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Review

Bipolar disorder in adults with Asperger's Syndrome: A systematic review

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ABSTRACT

Background: Asperger's Syndrome (AS) is a neurodevelopmental disorder included in the Autism Spectrum (ASD). The current literature shows growing evidence of a high rate of comorbidity between AS and other psychiatric disorders, particularly Bipolar Disorder (BD). We reviewed available epidemiological and clinical data on BD–AS comorbidity and its diagnostic and therapeutic implications

Methods: A systematic review of the literature was conducted through PubMed, Scopus and Psych-Info using combinations of the following search terms: Asperger's Syndrome, Bipolar Disorder, depression, mood disorder, psychiatric comorbidity, treatment, mood stabilizers, anticonvulsants, antipsychotics, and antidepressants.

Results: BD prevalence in adults with AS ranges from 6% to 21.4% of the cases. Relatives of patients with AS showed a doubled risk of being affected by BD and a BD prevalence near to 10%. When comorbid with AS, BD assumes peculiar features which might shape its under-recognition or misdiagnosis (especially schizophrenia when psychotic symptoms are prominent). Although controlled data on pharmacological treatments in BD–AS comorbidity are substantially lacking, information is derived by open observations, case series and chart reviews. Mood stabilizers should be considered the first choice, and antipsychotics, especially second generation drugs (SGA) with 5-HT2a antagonism, have been shown useful in controlling psychotic and behavioral symptoms and improving social withdrawal. Some evidence of efficacy for the treatment of anxiety, obsessive-compulsive symptoms and depression is reported for SSRI antidepressants. The use of these drugs should be carefully monitored, because activation with hypomanic or manic switches is reported up to 54% of the treated subjects.

Conclusion: BD in AS patients is frequent, usually it onsets during adolescence and is often characterized by atypical presentation, making its correct identification particularly difficult. A correct diagnosis of BD in AS individuals has relevant implications on the choice of adequate psychopharmacological, psychosocial and rehabilitative treatments.

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1. Introduction

Asperger's Syndrome (AS), formerly recognized as a specific diagnostic entity in DSM-IV-TR, has been recently included by DSM-5 in the Autism Spectrum Disorders (ASD), together with other Pervasive Developmental Disorders. ASD currently lump together different heterogeneous clinical subtypes such as AS and severe autism, based on a dimensional perspective. This DSM-5 spectrum view permit to include on the broad autistic spectrum not only AS but also many other ASD-variants labeled "high functioning autisms" (HFA) till now. In this perspective new severity "specifiers" permit to distinguish different ASD phenotypes. Indeed, high functioning autisms might be better indicated as ASD with "less marked general impairment" only "requiring support" (level 1), while classical "low functioning "autisms (e.g. with intellectual and language impairment) as "requiring very substantial support" (level 3).

Although it is true that diagnostic criteria are flawed and difficult to implement in clinical practice, patients with AS usually show some peculiar features and a less marked general impairment compared with other autistic phenotypes. Although intelligence and language abilities are always preserved, they usually present atypical features. Cognitive profile can be uneven, with high verbal abilities compared with poor non-verbal skills, visuo-spatial problem solving, and motor performances (included uncoordinated motion, clumsiness, and illegible handwriting). Furthermore, language is formally adequate and often precocious (particularly in lexicon), but usually pedantic, monotonous and poorly communicative. Typically, their ability to recognize non-verbal signals and social-emotional reciprocity are variously impaired. Moreover, AS subjects tend to show highly restricted and fixated interests that are abnormal in intensity or focus, associated with inflexible adherence to routines and hard and fast rules.

Considered a relatively common diagnosis in childhood and adolescence, AS has only recently gained some attention in adults. The data relative to AS prevalence are variable especially in reason of the dispute concerning the distinction from HFA. When not only AS is included in HFA but also many other high functioning ASD-variants the prevalence is likely to be much higher. Moreover, major psychiatric comorbidities, especially with mood disorders and psychoses, may contribute to the underestimation of AS. Indeed, reliable data on the actual AS prevalence among adults are not available. In childhood, the prevalence is estimated to be between 0.02% and 12.27% (Baird et al., 2000; Fombonne and Tidmarsh, 2003; Mattila et al., 2007). Similarly to other ASD forms, AS is considered a "life-long" disorder (Shattuck et al., 2007); as a result, its prevalence in adulthood could be comparable to that seen in childhood (Tantam and Girgis, 2009). Nonetheless, its phenotypic expression may vary in relation to age (Roy et al., 2009) and gender (Lai et al., 2011). Different outcomes can be observed on the basis of the severity of the symptoms: some individuals reach a functioning comparable to that of the general population, showing high levels of adaptation. On the contrary, other subjects present psychopathological manifestations and unusual behaviors, up to suffer from serious functional deficits.

