. Bradley E, Bolton P. Episodic psychiatric disorders in teenagers with learning disabilities with and without autism. Br J Psychiatry. 2006;189:361–6.
16. Bryson SA, Corrigan SK, McDonald TP, Holmes C. Characteristics of children with autism spectrum disorders who received services through community mental health centers. Autism. 2008;12(1):65–82.

17. Mukaddes NM, Fateh R, Kilincaslan A. Kleine-Levin syndrome in two subjects with diagnosis of autistic disorder. World J Biol Psychiatry. 2009;10(4 Pt 3):969–72.
18. Hutton J, Goode S, Murphy M, Le Couteur A, Rutter M. New-onset psychiatric disorders in individuals with autism. Autism. 2008;12(4):373–90.
19. Ghaziuddin M, Weidmer-Mikhail E, Ghaziuddin N. Comorbidity of Asperger syndrome: a preliminary report. J Intellect Disabil Res. 1998;42(Pt4):279–83.
20. Guinchat V, Cravero C, Diaz L, Perisse D, Xavier J, Amiet C, et al. Acute behavioral crises in psychiatric inpatients with autism spectrum disorder (ASD): recognition of concomitant medical or non-ASD psychiatric conditions predicts enhanced improvement. Res Dev Disabil. 2015;38:242–55.
21. Nahar A, Thippeswamy H, Shanker Reddy MS, Kishore MT, Chaturvedi SK. Psychiatric comorbidity in persons with high-functioning autism spectrum disorders: findings from a tertiary care neuropsychiatric hospital. Asian J Psychiatr. 2019;41:50–3.
22. Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry. 2006;63(10):1139–48.
23. Pine DS, Guyer AE, Goldwin M, Towbin KA, Leibenluft E. Autism spectrum disorder scale scores in pediatric mood and anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2008;47(6):652–61.
24. Johnson CR, Handen BL, Lubetsky MJ, Sacco KA. Affective disorders in hospitalized children and adolescents with mental retardation: a retrospective study. Res Dev Disabil. 1995;16(3):221–31.
25. Joshi G, Biederman J, Wozniak J, Doyle R, Hammerness P, Galdo M, et al. Response to second generation antipsychotics in youth with comorbid bipolar disorder and autism spectrum disorder. CNS Neurosci Ther. 2012;18(1):28–33.
26. Joshi G, Wozniak J, Petty C, Martelon MK, Fried R, Bolfek A, et al. Psychiatric comorbidity and functioning in a clinically referred population of adults with autism spectrum disorders: a comparative study. J Autism Dev Disord. 2013;43(6):1314–25.
27. Song J, Bergen SE, Kuja-Halkola R, Larsson H, Landen M, Lichtenstein P. Bipolar disorder and its relation to major psychiatric disorders: a family-based study in the Swedish population. Bipolar Disord. 2015;17(2):184–93.
28. Abu-Akel A, Clark J, Perry A, Wood SJ, Forty L, Craddock N, et al. Autistic and schizotypal traits and global functioning in bipolar I disorder. J Affect Disord. 2017;207:268–75.
29. Lugnegard T, Hallerbäck MU, Gillberg C. Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. Res Dev Disabil. 2011;32(5):1910–7.
30. Bolton PF, Pickles A, Murphy M, Rutter M. Autism, affective and other psychiatric disorders: patterns of familial aggregation. Psychol Med. 1998;28(2):385–95.
31. Ghaziuddin M, Greden J. Depression in children with autism/pervasive developmental disorders: a case-control family history study. J Autism Dev Disord. 1998;28:111–5.
32. Piven J, Palmer P. Psychiatric disorder and the broad autism phenotype: evidence from a family study of multiple-incidence autism families. Am J Psychiatry. 1999;156(4):557–63.
33. Asperger H. Die autistischen Psychopathen im Kindersalter. Arch Psychiatr Nervenkr. 1944;117:76–136.
34. Gillberg IC, Gillberg C. Asperger syndrome—some epidemiological considerations: a research note. J Child Psychol Psychiatry. 1989;30(4):631–8.
