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Review

Pharmacological treatments in autism spectrum disorder: a narrative review

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SUMMARY

Autism spectrum disorder (ASD) is a neurodevelopmental condition that affects about 1% of the population. It is characterized by deficits in social interaction and communication, as well as repetitive behaviors and/or interests. Individuals with ASD have a higher prevalence of psychiatric disorders compared to neurotypical samples. Although psychiatric medications are widely used in this population, evidence on effective pharmacological interventions for ASD-associated psychiatric problems is limited. Therefore, this narrative review aims to summarize the current evidence for efficacy of pharmacological treatments of ASD-related comorbidities, including emotional dysregulation, irritability and aggression, ADHD, tics and Tourette syndrome, anxiety, affective disorders such as unipolar and bipolar depression, sleep disorders, obsessive-compulsive disorder, and schizophrenia spectrum disorders. A comprehensive search of PubMed for all types of articles, except case reports, was conducted. The review synthesizes and presents all data in a narrative form. Aripiprazole and risperidone have shown effectiveness in treating irritability and aggression in ASD, while methylphenidate may be helpful in reducing hyperactivity and inattention in children with ADHD, although this group may be more susceptible to adverse effects. Melatonin is commonly used to address sleep problems in ASD and appears to be effective. Fluoxetine and fluvoxamine have shown some effectiveness in reducing symptoms of OCD. However, due to the lack of validated measures for assessing OCD in ASD and the challenges in distinguishing between the two disorders, clinicians must exercise caution when interpreting these results. In general, there is a lack of robust evidence for treating other co-occurring psychiatric problems, and caution should be exercised when using SSRIs in ASD. To address these gaps in knowledge, larger prospective trials are necessary.

Key words: autism, psychopharmacology, treatment response, neuropsychiatric disorders

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Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by early onset deficits in social communication and reciprocity, together with a restricted range of interests and repetitive behaviors [1]. The diagnosis of ASD has a population prevalence of about 1%, higher in males, with a median male to female ratio of 4.2 [2]. ASD is phenotypically and genetically heterogeneous, therefore level of severity varies widely depending on intelligence quotient, adaptive functioning and associated neurological disorders or associated behavioral comorbidities. Autistic patients are more likely to develop both medical and psychiatric comorbidities than the general population, possibly due to shared etiopathogenetic mechanisms linked to different clinical phenotypes [3]. Psychiatric comorbidities in ASD patients are common: 70% of people with ASD have at least one "comorbidity"; 41% have two or more [4]. The overall burden of the disease is highly influenced by the result of ASD symptoms severity and psychiatric and medical comorbidities. The most frequent psychiatric comorbidities of ASD are anxiety, depression,

schizophrenia spectrum disorders, obsessive-compulsive disorders, eating disorders, ADHD, and intellectual disability [5].

At the moment no pharmacological treatment has proven to be effective in reducing autistic symptoms, and no drug is available to target "core" symptoms. In the last decades different medications have tested in RCTs without differences between medication and placebo groups: oxytocin [6,7,8], balovaptan [9], memantine [10], fluoxetine [11,12] and bumetanide [13].

In clinical practice, however, psychopharmacological treatment is widely used to target symptoms of comorbidities even if the evidence of its efficacy and tolerability in ASD is in some cases rather limited. In the USA about 60% of people with ASD receive psychotropic medications and of these, one-third receive more than one medication concurrently [14]. Risperidone and aripiprazole are currently the only medications in the US that the Food and Drug Administration (FDA) has specifically approved for symptoms associated with ASD.

In this narrative review, available evidence is examined for the following groups of disturbances: emotional dysregulation, irritability and aggression, ADHD, tics and Tourette disorder, anxiety, depression, sleep disorders, obsessive compulsive disorder, schizophrenia spectrum disorders, and bipolar disorder. For each condition, in order to better describe the ASD heterogeneity, detailed data on both children and adults as on low and high functioning patterns and on males/females autism has been provided, when available. In this search of all the available evidence, all the literature was considered investigated, including small case series. Only case reports have been excluded from this review since evidence from single case reports is too anectodical. Even though ASD is a lifelong condition, most of the available literature on pharmacotherapy has been derived from studies in children and adolescents.