In adults, psychiatric intervention is usually required for the presence of comorbid mental disorders, including both anxiety and mood disorders and disruptive disorders, with impulsivity and aggression. Attention deficit hyperactivity disorder (ADHD) is also often comorbid with both AS and affective disorders. In such contexts, the diagnosis of AS is often underestimated or missed (Raja and Azzoni, 2008; Skeppar et al., 2013). On the other hand, the diagnosis of comorbid psychiatric disorders may also be complicated by the high frequency of atypical manifestations (Tantam and Girgis, 2009). One of the most common comorbidities in clinical settings is Bipolar Disorder (BD). The purpose of this review is to examine the relationship between AS and BD and their epidemiological, clinical and therapeutic implications.

2. Methods

A systematic review of the existing literature has been conducted through PubMed and Scopus using combinations of the following search terms: Asperger's Syndrome (AS), Autism Spectrum Disorders (ASD), Bipolar Disorder, depression, mood disorder, psychiatric comorbidity, treatment, mood stabilizers, anticonvulsants, antipsychotics, and antidepressants along with terms related to each of the areas of focus listed above. For prevalence and family data we considered eligible all the studies on general and clinical populations exploring AS and mood disorders in adults. We also considered data concerning other ASD variants, mostly the conditions labeled as HFA. This choice seems appropriate considering that several studies did not explicitly distinguish AS from other HFA.

For clinical implications, in reason of substantial lack of systematized studies on adults exploring clinical expression of mood disorders and phenotypes in adult AS, we reported available clinical studies, case-reports, case-series and expert descriptions. Regarding pharmacologic treatments, RCT only considering AS–BD adults are not available. So we mash up information from available clinical studies, case-reports, case-series and expert descriptions in adults and we report some results of RCT in adolescents, which seem to be pertinent to our discussion. Reference lists from each article were assessed for additional citations of interest. Unless otherwise specified, the studies included are referred to adults. We excluded articles in languages other than English. Two reviewers (G.V. and G.P.) evaluated the results of the searches on the basis of title and/or abstract and assessed them for the suitability for inclusion on the basis of full publications.

Table 1
Comorbidity rates of Bipolar Disorder and Asperger's Syndrome in adulthood.

Study	Type of study	Sample characteristics	Control group	Prevalence rates
Youths				
Axelson et al. 2006	Evaluation psychiatric comorbidity in clinical population of BD out- and in patients.	144 bipolar subjects: 7–17 years	None	AS+PDD-NOS= from 2.0 to 3.3%
Rosenberg et al. 2011	Online research database IAN-Community study.	4343 ASD subjects: 5–18 years	AS vs. autism	BD= 8.6% vs. 3.0% BD rate grows with the age: from 2.3% to 10.4%
Adults				
Tantam 1991	Follow-up history of AS subjects.	95 adult AS subjects	None	BD=8.4%
Stahlberg et al. 2004	Evaluation psychiatric comorbidity in ADHD or ASD subjects	129 ASD subjects (Autism 13, AS 49, Atypical Autism 67): 19–60 years	None	BD+autism=0% BD+AS=6% BD+atypical autism=9%
Munesue et al. 2008	Evaluation mood disorders comorbidity in outpatients population.	44 HFA subjects(27 AS): >12 years	None	BD=12.0% → BD I=2% BD II=6% BD-NOS=4%
Raja and Azzoni 2009	Case-series of AS–BD comorbidity	AS adult subjects	None	BD=21.4%
Hofvander et al. 2009	Evaluation psychiatric comorbidity in clinical population of ASD, normal IQ, subjects.	122 ASD (autism 2%, AS 74%, PDD-NOS 18%): 16–60 years	None	BD=8.5% → BD I=4.3% BD II= 1.7%

BD: Bipolar Disorder; AS: Asperger's Syndrome; PDD-NOS: Pervasive Developmental Disorder Not Otherwise Specified; ADHD: Attention Deficit/Hyperactivity Disorder; HFA-ASD: High-functioning Autism

3. Results

3.1. Comorbidity rates of Bipolar Disorder and Asperger's Syndrome in adulthood

Data regarding comorbidity between BD and AS in adults are relatively few and controversial (Table 1), although the presence of depressive symptoms and episodes of manic-depressive illness has been reported since the first descriptions of ASD (Rutter, 1970).

Most of the available literature on comorbidity between AS and Mood Disorders (MD) are limited to childhood and adolescence and, in generalizing the results to adulthood, some limitations should be considered. In clinical samples of very young subjects, with high frequency of atypical presentations of BD, depressive symptoms and psychiatric comorbidity may be more represented than hypomanic and manic symptoms, which could become manifest later in the course of the illness (Frazier et al., 2002; Tantam and Girgis, 2009).