35. Lajiness-O'Neill R, Menard P. Brief report: an autistic spectrum subtype revealed through familial psychopathology coupled with cognition in ASD. J Autism Dev Disord. 2008;38(5):982–7.
36. Piven J, Chase GA, Landa R, Wzorek M, Gayle J, Cloud D, et al. Psychiatric disorders in the parents of autistic individuals. J Am Acad Child Adolesc Psychiatry. 1991;30(3):471–8.
37. DeLong R. Autism and familial major mood disorder: are they related? J Neuropsychiatry Clin Neurosci. 2004;16(2):199–213.

38. DeLong GR, Dwyer JT. Correlation of family history with specific autistic subgroups: Asperger's syndrome and bipolar affective disease. J Autism Dev Disord. 1988;18(4):593–600.
39. DeLong R, Nohria C. Psychiatric family history and neurological disease in autistic spectrum disorders. Dev Med Child Neurol. 1994;36(5):441–8.
40. Cohen IL, Tsiouris JA. Maternal recurrent mood disorders and high-functioning autism. J Autism Dev Disord. 2006;36(8):1077–88.
41. Ghaziuddin M. A family history study of Asperger syndrome. J Autism Dev Disord. 2005;35(2):177–82.
42. Vasa RA, Anderson C, Marvin AR, Rosenberg RE, Law JK, Thorn J, et al. Mood disorders in mothers of children on the autism spectrum are associated with higher functioning autism. Autism Res Treat. 2012;2012:435646.
43. Sullivan PF, Magnusson C, Reichenberg A, Boman M, Dalman C, Davidson M, et al. Family history of schizophrenia and bipolar disorder as risk factors for autism. Arch Gen Psychiatry. 2012;69(11):1099–103.
44. Ng B, Au M, Verhoeven M, Johnston L, Perkins C. The diagnosis of Asperger's syndrome in an adult presenting with an index episode of mania. Gen Hosp Psychiatry. 2003;25(4):295–7.
45. Raja M, Azzoni A. Thought disorder in Asperger syndrome and schizophrenia: issues in the differential diagnosis. A series of case reports. World J Biol Psychiatry. 2009;10(4 Pt 3):944–52.
46. Fitzgerald M. Schizophrenia and autism/Asperger's syndrome: overlap and difference. Clin Neuropsychiatry. 2012;4(9):171–6.
47. Loveland KA, Pearson DA, Tunali-Kotoski B, Ortegon J, Gibbs MC. Judgments of social appropriateness by children and adolescents with autism. J Autism Dev Disord. 2001;31(4):367–76.
48. Van Schalkwyk GI, Peluso F, Qayyum Z, McPartland JC, Volkmar FR. Varieties of misdiagnosis in ASD: an illustrative case series. J Autism Dev Disord. 2015;45(4):911–8.
49. Tebartz van Elst L, Pick M, Biscaldi M, Fangmeier T, Riedel A. High-functioning autism spectrum disorder as a basic disorder in adult psychiatry and psychotherapy: psychopathological presentation, clinical relevance and therapeutic concepts. Eur Arch Psychiatry Clin Neurosci. 2013;263(Suppl 2):S189–96.
50. Abell F, Hare DJ. An experimental investigation of the phenomenology of delusional beliefs in people with Asperger syndrome. Autism. 2005;9(5):515–31.
51. Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. Am J Psychiatry. 2011;168(2):129–42.
52. Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. Am J Psychiatry. 2003;160(3):430–7.
53. Mazzone L, Ruta L, Reale L. Psychiatric comorbidities in Asperger syndrome and high functioning autism: diagnostic challenges. Ann Gen Psychiatry. 2012;11(1):16.
54. Dejong S, Frazier JA. Bipolar disorder in children with pervasive developmental disorders. In: Geller B, DelBello MP, editors. Bipolar disorder in childhood and early adolescence. New York: Guilford Press; 2003. p. 51–75.
55. Magnuson KM, Constantino JN. Characterization of depression in children with autism spectrum disorders. J Dev Behav Pediatr. 2011;32:332.
56. Ghaziuddin M, Ghaziuddin N, Greden J. Depression in persons with autism: implications for research and clinical care. J Autism Dev Disord. 2002;32(4):299–306.