Emotional dysregulation, irritability and aggression

Emotional dysregulation and irritability are common among people with ASD and may manifest with aggression towards self and others, tantrums, rapidly changing mood, affecting overall adaptive functioning, both in children [15] and in adults. Since people with autism present with poor emotional awareness, low competence in emotional language, poor flexibility, high sensitivity to change and to environmental stimulation they are particularly vulnerable to emotional dysregulation. Emotional dysregulation is defined as the ability to modify arousal and emotional reactivity to achieve goals and maintain adaptive behaviors [16]. Up to 68% of people with ASD can present with aggression or self injurious behaviors (SIB) [17], according to studies considering parent report measures, while considering more objective measures, the rate is lower. Irritability and aggression can lead to significant personal and social consequences, such as great functional impairment, increased family stress, and residential placement.

Through the last decades, researchers working on pharmacological treatment of irritability and aggression in ASD tested different drugs, such as antipsychotics, mood stabilizers, and glutamatergic blockers. However, up to date, only two drugs are authorized in the US and in most European countries specifically for ASD people: aripiprazole and risperidone, with indications limited to children and adolescents, not adults. Different meta-analyses have been published on the efficacy of aripiprazole and risperidone [18], of other atypical antipsychotics [19] of clonidine [20] and overall on pharmacological interventions [21] on irritability and emotional dysregulation in autism.

Atypical antipsychotics

According to Salazar de Pablo and colleagues' meta-analysis [21] the largest effect sizes and the lowest NNTs were observed for aripiprazole (effect size 1.179, 0.838 to 1.520; NNT 3-11) and risperidone (effect size 1.074, 0.818 to 1.331; NNT 3-11), as previously reported [18]. The most common adverse effect of aripiprazole is akathisia, while for risperidone it is weight gain. Adverse effects are documented in up to 61% of patients treated with aripiprazole and 77% of those treated with risperidone [22].

Beside the evidence of efficacy for aripiprazole and risperidone, there are few studies of other atypical antipsychotics such as quetiapine, ziprasidone and paliperidone, although these are still commonly used in clinical practice in the treatment of irritability and aggressive behavior in children and adults with ASD. Evidence for these medications is limited to naturalistic retrospective study, open label studies, chart reviews, case series or case reports. However, for olanzapine a placebo-controlled trial is available, even if very small (11 children), in which an improvement at CGI-I was documented [23], but weight gain was very frequently reported, thus limiting the prescription in clinical practice.

Clozapine represents an option in treatment-refractory patients with ASD who exhibit significant disruptive behaviors. Clozapine has largely shown efficacy for severe aggressiveness in schizophrenic patients [24], but data on autistic population are scarce, being mostly case series in which authors noted a significant decrease in aggressiveness after use of clozapine [25,26,27]. The use of clozapine is limited for the risk of agranulocytosis and myocarditis, two severe adverse events. Moreover, pe-

riodic monitoring of blood count is required, and this could represent a significant issue for autistic patients with aggression problems. As a result of this low evidence, atypical antipsychotics other than aripiprazole and risperidone should be considered in case of treatment resistance to risperidone or aripiprazole, monitoring carefully metabolic side effects.

First-Generation Antipsychotics

First generation antipsychotics, such as haloperidol or chlorpromazine, remain an option in clinical situations of treatment resistant irritability or aggression [28]. However, the possible emergence of extrapyramidal adverse effects should be closely monitored, especially with haloperidol.

Cannabidiol (CBD)

In the last years researchers focused on possible utilization of cannabidiol on irritability in ASD. Among other studies, two open label prospective trials [29,30] have been conducted with positive results but several methodological issues (such as the use of unblinded parent reports to evaluate improvement) [31] tested cannabidiol with a 12-week randomized double blind, placebo-controlled single-site trial in a population of 150 individuals with ASD. Participants received placebo or whole part cannabis plants or CBD. Researchers found that 49% of children receiving whole-plant cannabis extract had an improvement in disruptive behavior, significantly higher than the placebo, while no differences between pure CBD and placebo were observed [31]. Generally, cannabidiol seems to be well tolerated, as more common side effects are somnolence and appetite suppression, which can result in weight loss. More research, especially on the long term outcome of this treatment is needed in order to establish efficacy.

Antiepileptic drugs

Valproate was tested in a 12-week randomized, double-blind, placebo-controlled trial [32], with an overall improvement in 62.5% of divalproex subjects vs 9% of placebo subjects regarding irritability. The sample size was quite small (27 subjects), so further studies are needed to confirm this result.

N-Acetylcysteine (NAC)

N-acetylcysteine (NAC) functions as an antioxidant through its contribution to the production of glutathione, a major intracellular antioxidant within the central nervous system. Recently a meta-analysis of RCTs has been published [33], in which NAC, compared to placebo, was associated with a significant reduction in hyperactivity and irritability, but there were no differences in measures of social communication and stereotyped behavior.