Wozniak et al. (1997) explored the overlap between ASD and BD in an outpatient pediatric sample, and found that 21% of the youth with ASD had a comorbid BD, and 11% of the patients with BD had a comorbid ASD. More recently the same research group examined rates of ASD in a large set of 155 youth probands with BD I and found that up to 47 patients (30.3%) met criteria for ASD. This comorbidity was associated with and earlier onset of BD. The familial correlates and the phenotypic expression were similar in BD patients, irrespective of the association with ASD (Joshi et al., 2013).

In a clinical sample of 144 subjects aged between 7 and 17 years and suffering from a Bipolar Spectrum Disorder (BDS), referred to a third-level university centers, the prevalence of AS and PDD NOS, taken together, was 2.1% (respectively 2.0% in the BD type I, 3.3% in the BD type II and 2.0% in the BD NOS) (Axelson et al., 2006).

Rosenberg et al. (2011) estimated MDs prevalence among ASD patients and their relatives throughout the Interactive Autism Network (IAN). Of the 4343 ASD children and adolescents recruited, aged between 5 and 18, 1150 had an AS. BD is much more common in AS compared to autism (8.6% vs. 3.0%) and BD prevalence increases with growing age (from 2.3% to 10.4%) considering the overall sample. Furthermore, the authors reported that the comorbidity with at least one anxiety disorder correlates with an increased risk of developing BD (OR=1.7, CI=1.2–2.2). These data highlight that BD in AS subjects most commonly onsets in adolescence, further rising during young adulthood.

Clinical studies on adult population (Ghaziuddin and Greden, 1998, 2002; Bryson et al., 2008; de Bruin et al., 2007) indicated unipolar depression as the most common MD, with rates even higher than 50% (Lugnegard et al., 2011). Only Munesue et al. (2008) reported a different trend in this respect. In a third-level university center the Authors evaluated 44 subjects with high-functioning ASD, aged between 13 and 39 years, 27 of whom had a diagnosis of AS. MD comorbidity was observed in 36.4% of the patients, among whom 75% were affected by BD (BD type I 12.5%, BD type II 37.5%, BD NOS 25%). In a Swedish sample of 54 AS adult outpatients of Regional Centers of Public Health, BD prevalence were 9%: all patients received a BD type II diagnosis with a slight preponderance in the female gender (11% vs. 8%) (Lugnegard et al., 2011).

In another study carried out in two clinical centers in Paris and the third level center in Gothenburg (Hofvander et al., 2009), the 8.5% of the patients with ASD and normal intelligence were diagnosed with BD (4.3% BD type I, 1.7% BD type II). Similarly, analyzing data from the Gothenburg Neuropsychiatric Genetics Project, a BD diagnosis was observed in 3 (6%) out of 49 adults with AS (Stahlberg et al., 2004). High BD prevalence (21.4%) has been reported also in an Italian sample of 14 adults with AS, recruited in an inpatient Psychiatric Service; in 2 cases the manic symptoms had appeared after antidepressant treatment (Raja and Azzoni, 2008). Finally, Tantam describing a series of 95 adult patients with AS, found a history of psychotic disorders in 21.4% of the cases; 8 of these patients also reported previous episodes of mania (Tantam, 1991).

In summary, in clinical researches on adult AS, BD comorbidity ranges from 6% to 21.4% of the cases. The variability of rates may be accounted for by differences in sample selection and diagnostic criteria, and quite often data are drawn from post-hoc observations of non-specific study designs. Moreover results do not refer to specific clinical phenotypes but generically to ASD, in some cases regardless of the IQ subtyping. Finally, since the available data refer only to clinical samples, they should not be considered representative of the general population.

3.2. Familial comorbidity

Familial studies confirm the association between AS and BD among AS relatives (Bolton et al., 1998; Ghaziuddin and Greden, 1998; Piven and Palmer, 1999). Asperger (1944) himself was convinced that the syndromic picture he described had "by nature an important load of inheritance".