57. Kerbeshian J, Burd L. Case study: comorbidity among Tourette's syndrome, autistic disorder, and bipolar disorder. J Am Acad Child Adolesc Psychiatry. 1996;35(5):681–5.
58. McElroy SL. Diagnosing and treating comorbid (complicated) bipolar disorder. J Clin Psychiatry. 2004;65(Suppl 15):35–44.
59. Sterling L, Dawson G, Estes A, Greenson J. Characteristics associated with presence of depressive symptoms in adults with autism spectrum disorder. J Autism Dev Disord. 2008;38(6):1011–8.
60. Ghazziuddin M, Zafar S. Psychiatric comorbidity of adults with autism spectrum disorders. Clin Neuropsychiatry. 2008;5:9–12.

61. Rao U, Chen LA. Characteristics, correlates, and outcomes of childhood and adolescent depressive disorders. Dialogues Clin Neurosci. 2009;11(1):45–62.
62. Ghaziuddin M, Ghaziuddin N, Greden J. Depression in adults with autism: implications for research and clinical care. J Autism Dev Disord. 2002;32:299–306.
63. Lainhart JE, Folstein SE. Affective disorders in people with autism: a review of published cases. J Autism Dev Disord. 1994;24(5):587–601.
64. Naidu A, James I, Mukaetova-Ladinska E, Briel R. Diagnosis of Asperger syndrome in a 66-year-old male presenting with depression. Int Psychogeriatr. 2006;18(1):171–3.
65. Spencer L, Lyketsos CG, Samstad E, Dokey A, Rostov D, Chisolm MS. A suicidal adult in crisis: an unexpected diagnosis of autism spectrum disorder. Am J Psychiatry. 2011;168(9):890–2.
66. Upthegrove R, Abu-Akel A, Chisholm K, Lin A, Zahid S, Pelton M, et al. Autism and psychosis: clinical implications for depression and suicide. Schizophr Res. 2018;195:80–5.
67. Toal F, Bloemen OJ, Deeley Q, Tunstall N, Daly EM, Page L, et al. Psychosis and autism: magnetic resonance imaging study of brain anatomy. Br J Psychiatry. 2009;194(5):418–25.
68. Takaoka K, Takata T. Catatonia in high-functioning autism spectrum disorders: case report and review of literature. Psychol Rep. 2007;101(3 Pt 1):961–9.
69. Fink M. Rediscovering catatonia: the biography of a treatable syndrome. Acta Psychiatr Scand Suppl. 2013;441:1–47.
70. Quigley J, Lommel KM, Coffey B. Catatonia in an adolescent with Asperger's disorder. J Child Adolesc Psychopharmacol. 2009;19(1):93–6.
71. Wing L, Shah A. Catatonia in autistic spectrum disorders. Br J Psychiatry. 2000;176:357–62.
72. Billstedt E, Gillberg IC, Gillberg C. Autism after adolescence: population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. J Autism Dev Disord. 2005;35(3):351–60.
73. Kakooza-Mwesige A, Wachtel LE, Dhossche DM. Catatonia in autism: implications across the life span. Eur Child Adolesc Psychiatry. 2008;17(6):327–35.
74. Fink M, Taylor MA, Ghaziuddin N. Catatonia in autistic spectrum disorders: a medical treatment algorithm. Int Rev Neurobiol. 2006;72:233–44.
75. Politte LC, McDougle CJ. Atypical antipsychotics in the treatment of children and adolescents with pervasive developmental disorders. Psychopharmacology (Berl). 2014;231(6):1023–36.
76. Doyle CA, McDougle CJ. Pharmacotherapy to control behavioral symptoms in children with autism. Expert Opin Pharmacother. 2012;13(11):1615–29.
77. DeLong GR, Aldershof AL. Long-term experience with lithium treatment in childhood: correlation with clinical diagnosis. J Am Acad Child Adolesc Psychiatry. 1987;26(3):389–94.
78. DeLong R. Children with autistic spectrum disorder and a family history of affective disorder. Dev Med Child Neurol. 1994;36:674–87.