Clonidine

The use of clonidine, an alpha-2 receptor agonist, in managing disruptive behavior in ASD population was examined in two cross-over studies, one open-label case series, and several case reports with an overall very low level of evidence [20]. Some benefit has been reported, but overall clonidine has a limited evidence base for use in the management of behavioral problems in patients with ASD.

Attention deficit hyperactivity disorder (ADHD)

ADHD is among those conditions that are commonly found to co-exist with ASD at a reported rate of 21% [34]. Individuals in whom the disorders are comorbid show more severe impairment because of deficits in the processing of social situations, adaptive functioning, and executive control than individuals with one disorder alone [35]. Latest updated recommendations for the pharmacological treatment in children and adults with comorbid ADHD and ASD stated that a 'low and slow' approach should be adopted as people with both conditions may be more treatment resistant and more sensitive to side effects [36].

The evidence for a therapeutic effect on hyperactivity and inattention seems best for methylphenidate, atomoxetine, certain atypical antipsychotics, and alpha-2 adrenergic agonists. Literature on the use of SSRIs, venlafaxine, benzodiazepines, or AED mood stabilizers on ADHD in ASD is not encouraging, as for tricyclic antidepressants, cholinesterase inhibitors, and NMDA receptor blockers, whose use for hyperactivity should be viewed as experimental [37].

Methylphenidate

Methylphenidate is a psychostimulant agent and the first drug to see widespread use for the treatment of ADHD. Evidence suggests that it must be considered a reasonable first therapeutic choice for previously untreated children with ASD and uncomplicated ADHD, even though it doesn't work as well, on average, as it does in typically developing children [38]. In a meta-analysis of 4 placebo-controlled RCTs and 117 children with ASD, MPH was associated with a reduction of ADHD symptoms [39]. Indeed, even though psychostimulants agents are reported to produce highly variable responses in children with ASD and ADHD symptoms (from substantial improvement with minor side effects to more problematic behavior and physical and/or behavioral side effects [40], MPH treatment was generally associated with significant declines in hyperactive and impulsive behavior [41].

Children with autism may be more prone to adverse side effects (especially at doses in the 0.6 mg/kg range)

but there do not appear to be any factors (e.g, IQ, age) that would be predictive of a differential outcome [45], as confirmed by RUPP Autism Network in 2005. Most common side effects reported are: appetite decrease, sleep problems, irritability, headache, and stomach discomfort [39]. Methylphenidate use was also associated with several positive social outcomes, including improved initiation for joint attention, improved response to bids for joint attention, better self-regulation, and more regulated affective state [43].

Atomoxetine

Atomoxetine is a noradrenergic reuptake inhibitor frequently used to control symptoms of ADHD in typically-developing children. A review on the administration of atomoxetine for treating children and adolescents with ASD and ADHD underlines the potential efficacy of atomoxetine [44]. A clinical trial comparing atomoxetine to placebo to evaluate the effectiveness and tolerability in the treatment of autistic features in patients with ADHD, shows that atomoxetine add-on therapy may be effective in symptoms of ASD while adverse effects tend to subside [45]. Atomoxetine, compared with placebo, was associated with improvement in ADHD symptoms in a meta-analysis of 4 RCTs (237 children with ASD). Side effects reported were appetite decrease, irritability, sleep problems and vomiting [39].

Atypical antipsychotic

Even though risperidone is one among few FDA approved medications in ASD people, literature about its role in inattentiveness and hyperactivity in those patients is inconsistent. Evidence shows a significant lowering in the ABC Hyperactivity subscale compared with placebo after 8 weeks of treatment [46,47]. On the other hand, an open-label study of risperidone with a double-blind placebo-controlled discontinuation phase reported no significant drug group differences on focused attention, but the risperidone group performed better on the divided attention task. However, the parent-rated ABC Hyperactivity subscale showed no significant group differences [48].

One pilot open label randomized control study investigated the effectiveness of both aripiprazole and risperidone in ADHD symptoms in patients with ASD. Both medications appeared to have similar benefits in terms of efficacy and tolerability and both groups showed a significant improvement in ADHD symptoms after 24 weeks of treatment [35].

Alpha2 Adrenergic Agonists

Clonidine and guanfacine act on α2-adrenergic presynaptic receptors to inhibit noradrenergic release and synaptic transmission. Only two small studies have investigated clonidine for hyperactivity in autistic disorder: Fankhauser et al., in which CGI-Improvement ratings showed significant gains and Jaselskis et al. where the results were mixed, showing a significant improvement in ADHD symptoms on the parent-rated CASQ and the teacher-rated ABC Hyperactivity subscale, but not on the clinician rated CPRS Hyperactivity subscale [49,50].