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 (Gillberg and Gillberg, 1989). Several studies reported higher prevalence of depression and BD among ASD patients' relatives compared to family members of children with other types of disabilities (Bolton et al., 1998; Lajiness-O'neill and Menard, 2008; Piven et al., 1991). Familiarity for MDs seems to represent an important determinant for more specific clinical phenotypes. DeLong has suggested that there are two distinct classes ("taxa") of ASDs: the first usually consists of high-functioning subjects, with prominent anxiety, obsessive symptoms, a mood imbalance and a positive family history for major MDs. In the other class of ASDs, language and learning disorders and lack of family history for MDs represent discriminant characteristics (DeLong, 2004). In a 1988 study DeLong and Dwyer (1988) 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 (DeLong and Nohria, 1994). The majority of the studies on psychiatric morbidity of ASD patients' parents show that the MD onset usually precedes the birth of the ASD offspring. This observation seems to suggest the prevalence of biological and genetic underpinnings in MDs among relatives of particularly high-functioning ASD patients; on the contrary, a reactive component linked to the stress of caregiving a disabled child might have less pathogenetic weight (Bolton et al., 1998; Cohen and Tsiouris, 2006).

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 MDs (Ghaziuddin, 2005). The author noted that not having found a specific correlation with BD might be attributable to the use of diagnostic criteria different from previous studies.

A recent U.S. study (Vasa et al., 2012), carried out on 988 couples of mother and child participating in the online research project named IAN, examined the potential association between maternal history of MD and high-functioning ASD phenotypes. 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 AS probands compared with autistics' mothers. Women with a MD, particularly those with BD, showed higher rates of depressive recurrences; moreover, the majority of mothers affected by depression and BD reported the MD onset as preceding the first pregnancy. On the other hand, the BD history in this population was associated with a significantly higher risk of bearing an AS than autistic child (OR 2.11, CI 1.20–3.69).

To sum up, AS seems more closely related to BD than other ASDs and among the relatives of AS patients high prevalence of MDs, in general, and BD, in particular, have been found.

3.3. Clinical features

Large systematic studies exploring clinical features of bipolar disorder in AS during adulthood are substantially lacking. However, useful indications can be obtained from case-reports, case-series and expert opinions as well as studies in adolescents.

Consistently with our experience, Skeppar et al. (2013) observed that comorbid affective disorders in adults with AS are often diagnosed as Schizophrenia because of the atypical presentations of the mood episodes and the peculiarities of the inter-episodic behavioral patterns.

Manic episodes in adult AS seem to be frequently characterized by mixed features such as irritable, instable and dysphoric mood, hostility, restlessness, anxiety, perplexity, aggression, violent behavior and insomnia, while classic euphoric mood, elation and jocularity seem to be very uncommon (Frazier et al., 2002; Joshi et al., 2013; Ng et al., 2003; Raja and Azzoni, 2008, 2009; Skeppar et al., 2013). To our knowledge, however, frequencies of mixed vs. classic manic features were not systematically studied in this context.

In many cases psychotic symptoms might overwhelm other features. Indeed, during manic phases hallucinations, psychotic interpretations and delusional ideas (mostly with persecutory, reference and grandiose content) may be so prominent that other manic symptoms remain unrecognized (Ng et al., 2003; Raja and Azzoni, 2008, 2009; Skeppar et al., 2013). 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 AS subjects also during euthymia (Fitzgerald, 2012; Ghaziuddin et al., 1998; Loveland et al., 2001; Raja and Azzoni, 2009). It has been suggested that during manic episodes the peculiar way of thinking of AS subjects becomes more prominent or that they become more prone to share their thoughts with the others (Fitzgerald, 2012; Skeppar et al., 2013).

This is an important node for the distinction from other psychotic conditions. 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 AS than in schizophrenia (Abell and Hare, 2005; Fitzgerald, 2012). Proper systematic studies exploring affective symptoms with rating scales (e.g. MADRS and BDI), during these stable and long-lasting phases are lacking. Hence, the qualitative difference in the bizarreness of thoughts between AS and patients diagnosed as schizophrenic may be related to persisting low-grade affective symptoms in AS. Both concomitant affective symptoms in the stable phase, and some AS peculiarities may individually or together produce the clinical picture of schizophrenia.

In BD type II and other soft bipolar spectrum conditions, the correct identification of elation is even harder, particularly if it is characterized by irritability, excessive mood reactivity, increase of energy and activity, psychomotor activation and diminished need for sleep. Such symptoms might be elicited by the difficulty in the modulation of arousal, for example when changing routines or during exposition to new and/or social situations (Leibenluft, 2011; Leibenluft et al., 2003, Mazzone et al., 2012). For this reason, an accurate clinical interview is necessary and the systematic use of specific assessment instruments for mood symptoms may be helpful, especially when recurrences and cyclicity are observed and a bipolar diathesis should be suspected (Dejong and Frazier, 2003; Frazier et al., 2002; Magnuson and Constantino, 2011; Tantam and Girgis, 2009). The presence of a family history for BD in first-degree relatives, special abilities, anxiety and/or multiple psychiatric comorbidities and comorbid Tourette's Syndrome are other important indicators of bipolarity (Bolton et al., 1998; Delong, 2004; Ghaziuddin et al., 2002; Kerbeshian and Burd, 1996; Mcelroy, 2004; Piven and Palmer, 1999; Rosenberg et al., 2011; Sterling et al., 2008).