79. Komoto J, Usui S, Hirata J. Infantile autism and affective disorder. J Autism Dev Disord. 1984;14:81–4.
80. Steingard R, Biederman J. Lithium responsive manic-like symptoms in two individuals with autism and mental retardation. J Am Acad Child Adolesc Psychiatry. 1987;26:932–5.
81. Brendel DH, Bodkin JA, Hauptman B, Ornstein A. "I see dead people": overcoming psychic numbness. Harv Rev Psychiatry. 2002;10:166–78.
82. Bishop DV. Autism, Asperger's syndrome and semantic pragmatic disorder: where are the boundaries? Br J Disord Commun. 1989;24:107–21.
83. Kerbeshian J, Burd L, Fisher W. Asperger's syndrome: to be or not to be? Br J Psychiatry. 1990;156:721–5.
84. Kerbeshian J, Burd L, Fisher W. Lithium carbonate in the treatment of two patients with infantile autism and atypical bipolar symptomatology. J Clin Psychopharmacol. 1987;7(6):401–5.
85. Tsai LY. Medical treatment. In: Berkell Zager DE, editor. Autism: identification, education, and treatment. 2nd ed. Mahweh: Lawrence Erlbaum; 1999. p. 199–257.
86. Krishnamoorthy ES, Trimble MR, Blumer D. The classification of neuropsychiatric disorders in epilepsy: a proposal by the ILAE Commission on Psychobiology of Epilepsy. Epilepsy Behav. 2007;10(3):349–53.

87. Tsai LY. Psychopharmacology in autism. Psychosom Med. 1999;61(5):651–65.
88. Sovner R. The use of valproate in the treatment of mentally retarded persons with typical and atypical bipolar disorders. J Clin Psychiatry. 1989;50:40–3.
89. Hollander E, Dolgoff-Kaspar R, Cartwright C, Rawitt R, Novotny S. An open trial of divalproex sodium in autism spectrum disorders. J Clin Psychiatry. 2001;62(7):530–4.
90. Ruedrich S, Swales TP, Fossaceca C, Toliver J, Rutkowski A. Effect of divalproex sodium on aggression and self-injurious behaviour in adults with intellectual disability: a retrospective review. J Intellect Disabil Res. 1999;43(Pt 2):105–11.
91. Verhoeven WMA, Tuinier S. Cyclothymia or unstable mood disorder? A systematic treatment evaluation with valproic acid. J Appl Res Intellect Disabil. 2001;14:147–54.
92. Bhaumik S, Branford D, Barrett M, Satheesh KG. The Frith prescribing guidelines for people with intellectual disability. 3rd ed. Oxford: Wiley; 2015.
93. Vanstraelen M, Tyrer SP. Rapid cycling bipolar affective disorder in people with intellectual disability: a systematic review. J Intellect Disabil Res. 1999;43(Pt 5):349–59.
94. Reid AH, Naylor GJ, Kay DS. A double-blind, placebo controlled, crossover trial of carbamazepine in overactive, severely mentally handicapped patients. Psychol Med. 1981;11(1):109–13.
95. Smith DA, Perry PJ. Nonneuroleptic treatment of disruptive behavior in organic mental syndromes. Ann Pharmacother. 1992;26(11):1400–8.
96. Uvebrant P, Bauziene R. Intractable epilepsy in children. The efficacy of lamotrigine treatment, including non-seizure-related benefits. Neuropediatrics. 1994;25(6):284–9.
97. Campbell M, Rapoport JL, Simpson GM. Antipsychotics in children and adolescents. J Am Acad Child Adolesc Psychiatry. 1999;38:537–45.
98. Martin A, Koenig K, Scahill L, Bregman J. Open-label quetiapine in the treatment of children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol. 1999;9:99–107.
99. Anderson LT, Campbell M, Grega DM, Perry R, Small AM, Green WH. Haloperidol in the treatment of infantile autism: effects on learning and behavioral symptoms. Am J Psychiatry. 1984;141:1195–202.
100. Campbell M, Anderson LT, Meier M, Cohen IL, Small AM, Samit C, Sachar EJ. A comparison of haloperidol and behavior therapy and their interaction in autistic children. J Am Acad Child Adolesc Psychiatry. 1978;17:640–55.