A prospective open trial on children with a diagnosis of ASD accompanied by hyperactivity who had failed to respond or could not tolerate MPH and thus were treated with guanfacine therapy. The results showed significant improvement on the parent rated ABC Hyperactivity subscale [51]. Later, a RCT compared extended-release guanfacine with placebo in 62 children with ASD and ADHD symptoms. The result showed that extended-release guanfacine appears to be safe and effective for reducing hyperactivity, impulsiveness, and distractibility in children with ASD [52], but future controlled studies are needed to further assess the efficacy and tolerability of guanfacine in patients with ASD.

N-Acetylcysteine (NAC)

As reported above (see the emotional dysregulation section) NAC seems to be more effective than placebo in reducing hyperactivity [33].

Tics and Tourette Syndrome

Both ASD and Tourette Syndrome (TS) are neurodevelopmental disorders, as defined by DSM-5, and they frequently co-occurr [53], like many neurodevelopmental conditions. TS is characterized by the presence of motor tics and at least one vocal tic that persist for more than one year, with an onset age before 18 years [1]. The reported TS rate in ASD population varies from 2.6 to 11% [54]. In a large international cohort (Tourette Syndrome International Database Consortium Registry), the rate of ASD in TS is about 4.6% [53], while in a more recent study on an Italian cohort the prevalence of ASD among children with TS is 8.9% [55]. The association is higher than expected, revealing some common underlying etiologic factors, as recently point out by the description of genetic alterations, as deletions and microduplications and of connectivity alterations in neuroimaging studies.

Differential diagnosis of stereotypies and tics can sometimes be a challenge [56]. Tics are defined as rapid, repetitive, non-rhythmic movements or vocalizations, while stereotypies are repetitive, seemingly driven and apparently purposeless motor behaviors, according to DSM 5. In terms of clinical phenomenology, stereotypies tend to be more fixed, rhythmic, and prolonged in duration than tics, which are rapid and fluctuating in both intensity and frequency [57]. Sometimes tics and stereotyped movements can co-occur in the same patient, but could be clinically relevant because of treatment implications: while pharmacological treatment can be

effective in modulating tics, stereotypies usually show a poor response to medication.

Despite a quite high comorbidity rate between ASD and TS, there are very few published studies specifically on pharmacological treatment of tics in people with ASD. The only review on the topic has been published in 2010 [58], and points out the lack of high quality studies. Authors divided pharmacological treatment of tics and pharmacological treatment of stereotypies; regarding tics, they found some evidence of efficacy for topiramate [59], while levetiracetam was not effective in two controlled clinical trials [60]. Rajapakse and colleagues also analyzed pharmacological treatment of stereotypies, and found that risperidone showed efficacy in reducing stereotyped movements in children with ASD in both a Cochrane review [61] and two subsequent RCTs [62]. In another RCT, Akhondzadeh and Colleagues [63] found a significant treatment difference between pentoxifylline (a methylated xanthine derivative that increases red blood cell deformability, reduces blood viscosity and decreases the potential for platelet aggregation and thrombus formation) and risperidone versus placebo and risperidone in the ABC stereotypic behavior subscale.

Aripiprazole

Since 2011, more evidence on the use of aripiprazole in TS have been published, as aripiprazole becoming a main focus of research for pharmacological treatment of tics) [64] and many publications consistently documenting its efficacy in reducing tics, with effect sizes comparable to those seen with haloperidol and risperidone [65,66]. Recently (2022), the European clinical guidelines for Tourette syndrome and other tic disorders have been published [64], indicating that the largest amount of evidence supports the use of dopamine blocking agents, preferably aripiprazole because of a more favorable profile of adverse events than first- and second-generation antipsychotics. Other agents that can be considered include tiapride, risperidone, and especially in case of co-existing attention deficit hyperactivity disorder (ADHD), clonidine and guanfacine. Specific mention to ASD in the Guidelines is made with referral to “cases with stereotypies that are debilitating and involving harm and injury to self and others” in which treatment with risperidone or fluoxetine may be considered [64]. Since aripiprazole has a documented beneficial effect on irritability in ASD [67] and is the first choice for tics treatment, according to latest European guidelines, it seems reasonable to consider aripiprazole as the first choice in ASD patients with impairing tics, even though no specific RCT have examined the effectiveness of aripiprazole in reducing tics specifically in ASD.