In AS individuals, depression may be not recognized, because it is frequently characterized by mild severity and long-lasting, often

chronic, course. Depressive symptoms are not easily evidenced if not specifically investigated and their impact on social and personal functioning is easily confused with some of the core autistic dimensions, e.g. blunt affect and social withdrawal (Skeppar et al., 2013). Moreover, difficulties in social communication and introspection, idiosyncratic thinking and feelings might add difficulties in investigating or correctly interpreting the "inner" dimension of depression (Rosenberg et al., 2011; Skeppar et al., 2013). To improve the capacity of detecting depression in clinical settings, it could be useful the systematic utilization of specific assessment instruments, both self- and hetero-administered rating scales (e.g. MADRS, BDI).

The reduction of the number and involvement in usual interests and activities, anhedonia, apathy, feelings of worthlessness or guilt, low self-esteem and recurrent thought of death, diminished concentration, indecisiveness are common as in other depressive patients (Ghaziuddin et al., 2002; Magnuson and Constantino, 2011; Mazzone et al., 2012; Tantam and Girgis, 2009). Equally important are neuro-vegetative signs, such as changes in appetite or weight and new-onset sleep disturbances (from hypersomnia to insomnia) (Ghazziuddin and Zafar, 2008; Magnuson and Constantino, 2011; Rao and Chen, 2009; Rosenberg et al., 2011). As well as for hypomanic or manic phases, the diagnosis of depression in AS subjects is more difficult when mixed features predominate the clinical picture. Mood instability, atypical, violent and sudden affective changes, from lability to irritability, aggression, self-injuring and agitation are not uncommon (Lainhart and Folstein, 1994; Naidu et al., 2006; Spencer et al., 2011; Tantam and Girgis, 2009).

Little attention has been paid to the possible combination of ADHD and AS in adulthood. In particular during the process of first ADHD-diagnosis in adults, a comorbid AS is scarcely taken into account. ASD and ADHD share about 50–72% of their genetic factors, which is the most likely explanation for their frequent co-occurrence within the same patient or family (van Steijn et al., 2012). Based on a national online registry to examine variation in cumulative prevalence of community diagnosis of psychiatric comorbidity in 4343 children with autism ASD, ADHD resulted the most frequently reported comorbidity (38.1%) (Rosenberg et al., 2011). Given that ADHD can be an antecedent of mood disorders, namely BD (Masi et al., 2012), an early diagnosis of ADHD may be a window of opportunity for a timely recognition of BD, a more precise clinical characterization, and a more effective treatment plan.

Consistently with our experience, movement disorders and catatonia have also been frequently reported in adults with AS and ASD (Takaoka and Takata, 2007; Fink, 2013; Quigley et al., 2009). Catatonia can be identified in the 12–17% of clinical samples of ASD adolescents and young (Wing and Shah, 2000; Billstedt et al., 2005). In the study of Wing and Shah the 47% of catatonic ASD patients had received an AS diagnosis. Catatonia in ASD subjects seems to be often associated with repetitive self-injuries, posturing and negativism (Fink, 2013). In those cases, while lorazepam has demonstrated a certain efficacy, electroconvulsive therapy seems to be the most and persistently successful treatment (Kakooza-Mwesige et al., 2008).

3.4. 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 (Doyle and Mcdougle, 2012).

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

3.4.1. Mood stabilizers

Although controlled studies are substantially lacking, numerous case reports and case-series support the efficacy of lithium for mood instability and cyclicity in ASD subjects, both in childhood and in adulthood (DeLong and Aldershof, 1987; DeLong, 1994; Komoto et al., 1984; Steingard and Biederman, 1987). Some authors recommend lithium as the first choice for the treatment of manic symptoms, especially in those AS patients with a heavy BD family history (Brendel et al., 2002; Bishop, 1989; Kerbeshian and Fisherw, 1990). Positive family history (Piven et al., 1991), 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 (Kerbeshian et al., 1987) are considered predictors of favorable lithium response. Lithium seems to be effective in controlling aggression and hyperactivity in some cases, as well as in reducing manic symptoms and mood swings (Tsai, 1999a).