101. Cohen IL, Campbell M, Posner BA, Small AM, Triebel D, Anderson LT. Behavioural effects of haloperidol in young autistic children. J Am Acad Child Adolesc Psychiatry. 1980;19:665–77.
102. Ernst M, Magee HJ, Gonzalez NM, Locascio JJ, Rosenberg CR, Campbell M. Pimozide in autistic children. Psychopharmacol Bull. 1992;28:187–91.
103. Naruse H, Nagahata M, Nakane Y, Shirahashi K, Takesada M, Yamazaki K. A multi-centre double-blind trial of pimozide (Orap), haloperidol and placebo in children with behavioral disorders, using crossover design. Acta Paedopsychiatr. 1982;48:173–84.
104. Campbell M, Armenteros JL, Malone RP, Adams PB, Eisenberg ZW, Overall JE. Neuroleptic-related dyskinesias in autistic children: a prospective, longitudinal study. J Am Acad Child Adolesc Psychiatry. 1997;36:835–43.
105. Perry R, Campbell M, Adams P, Lynch N, Spencer EK, Curren EL, Overall JE. Long-term efficacy of haloperidol in autistic children: continuous versus discontinuous drug administration. J Am Acad Child Adolesc Psychiatry. 1989;28:87–92.
106. Canitano R, Scandurra V. Risperidone in the treatment of behavioral disorders associated with autism in children and adolescents. Neuropsychiatr Dis Treat. 2008;4(4):723–30.
107. Jensen PS, Buitelaar J, Pandina GJ, Binder C, Haas M. Management of psychiatric disorders in children and adolescents with atypical antipsychotics: a systematic review of published clinical trials. Eur Child Adolesc Psychiatry. 2007;16(2):104–20.
108. McDougle CJ, Holmes JP, Bronson MR, Anderson GM, Volkmar FR, Price LH, et al. Risperidone treatment of children and adolescents with pervasive developmental disorders: a prospective open-label study. J Am Acad Child Adolesc Psychiatry. 1997;36:685–93.

109. McDougle CJ, Scahill L, Aman MG, McCracken JT, Tierney E, Davies M, et al. Risperidone for the core symptom domains of autism: results from the study by the Autism Network of the Research Units on Pediatric Psychopharmacology. Am J Psychiatry. 2005;162:1142–8.
110. Arnold LE, Farmer C, Kraemer HC, Davies M, Witwer A, Chuang S, et al. Moderators, mediators, and other predictors of risperidone response in children with autistic disorder and irritability. J Child Adolesc Psychopharmacol. 2010;20(2):83–93.
111. Malone RP, Maislin G, Choudhury MS, Gifford C, Delaney MA. Risperidone treatment in children and adolescents with autism: short- and long-term safety and effectiveness. J Am Acad Child Adolesc Psychiatry. 2002;41(2):140–7.
112. McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, et al. Risperidone in children with autism and serious behavioral problems. N Engl J Med. 2002;347(5):314–21.
113. McDougle CJ, Scahill L, Aman MG, McCracken JT, Tierney E, Davies M, et al. Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. Am J Psychiatry. 2005;162(6):1142–8.
114. Aman MG, Arnold LE, McDougle CJ, Vitiello B, Scahill L, Davies M, et al. Acute and long-term safety and tolerability of risperidone in children with autism. J Child Adolesc Psychopharmacol. 2005;15(6):869–84.
115. Gagliano A, Germano E, Pustorino G, Impallomeni C, D'Arrigo C, Calamoneri F, et al. Risperidone treatment of children with autistic disorder: effectiveness, tolerability, and pharmacokinetic implications. J Child Adolesc Psychopharmacol. 2004;14(1):39–47.
116. Kowalski JL, Wink LK, Blankenship K, Habenicht CD, Erickson CA, Stigler KA, et al. Paliperidone palmitate in a child with autistic disorder. J Child Adolesc Psychopharmacol. 2011;21(5):491–3.
117. Rausch JL, Sirota EL, Londino DL, Johnson ME, Carr BM, Bhatia R, et al. Open-label risperidone for Asperger's disorder: negative symptom spectrum response. J Clin Psychiatry. 2005;66(12):1592–7.