Anxiety

Anxiety disorders are among the most common comorbidities in ASD [68], with a prevalence in youth with ASD ranging from 35 to 75 % depending on assessment methods [69,70]), with higher rates observed with parent-report measures [71]). Compared to depression, anxiety symptoms show an earlier increase and tend to remain stable in adult samples [72]). Patients with ASD are 3.5 times more at risk of developing anxiety than neurotypical samples [73] and at a higher risk compared to youth with other neurodevelopmental disorders [74]. Comorbid anxiety can worsen ASD core symptoms, cause distress, and trigger behavioral problems [75].

Both males and females with autism are at increased risk for anxiety, but some studies have reported that females with ASD without ID may experience higher rates of anxiety than males [76]. Some evidence suggests that anxiety rates may be higher in ASD samples with higher IQ [77], albeit rates may be biased due to the difficulties in recognizing and expressing symptoms in people with intellectual disabilities [78].

Despite the high occurrence of anxiety in people with ASD, evidence for the efficacy of pharmacological treatments is limited. To date, to our knowledge, there are no RCTs in people with ASD aimed at assessing the efficacy of antidepressants or antianxiety medications on anxiety symptoms [79,80], except for a small (30 subjects) placebo-controlled pilot trial of mirtazapine [81]. Thus, available data are extrapolated from RCTs designed to evaluate the efficacy of treatments on ASD core symptoms or associated behaviors (e.g, irritability, aggression or RRBs), and from studies with higher risk of bias (e.g, open-label trials).

Selective Serotonin Reuptake Inhibitors (SSRIs)

As mentioned above, despite the high rates of anxiety in individuals with ASD, there are no RCTs specifically aimed at evaluating the efficacy of SSRIs for anxiety symptoms in ASD [82], using data from a RCT designed to examine the efficacy of citalopram for autism core symptoms in youth with ASD [83], didn’t find a statistically significant intergroup difference in parent-reported anxiety levels. Conversely, a retrospective review by [84] found that 59% children with ASD treated with citalopram (5-40 mg a daily) for two months were much improved or very much improved on the Clinical Global Impressions-Improvement subscale (CGI-I). Citalopram was particularly effective on anxiety and irritability, with minimal side effects. A placebo-controlled RCT of fluoxetine involving 45 children with ASD aimed at evaluating the effect on core symptoms found a significant reduction in anxiety symptoms in patients treated with fluoxetine compared to placebo [85] in consistence with findings from a previous small RCT by [86].

Potter et al. [87] in a parallel design study didn't find any significant difference in patients treated with sertraline versus placebo in any outcome measure, including anxiety levels measured with PAS-R (i.e, Preschool Anxiety Scale-Revised). By contrast, Steingard et al. [88] in a small open-label study in children with ASD found an overall improvement in anxiety and irritability related to changes in daily routine with sertraline at low doses. Sertraline showed a good tolerance, except for behavioral activation which was common among participants.
Martin et al. [89], in a small prospective open label study of low-doses of fluvoxamine in-children and adolescents with ASD found no statistical improvement in anxiety symptoms, measured by the Screen for Child Anxiety Related Disorders (SCARED). Behavioral activation was the most common side effect, which required the interruption of the treatment in some cases.

Noradrenergic and specific serotonergic antidepressants (NaSSA)

A naturalistic open-label study of mirtazapine in youth with ASD showed a modest effectiveness on anxiety and other target symptoms, with around one third of the patients being rated as responders. Mirtazapine showed only minimal side effects, such as increased appetite, irritability, and sedation [90]. McDougle et al. [81]in a double-blind, placebo-controlled pilot trial investigating the efficacy of mirtazapine in reducing anxiety symptoms in youth with ASD, found an improvement in anxiety symptoms in patients treated with mirtazapine compared to placebo, albeit not statistically significant.

Buspirone

A retrospective chart review in youth with ASD without ID treated with buspirone, a serotonin 5-HT_{1A} receptor agonist, showed a significant improvement in anxiety symptoms and a good tolerance profile [91]. This is in line with another open-label study in youth with ASD, which reported an improvement in anxiety and irritability on the CGI-I after buspirone treatment [92]. Conversely, a placebo-controlled trial involving 166 children with ASD aimed at evaluating the effect of buspirone on restrictive and repetitive behaviors and other ASD core symptoms didn't find a statistically significant improvement in anxiety symptoms, in patients on buspirone versus placebo [93].