Valproate is the anticonvulsant with the largest number of observations in comorbid ASD and BD. It is not clear whether the anticonvulsants have an impact on the autistic "core" symptoms beyond the control of epilepsy, often associated. Several reports, in adults, suggest its efficacy in mitigating hyper-arousal symptoms, including irritability, dysphoria and anxiety (Tsai, 1999b). Sovner (1989) described the favorable effect of valproate in ASD subjects with mental retardation and typical and atypical BD, including rapid cycling. In a retrospective study on 14 patients with AS or PDD-NOS, valproate has been proved to be effective on affective instability, impulsivity and aggression, independently from the presence of seizures and EEG abnormalities (Hollander et al., 2001). There are also few observations of oxcarbazepine efficacy in combination with low doses of second-generation antipsychotics in low doses in AS–BD adults (Raja and Azzoni, 2008).

3.4.2. Antipsychotics

The literature on antipsychotics in ASDs is more consistent, although mainly referred to small samples of children and adolescents. Moreover, the populations selected for clinical trials comprised mainly individuals with severe behavioral problems, without a clear distinction among specific clinical phenotypes, IQ level and presence of psychiatric comorbidity. As a consequence data derived from these studies seem to be poorly generalizable.

In the past, the first generation antipsychotics (FGA) were the most prescribed drugs (Campbell et al., 1999; Martin et al., 1999). The efficacy of haloperidol in mitigating motor stereotypies, hyperactivity, emotional outbursts and temper tantrums has been demonstrated since the late 70's (Campbell et al., 1978; Cohen et al., 1980; Anderson et al., 1984) A similar effect has been attributed to pimozide (Naruse et al., 1982; Ernst et al., 1992). Both these drugs were frequently associated with extrapyramidal symptoms (EPS) and dyskinesias (5–15%) (Campbell et al., 1997; Perry et al., 1989).

In the last decades FGA have been replaced by second-generation antipsychotics (SGA). Among SGAs risperidone and aripiprazole have been extensively studied and represent the only ones with a FDA indication for the treatment of irritability in ASD children (Politte and Mcdougle, 2014). Risperidone, widely used in ASD children and adolescents, has proved its effectiveness in reducing repetitive, aggressive and impulsive behaviors and in improving some aspects of sociality (Canitano and Scandurra, 2008; Jensen et al., 2007; Mcdougle et al., 1997, 2005). Severity of irritability and aggressive behavior seems to represent a positive response predictor, especially as far as irritability dimension is

concerned (Arnold et al., 2010). Although to lesser extent than haloperidol, risperidone often induces EPS and tardive dyskinesia; in addition weight gain, drowsiness, and hyperprolactinemia are frequent and, in some cases, would require drug discontinuation (Malone et al., 2002; Mccracken et al., 2002; Mcdougle et al., 2005; Aman et al., 2005; Gagliano et al., 2004). Recently paliperidone has been suggest as an alternative, even in long-acting formulation (Kowalski et al., 2011). The only study on risperidone in AS showed a significant reduction in negative symptoms in the 70% of 13 subjects (6–12 years-old) treated with risperidone (Rausch et al., 2005). Risperidone is widely used, in childhood as well as in adulthood, for the treatment of manic symptoms and related behavioral problems in BD (Frazier et al., 1999). In the case-series described by Raja and Azzoni (2008), risperidone low-doses associated with anticonvulsants have shown a good efficacy in the therapy of BD–AS comorbidity.

Aripiprazole (mean dose 7.5 mg/day) was effective in reducing irritability, aggression, self-injury and temper tantrums in 88% of cases in a study on children and adolescents with AS and PDD-NOS (Stigler et al., 2009). The drug was well tolerated in the short term and the most common side effects were: weight gain, hyperprolactinemia, dose-dependent sedation and sialorrhoea. The long-term prevalence of EPS and tardive dyskinesia is not negligible and requires careful monitoring.

Olanzapine demonstrates little effect on specific ASD symptoms; its use is also burdened by side effects such as sedation and weight gain (Potenza et al., 1999; Kemner et al., 2002). The role of quetiapine in ASDs is also uncertain; the drug showed some efficacy in the control of aggressive behavior and sleep disturbances, but did not seem to influence autistic symptoms (Golubchik et al., 2011; Findling et al., 2004; Corson et al., 2004). For these reasons, olanzapine and quetiapine should not be considered first choice drugs in the treatment of ASDs. Specific studies, looking at the use of SGAs in AS patients with and without BD, are lacking.

Data from clinical trials have been examined to evaluate the antimanic short-term (8 weeks) effectiveness of various SGA (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole) in youth with comorbid ASD and BD. Twenty-three out of 151 BD patients (15%) presented a comorbid ASD. 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% at the same measure (Joshi et al., 2012).