118. Frazier JA, Meyer MC, Biederman J, Wozniak J, Wilens TE, Spencer TJ, et al. Risperidone treatment for juvenile bipolar disorder: a retrospective chart review. J Am Acad Child Adolesc Psychiatry. 1999;38(8):960–5.
119. Zarcone JR, Hellings JA, Crandall K, Reese RM, Marquis J, Fleming K, et al. Effects of risperidone on aberrant behavior of persons with developmental disabilities: I. A double-blind crossover study using multiple measures. Am J Ment Retard. 2001;106(6):525–38.
120. Kent JM, Kushner S, Ning X, Karcher K, Ness S, Aman M, et al. Risperidone dosing in children and adolescents with autistic disorder: a double-blind, placebo-controlled study. J Autism Dev Disord. 2013;43(8):1773–83.
121. Scahill L, McDougle CJ, Aman MG, Johnson C, Handen B, Bearss K, et al. Effects of risperidone and parent training on adaptive functioning in children with pervasive developmental disorders and serious behavioral problems. J Am Acad Child Adolesc Psychiatry. 2012;51(2):136–46.
122. Stigler KA, Diener JT, Kohn AE, Li L, Erickson CA, Posey DJ, et al. Aripiprazole in pervasive developmental disorder not otherwise specified and Asperger's disorder: a 14-week, prospective, open-label study. J Child Adolesc Psychopharmacol. 2009;19(3):265–74.
123. Hellings JA, Boehm D, Yeh HW, Butler MG, Schroeder SR. Long-term aripiprazole in youth with developmental disabilities including autism. J Ment Health Res Intellect Disabil. 2011;4(1):40–52.
124. Shastri M, Alla L, Sabaratnam M. Aripiprazole use in individuals with intellectual disability and psychotic or behavioural disorders: a case series. J Psychopharmacol. 2006;20(6):863–7.
125. Potenza MN, Holmes JP, Kanes SJ, McDougle CJ. Olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study. J Clin Psychopharmacol. 1999;19(1):37–44.
126. Kemner C, Willemsen-Swinkels SH, de Jonge M, Tuynman-Qua H, van Engeland H. Open-label study of olanzapine in children with pervasive developmental disorder. J Clin Psychopharmacol. 2002;22(5):455–60.

127. Golubchik P, Sever J, Weizman A. Low-dose quetiapine for adolescents with autistic spectrum disorder and aggressive behavior: open-label trial. Clin Neuropharmacol. 2011;34(6):216–9.
128. Findling RL, McNamara NK, Gracious BL, O'Riordan MA, Reed MD, Demeter C, et al. Quetiapine in nine youths with autistic disorder. J Child Adolesc Psychopharmacol. 2004;14(2):287–94.
129. Corson AH, Barkenbus JE, Posey DJ, Stigler KA, McDougle CJ. A retrospective analysis of quetiapine in the treatment of pervasive developmental disorders. J Clin Psychiatry. 2004;65(11):1531–6.
130. McDougle CJ, Holmes JP, Carlson DC, Pelton GH, Cohen DJ, Price LH. A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. Arch Gen Psychiatry. 1998;55(7):633–41.
131. McDougle CJ, Scahill L, McCracken JT, Aman MG, Tierney E, Arnold LE, et al. Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. Background and rationale for an initial controlled study of risperidone. Child Adolesc Psychiatr Clin N Am. 2000;9(1):201–24.
132. Buitelaar JK, Willemsen-Swinkels SH. Medication treatment in subjects with autistic spectrum disorders. Eur Child Adolesc Psychiatry. 2000;9(Suppl 1):I85–97.
133. Carneiro AM, Airey DC, Thompson B, Zhu CB, Lu L, Chesler EJ, et al. Functional coding variation in recombinant inbred mouse lines reveals multiple serotonin transporter-associated phenotypes. Proc Natl Acad Sci U S A. 2009;106(6):2047–52.
134. Carneiro AM, Cook EH, Murphy DL, Blakely RD. Interactions between integrin alphaIIb-beta3 and the serotonin transporter regulate serotonin transport and platelet aggregation in mice and humans. J Clin Invest. 2008;118(4):1544–52.