Benzodiazepines

There are no RCT on the use of benzodiazepines in the long-term for anxiety symptoms in ASD. Indeed, benzodiazepines are not recommended in the long-term because of their effect on cognition, paradoxical effects (e.g, aggression and behavioral activation), tolerance, and risk of addiction. Nonetheless, evidence is poor and mostly derived from studies on people with intellectual disabilities, or adults with autism. However, benzodiazepines are commonly used in youth with ASD especially for sleep disturbances and acute anxiety [80].

Depression

Depression is one of the most common comorbidities in ASD [94], along with ADHD and anxiety. People with ASD are four times more likely to experience depression in their lifetime than neurotypically developing individuals [94], with increasing rates from late adolescence to middle adulthood. Rates of depression vary widely across studies, a recent umbrella review found prevalence ranging from 2.5 to 47.7% [95]. Variations in depression rates among studies on ASD could be attributed to differences in assessment methods, recruitment settings, and the absence of standardized instruments to measure depression in this population [94,96].
Hudson et al. [94] in a recent meta-analysis found that the pooled lifetime and current prevalence across ASD samples comprising children, adolescents, and adults were 14% and 12% respectively. Another meta-analysis in adults with ASD found that the pooled current and lifetime prevalence rates were 37% and 23%, respectively [72].
Rates of depression in children and adolescents with ASD are also high, ranging between 8% and 54%, with higher rates found with clinician-reported measures than with self-rated ones [97,69]. Depression in ASD may be associated with severe consequences, including poorer quality of life and social functioning [98], higher need of care and suicidality [96]. Conversely to what have been reported in neurotypical samples, females with ASD without ID seem to present higher risk of completed suicide compared to their male counterpart [99].
Additionally, depression diagnosis can be challenging in individuals with ASD due to atypical presentation and diagnostic overshadowing by core ASD symptoms [100].
Findings regarding sex differences in depressive symptoms presentation in ASD are somehow inconsistent: while some authors reported higher rates of depressive symptoms in females [101,69], others didn't find any difference between genders 102, or even a higher prevalence in males [103].
Depressive symptoms also seem to be related with higher cognitive abilities, albeit people with poor IQ may be underdiagnosed due to their difficulties in identifying and communicating their feelings [98]. Among the risk factors possibly implicated in depression onset, traumatic events, social rejection, bullying victimization and a family history of depression seem to be the most important.
Despite the increased risk of depression in ASD, studies specifically exploring pharmacological therapies targeting depressive symptoms in ASD are lacking [79]

and limited by small sample size, differences in age and IQ. Deb et al. (2021), in a recent meta-analysis on anti-anxiety and antidepressant medications in ASD, found no RCTs in ASD population specifically using outcome measures for depression and anxiety, with the majority of RCTs excluding individuals with ASD and co-occurring conditions.

Selective Serotonin Re-uptake Inhibitors (SSRIs)

While in neurotypically developing samples the SSRIs have shown a good efficacy on depressive symptoms, especially when associated with CBT [104], this association has not yet been studied in people with ASD. Indeed, albeit SSRIs are commonly prescribed in persons with ASD [105], evidence regarding the efficacy and tolerability of SSRIS in this population is scarce. A Cochrane review investigating the role of SSRIs in child and adult with ASD, both on core symptoms and on other comorbidities, found that there's limited evidence in adult ASD population on the efficacy of SSRIs, while there's no evidence in children with ASD, who also seem to be more vulnerable to side effects, such as behavioral activation [106].

Selective Noradrenaline Re-uptake Inhibitors (SNRI) and Methylphenidate

Two open label trials by Golubchik et al. [107,108] in youth with ASD, using reboxetine, an SNRI, in association with Methylphenidate, and Methylphenidate alone respectively, showed significant improvement in depressive symptoms. While 91 % of people treated with reboxetine showed some side effects, the patients treated with Methylphenidate alone reported only minor adverse effects, which did not require the interruption of the treatment.

Atypical antipsychotics

An open label trial by Rausch et al. [109] on male children and adolescents with ASD found a marked improvement in depressive symptoms after a treatment with risperidone, albeit many participants reported adverse effects (e.g, weight gain, sedation, and extrapyramidal side effects).

Sleep disorders

Sleep disorders are really common among children with ASD, with a reported prevalence ranging between 50 to 80% [110], significantly higher than in typically developing children (25%). In the ASD population the sleep duration reduction starts from around 30 months of age and persists until adolescence. Moreover ASD children are reported to have shorter total sleep time, longer sleep latency periods, and decreased sleep efficacy as compared with TD peers [111].