Molecular and biological studies in subjects with ASD observed some alterations involving the serotonergic system such as “hyperserotoninemia” (Carneiro et al., 2009, 2008; Veenstra-Vanderweele et al., 2012; JanušOnis et al., 2006), high brain tissue 5-HT concentration, especially in the cortex (Azmitia et al., 2011), alteration in the brain 5-HT synthesis (Chugani et al., 1999; Chugani, 2002), reduction of the 5-HT2A receptor binding capacity (Murphy et al., 2006) (negatively related to the platelet 5-HT concentration), reduction of the 5-HTT binding capacity, especially in the anterior and posterior cingulate cortex (Nakamura et al., 2010). Although these results are not always replicated, they represent one of the most interesting perspective research on the pathophysiological basis of ASDs. These findings constitute the rationale for the choice of drugs with antagonism to the dopamine receptors joined with a serotonergic activity, by using antipsychotics highly selective on the serotonin transporter (5-HTT) and the 5-HT2A receptors (Mcdougle et al., 1998, 2000; Buitelaar and Willemsen-Swinkels, 2000). Among the SGA, risperidone and aripiprazole are the most potent antagonists of 5-HT2A receptors, while, among the FGA, chlorpromazine should be mentioned.

3.4.3. Antidepressants

Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI) have been widely described for the treatment of comorbid anxiety, depressive and obsessive symptoms in ASD patients, both in childhood-adolescence and in adulthood. However there is not any evidence of antidepressants efficacy in ASD (Hurwitz et al., 2012; Williams et al., 2013). Studies investigating their use in cases with comorbid BD are lacking; however, information can be drawn from a number of 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 (Couturier and Nicolson, 2002; Hollander et al., 2012; Khouzam et al., 2004; Steingard et al., 1997; Tantam and Girgis, 2009). However results are contradictory in youth and not conclusive in adulthood (Williams et al., 2013). In the case of ineffectiveness of an SSRI, a second attempt with a different SSRI has been reported as “often unsuccessful” (Henry et al., 2009).

Especially in children and adolescents, the use of these drugs should be carefully monitored, because SSRI antidepressants often cause activation, with increased agitation, aggression, self-injuring, insomnia, suicidal and, in some cases, also homicidal thoughts (Frazier et al., 2001; Henry et al., 2006); EPS have also been reported (Sokolski et al., 2004). In a study focused on the short-term outcome, charts were reviewed for 89 young outpatients, with a DSM-IV diagnosis of PDD, who were treated with SSRIs. Although 44.9% of the subjects were considered responders, the 54% showed activation that, in the 35.4% of them, led to drug discontinuation (Henry et al., 2006).

In AS subjects with comorbid BD these problems may be more pronounced and there are several observations and case series showing that antidepressants, especially SSRIs, can cause hypomanic or manic switches (Damore et al., 1998; Ng et al., 2003; Raja and Azzoni, 2008; Todd, 1991). In addition, antidepressant therapy may result in a negative effect on the BD long-term course causing increased affective instability, chronic mixed states and rapid cycling (Pacchiarotti et al., 2013; Henry et al., 2006).

For AS patients with depressive or anxiety symptoms it is therefore necessary a very careful personal and family medical history survey to exclude a bipolar diathesis. It is also required a careful monitoring of the treatment for the early detection of side effects. The possible use of an antidepressant in combination with a mood stabilizer reduces but does not eliminate the possibility of mood switches and mood destabilization (Pacchiarotti et al., 2013).

3.4.4. Stimulants

No controlled studies explored the use of stimulants (methylphenidate [MPH], dexmethylphenidate, dextroamphetamine, mixed amphetamine salts, dextromethamphetamine and lysdexamfetamine) in adults with AS–BD. However, taking into account the high rate of comorbidity between AS and ADHD (Grzadzinski et al., 2011), it seems to be appropriate to mention the literature data regarding the use of stimulants in AS and other ASD presenting with ADHD or ADHD-like symptoms. Research in this field is lacking especially because DSM-IV-TR ADHD criterion E did not allow an ADHD diagnosis in ASD. This is also one of the reasons because ADHD-like symptoms in this population are often under-recognized and under-treated, although some patients with HFA, in particular with AS, refer to clinical setting for ADHD and not for mild ASD symptoms (Reiersen and Todd, 2008).

Recently, Cortese et al. (2012) systematically reviewed the current literature on the efficacy and tolerability of stimulants for ADHD-like symptoms in individuals with ASD, assessing both randomized-controlled and uncontrolled studies. They also

examined expert commentaries. Results showed that stimulants might be effective in ASD in the treatment of ADHD-like symptoms. The frequency of adverse events was higher than that commonly seen in children with ADHD without ASD. However, stimulants seem to be more efficacious and better tolerated in AS than in other ASD (Di Martino et al., 2004; Stigler et al., 2004). The adverse events more commonly reported are: decreased appetite (especially with medium and high doses of methylphenidate), difficulty falling asleep, stomach or abdominal discomfort, irritability and emotional outburst (RUPP, 2005; Posey et al., 2007).