135. Veenstra-Vanderweele J, Muller CL, Iwamoto H, Sauer JE, Owens WA, Shah CR, et al. Autism gene variant causes hyperserotonemia, serotonin receptor hypersensitivity, social impairment and repetitive behavior. Proc Natl Acad Sci U S A. 2012;109:5469–74.
136. Janušonis S, Anderson GM, Shifrovich I, Rakic P. Ontogeny of brain and blood serotonin levels in 5-HT1A receptor knockout mice: potential relevance to the neurobiology of autism. J Neurochem. 2006;99:1019–31.
137. Azmitia EC, Singh JS, Whitaker-Azmitia PM. Increased serotonin axons (immunoreactive to 5-HT transporter) in postmortem brains from young autism donors. Neuropharmacology. 2011;60:1347–54.
138. Chugani DC, Muzik O, Behen M, Rothermel R, Janisse JJ, Lee J, et al. Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. Ann Neurol. 1999;45(3):287–95.
139. Chugani DC. Role of altered brain serotonin mechanisms in autism. Mol Psychiatry. 2002;7(Suppl 2):S16–7.
140. Murphy DG, Daly E, Schmitz N, Toal F, Murphy K, Curran S, et al. Cortical serotonin 5-HT2A receptor binding and social communication in adults with Asperger's syndrome: an in vivo SPECT study. Am J Psychiatry. 2006;163(5):934–6.
141. Nakamura K, Sekine Y, Ouchi Y, Tsujii M, Yoshikawa E, Futatsubashi M, et al. Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. Arch Gen Psychiatry. 2010;67(1):59–68.
142. Lee ES, Vidal C, Findling RL. A focused review on the treatment of pediatric patients with atypical antipsychotics. J Child Adolesc Psychopharmacol. 2018;28(9):582–605.
143. DelBello MP, Goldman R, Phillips D, Deng L, Cucchiaro J, Loebel A. Efficacy and safety of lurasidone in children and adolescents with bipolar I depression: a double-blind, placebo-controlled study. J Am Acad Child Adolesc Psychiatry. 2017;56(12):1015–25.
144. Loebel A, Brams M, Goldman RS, Silva R, Hernandez D, Deng L, et al. Lurasidone for the treatment of irritability associated with autistic disorder. J Autism Dev Disord. 2016;46(4):1153–63.
145. Millard PH, McLaren JL, Coffey DB. Lurasidone treatment in a child with autism spectrum disorder with irritability and aggression. J Child Adolesc Psychopharmacol. 2014;24(6):354–6.

146. Hurwitz R, Blackmore R, Hazell P, Williams K, Woolfenden S. Tricyclic antidepressants for autism spectrum disorders (ASD) in children and adolescents. Cochrane Database Syst Rev. 2012;(3):CD008372.
147. Williams K, Brignell A, Randall M, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). Cochrane Database Syst Rev. 2013;(8):CD004677.
148. Couturier JL, Nicolson R. A retrospective assessment of citalopram in children and adolescents with pervasive developmental disorders. J Child Adolesc Psychopharmacol. 2002;12(3):243–8.
149. Hollander E, Soorya L, Chaplin W, Anagnostou E, Taylor BP, Ferretti CJ, et al. A double-blind placebo-controlled trial of fluoxetine for repetitive behaviors and global severity in adult autism spectrum disorders. Am J Psychiatry. 2012;169(3):292–9.
150. Khouzam HR, El-Gabalawi F, Pirwani N, Priest F. Asperger's disorder: a review of its diagnosis and treatment. Compr Psychiatry. 2004;45(3):184–91.
151. Steingard RJ, Zimnitzky B, DeMaso DR, Bauman ML, Bucci JP. Sertraline treatment of transition-associated anxiety and agitation in children with autistic disorder. J Child Adolesc Psychopharmacol. 1997;7(1):9–15.
152. Henry CA, Shervin D, Neumeyer A, Steingard R, Spybrook J, Choueiri R, et al. Retrial of selective serotonin reuptake inhibitors in children with pervasive developmental disorders: a retrospective chart review. J Child Adolesc Psychopharmacol. 2009;19(2):111–7.