Even if concurrent IQ may moderate these results, only a few studies examine the difference between low functioning and high functioning ASD children. Results seem to suggest that the high-functioning autistic group sleep less than the low-functioning group and both groups had longer sleep latencies than compared to control groups [112]. Other studies trying to investigate cognitive functioning associated with sleep problems in children with ASD reported mixed results [113]. By contrast, other evidence found that individuals with ASD report sleep problems regardless of their cognitive level and that bedtime resistance, anxiety, sleep onset delay and daytime sleepiness may more be related to core symptoms [114]. Sleep problems in ASD are significantly related to emotional dysregulation [115].

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone secreted by the pineal gland, but also in other non-endocrine organs and tissues. Melatonin synthesis and secretion is regulated by the suprachiasmatic nucleus (SCN). The hormone modulates the SCN and peripheral clocks throughout the body, acting as a marker of circadian rhythm. Because of the multifactorial etiology of sleep disorders, no single intervention seems to be effective across all sleep problems in children with ASD. However, melatonin, behavioral interventions, and parent education/education program interventions appear the most effective at ameliorating multiple domains of sleep problems compared with other interventions [116].
The bulk of the evidence for the pharmacological treatment is for melatonin, with a meta-analysis of five double-blind RCTs showing a large effect size, favoring melatonin, in sleep duration and sleep-onset latency [117]. Melatonin as a sleep inductor, can be used 30 minutes before bedtime in a dose between 1-5 mg. For delayed sleep phase syndrome doses between 0.2-0.5 mg were most effective when given 6 to 8 hours before the desired sleep time. Dual therapy for insomnia in ASD with the use of melatonin and behavioral techniques is also gaining support. As described in literature, parents and caregivers often describe melatonin as being beneficial for initiating sleep but not maintaining sleep. Effects of prolonged-release melatonin were investigated in a clinical trial noting enrolling 121 children with autism. The results show a large increase in total sleep time and also time to fall asleep dropped by about 40 minutes by the study's end [118]. Moreover, an overall improvement of one hour in total sleep time, sleep latency or both, over baseline, were reported in Maras et al. double-blind randomized placebo-controlled study [119]. In addition, long-term melatonin treatment in combination with adequate sleep hygiene interventions may afford clinical benefits to children with ASD [120].

Clonidine (alpha 2 adrenergic receptor agonist)

Clonidine is an antihypertensive medication that acts on alpha-adrenergic and imidazoline receptor agonists. An open labeled retrospective study, involving seventeen children with sleep and behavioral disorders, reported that clonidine was effective in reducing sleep initiation latency and night awakening, to a less degree in improving attention deficits hyperactivity, mood instability and aggressiveness [121].

Clonazepam

Clonazepam such as other benzodiazepines exhibit inhibitory effects through GABA receptors. Its application in sleep problems was studied only among children with sleep-related REM behavioral disorder with a successful rate of 75% [122]. Limitations for the use of clonazepam include concerns about its tolerability profile, potential for drug dependence, and the lack of evidence-based data in the pediatric population.

Obsessive compulsive symptoms/disorder

The occurrence of obsessive compulsive symptoms among people with ASD is estimated between 17 and 37% [123], while the proportion of people with ASD reaching DSM 5 diagnostic criteria for obsessive compulsive disorder (OCD) is not so defined, as for many of other mental health conditions, which are difficult to assess in people with autism, since the interview schedules used are designed for the non-autistic population. Both people with ASD and people with OCD present repetitive behaviors, and this can lead to diagnostic confusion. One of the main differences is that usually in OCD repetitive behaviors are perceived as ego-dystonic, while in ASD thoughts or behaviors that are not related to OCD are perceived as egosyntonic. Given that, some Authors consider that some enjoyable repetitive motions are not appropriate targets for intervention, since that autistic people generally "derive pleasure or relief" from the repetition [124], unlike the anxiety and difficulty with inhibiting urges that underlie obsessive-compulsive disorder symptoms. As reported by the editorial of Ne'eman and colleagues, "efforts to eliminate such traits may actually harm autistic people" [125]. Nevertheless, compulsions and repetitive, stereotyped behaviors can be difficult to differentiate in a patient with ASD, especially those with lower function, since the motivation that sustain the specific repetitive movement should imply the ability to explain and communicate, and also the presence of obsessive thoughts should be explored with the ability to describe verbally such intrusive thoughts and ideas.

Despite the fact that OCD is usually a treatable condition, people with OCD and ASD have a poorer outcome compared to people with OCD and a typically development trajectory [126]. Different reasons have been advanced in order to explain the overlap between ASD and OCD, including genetic, anatomic, biochemical reasons.