4. Discussion

An increasing body of evidence indicates a frequent association between BD and AS in clinical samples, although it is difficult to estimate the actual prevalence of this comorbidity in general population. The literature also strongly supports that ASDs may be associated with a family history for mood disorders (Bolton et al., 1998; Ghaziuddin, 2005; Lajiness-O'neill and Menard, 2008; Piven et al., 1991) and that the most frequent association is reported with BD in family members of AS patients (DeLong and Dwyer, 1988; DeLong, 2004; Vasa et al., 2012). This last finding suggests that AS is probably more homogenous than ASD (DeLong and Nohria, 1994; Rosenberg et al., 2011). On the other hand, in genetic research AS is not considered as a distinct diagnostic category from other ASDs. Further research taking into account more specific phenotypes and patterns of comorbidity is necessary.

Up to 20% of AS subjects referred to clinical settings report BD comorbidity (Munesue et al., 2008; Raja and Azzoni, 2008). Many of these patients are not adequately diagnosed and appropriately treated (Fitzgerald, 2002, 2012; Raja and Azzoni, 2008; Skeppar et al., 2013). AS has been introduced in the official classification of mental disorders for the first time with the DSM-IV and, for many adult psychiatrists, it is a relatively unfamiliar diagnostic category. The presence of AS is often not correctly identified and the related features are interpreted as personality and/or schizophrenia spectrum disorders (Barneveld et al., 2011, Esterberg et al., 2008; Fitzgerald, 2002, 2012; Lugnegard et al., 2012, Skeppar et al., 2013). The BD–AS comorbidity is also burdened by the "diagnostic overshadowing" phenomenon. Indeed, in adolescents affective and behavioral derangement are often overlooked or attributed to the AS rather than to any mood disorder, in spite of their episodic or cyclic course (DeJong and Frazier, 2002). On the other hand, psychiatrists may neglect AS features in adult BD subjects (Einfeld and Tonge, 1996).

In adult patients with comorbid AS and MDs, Schizophrenia is a frequent misdiagnosis (Skeppar et al., 2013). This is mainly due to the following reasons: 1. The (hypo)manic phases are often characterized by irritability, aggression, outbursts of anger more than typical manic signs, e.g. euphoric mood. If present, psychotic symptoms often become predominant on the clinical picture, shifting clinician attention more on psychotic than affective domain; 2. the depressive phases often tend to be chronic and attenuated. Rather than mood and affectivity, motivation, volition, and psychomotor domains are mainly involved, widely overlapping with the area of the negative and residual symptoms of schizophrenia; 3. odd thinking, bizarre ideas and idiosyncratic views can be interpreted as delusional or psychotic thoughts. These features in ASD both become more frequent and take on psychotic value during affective episodes; 4. the categorical DSM-mediated approach, based on the search of operational criteria, may favor the focus on the cross-sectional picture. This approach implies a hierarchical and arbitrary method to evaluate the importance of different symptoms. Conversely, a better clinical practice should provide a more comprehensive evaluation of the affective domain in any patient presenting with acute psychiatric illness episodes with psychotic symptoms. This may be achieved, apart through noting the patient history without missing childhood and adolescence and also noting status, through using specific assessing instruments.

A correct diagnosis of BD in AS individuals and vice-versa has relevant implications on the choice of correct psychopharmacological, psychological, social and rehabilitative treatments. Notably, there is a little number of controlled trials. Moreover, individuals with atypical patterns and comorbidity with other mental disorders are usually excluded from clinical trials. Nevertheless, the literature provides some useful suggestion 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 adverse effects, especially as far as neuro-behavioral effects are concerned. SGA with 5-HT2A antagonists should be preferred. Antidepressants, in particular SSRIs, should be used with caution and careful monitoring, in the attempt of an early detection of activation and switch phenomena. It is likely that ASD comorbidity in major depressive patients may contribute to antidepressants resistance through the persistence of residual symptoms and the frequent induction of mood instability. Stimulants for the treatment of ADHD-like symptoms should be used cautiously in AS patients, taking into account the higher frequency of adverse events than in patients with ADHD without AS.

The literature on this issue is still incomplete and the available data are often not generalizable; long-term controlled studies on large samples are needed to enrich the knowledge in the field. Finally, an educational intervention concerning the ASD–BD comorbidity issue and involving pediatricians, neurologists, childhood and adulthood psychiatrists appears crucial to ensure that patients receive appropriate diagnosis and treatment. A personalized psycho-educational and rehabilitative intervention should be also provided pursuing the goodness of fit. These interventions should also be specifically designed on the basis of AS features and differentiated from programs commonly used in other psychotic patients.

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