153. Frazier JA, Biederman J, Bellordre CA, Garfield SB, Geller DA, Coffey BJ, et al. Should the diagnosis of attention deficit hyperactivity disorder be considered in children with pervasive developmental disorder? J Atten Disord. 2001;4:203–11.
154. Henry CA, Steingard R, Venter J, Guptill J, Halpern EF, Bauman M. Treatment outcome and outcome associations in children with pervasive developmental disorders treated with selective serotonin reuptake inhibitors: a chart review. J Child Adolesc Psychopharmacol. 2006;16(1–2):187–95.
155. Sokolski KN, Chicz-Demet A, Demet EM. Selective serotonin reuptake inhibitor-related extrapyramidal symptoms in autistic children: a case series. J Child Adolesc Psychopharmacol. 2004;14(1):143–7.
156. Damore J, Stine J, Brody L. Medication-induced hypomania in Asperger's disorder. J Am Acad Child Adolesc Psychiatry. 1998;37(3):248–9.
157. Todd RD. Fluoxetine in autism. Am J Psychiatry. 1991;148(8):1089.
158. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry. 2013;170(11):1249–62.
159. Grzadzinski R, Di Martino A, Brady E, Mairena MA, O'Neale M, Petkova E, et al. Examining autistic traits in children with ADHD: does the autism spectrum extend to ADHD? J Autism Dev Disord. 2011;41(9):1178–91.
160. Reiersen AM, Todd RD. Co-occurrence of ADHD and autism spectrum disorders: phenomenology and treatment. Expert Rev Neurother. 2008;8(4):657–69.
161. Cortese S, Castelnau P, Morcillo C, Roux S, Bonnet-Brilhault F. Psychostimulants for ADHD-like symptoms in individuals with autism spectrum disorders. Expert Rev Neurother. 2012;12(4):461–73.
162. Di Martino A, Melis G, Cianchetti C, Zuddas A. Methylphenidate for pervasive developmental disorders: safety and efficacy of acute single dose test and ongoing therapy: an open-pilot study. J Child Adolesc Psychopharmacol. 2004;14(2):207–18.
163. Stigler KA, Desmond LA, Posey DJ, Wiegand RE, McDougle CJ. A naturalistic retrospective analysis of psychostimulants in pervasive developmental disorders. J Child Adolesc Psychopharmacol. 2004;14(1):49–56.
164. Posey DJ, Aman MG, McCracken JT, Scahill L, Tierney E, Arnold LE, et al. Positive effects of methylphenidate on inattention and hyperactivity in pervasive developmental disorders: an analysis of secondary measures. Biol Psychiatry. 2007;61(4):538–44.

165. Munesue T, Ono Y, Mutoh K, Shimoda K, Nakatani H, Kikuchi M. High prevalence of bipolar disorder comorbidity in adolescents and young adults with high-functioning autism spectrum disorder: a preliminary study of 44 outpatients. J Affect Disord. 2008;111(2–3):170–5.
166. La Malfa G, Lassi S, Salvini R, Giganti C, Bertelli M, Albertini G. The relationship between autism and psychiatric disorders in Intellectually Disabled Adults. Res Autism Spectr Disord. 2007;1:218–28.
167. Fitzgerald M. Misdiagnosis of Asperger syndrome as anankastic personality disorder. Autism. 2002;6(4):435.
168. Einfeld SL, Tonge BJ. Population prevalence of psychopathology in children and adolescents with intellectual disability: I. Rationale and methods. J Intellect Disabil Res. 1996;40(2):91–8.
169. Barneveld PS, Pieterse J, de Sonneville L, van Rijn S, Lahuis B, van Engeland H, et al. Overlap of autistic and schizotypal traits in adolescents with Autism Spectrum Disorders. Schizophr Res. 2011;126(1–3):231–6.
170. Esterberg ML, Trotman HD, Brasfield JL, Compton MT, Walker EF. Childhood and current autistic features in adolescents with schizotypal personality disorder. Schizophr Res. 2008;104(1–3):265–73.
171. Lugnegard T, Hallerback MU, Gillberg C. Personality disorders and autism spectrum disorders: what are the connections? Compr Psychiatry. 2012;53(4):333–40.