Pharmacological treatments for OCD include selective serotonin reuptake inhibitors (SSRIs), and some antipsychotic medications. Few specific RCTs have been conducted to evaluate OCD in the ASD population [127]. Moreover, available data are derived from RCTs designed to evaluate the efficacy of treatments on ASD core symptoms as restricted and repetitive behaviors which are commonly explored with Y-BOCS (Yale-Brown Obsessive- Compulsive Scale) or CY-BOCS (Children's Yale-Brown Obsessive- Compulsive Scale) to measure obsessive compulsive symptoms, but without adaptation of the instrument to the ASD population, while in other case the CYBOCS-ASD, Children's Yale-Brown Obsessive- Compulsive Scale-Modified for ASD or CY-BOCS-PDD, Children's Yale-Brown Obsessive Compulsive Scale-Modified for Pervasive Developmental Disorders has been used. For the purpose of this review, studies specifically examining RRB symptoms with these instruments were examined. Given the scarcity of studies designed on OCD pharmacotherapy in ASD we'll provide information on pharmacological treatment of RRB, since the majority of available evidence is on this theme, keeping in mind that RRBs are not always overlapping with OCD symptoms. Nevertheless, especially in low functioning ASD population the distinction between OCD symptoms and RRBs represent a challenge and could be a significant factor involved in the inconclusive results of most of the studies.

Tricyclic Antidepressants (TCAs)

Clomipramine was examined in ASD population in two double blind studies: in the first one, which had a very small sample size of 7 autistic patients (ages 6-18 years) Gordon and Colleagues performed a 10-week double-blind, crossover trial of clomipramine and desipramine following a 2-week single-blind, placebo phase. Clomipramine was superior to desipramine and placebo, also on repetitive and compulsive behaviors, so that parents of all seven subjects elected to have their children continue to take clomipramine after the study [128]. In another study clomipramine to be superior both to placebo and desipramine in improving autistic symptoms, anger, and repetitive behaviors in 57% of the autistic subjects [129]. More recently clomipramine has been compared to haloperidol and placebo in 31 subjects with ASD (10-36 years), with no difference between clomipramine and placebo in stereotypy, irritability or hyperactivity measured using the total scores of the Aberrant Behavior Checklist (ABC). Clomipramine frequently shows side effects due to its anticholinergic activity, such as dry mouth, dizziness and constipation, heart rate changes and it also increases the risk

of developing seizures. At the moment, clomipramine remains a second-choice indication especially for repetitive behaviors in ASD and for co-morbid obsessive-compulsive disorder (OCD), especially in adolescents and young adults [80].

Selective serotonin reuptake inhibitors (SSRIs)

Low dose fluoxetine was superior to placebo in the treatment of repetitive behaviors by CY-BOCS compulsion scale, with an effect size in moderate to large range [185] in children and in adults with ASD, measured with YBOCS [130]. Low dose and slow dose titration is preferable since it could trigger irritability, aggression and hyperactivity at a higher dosage [80]. A specific study on OCD behaviors in ASD population showed that treatment with fluoxetine compared with placebo resulted in significantly lower scores for obsessive-compulsive behaviors at 16 weeks, although the difference was no longer significant after adjustment [127], while another study on 158 individuals with ASD (5-17 years) reported no significant difference between fluoxetine and placebo on RRB symptoms [131].

Since 1996, fluvoxamine was also found to be effective on RRBs in adults with autism [132]. Subsequent results on 34 ASD patients, range 5-18 years, found fluvoxamine to be minimally effective and poorly tolerated (McDouglas, 2000 [133], without any info on which scale has been used to assess RRB. Martin and Colleagues in a prospective open label study of low-doses of fluvoxamine among children and adolescents with ASD found no statistical improvement at the C-YBOCS [134]. In 2005 a RCT on a small population (18 patients), showed that 55.6% of ASD children responded to lower doses but with high side effects, as insomnia, aggressiveness, increased rituals, anxiety, anorexia, increased appetite, irritability, decreased concentration, and increased impulsivity [135]. This latest RCT did not assess RRB specifically (symptoms were assessed using Childhood Autism Rating Scale and Behavioral Assessment Scale).

A negative result was obtained in a RCT comparing citalopram with placebo [83] using CYBOCS-PDD.

An open label trial showed the short-term efficacy and tolerability of sertraline for adults with ASD, with 57% of 42 patients that showed significant improvement, primarily in repetitive and aggressive symptoms [136], with minimal side effects. Two open label trials have been conducted on escitalopram but without specific measures on obsessive compulsive symptomatology.

Antiepileptic drugs

Other compounds such as antiepileptic drug levetiracetam were used to evaluate autistic symptoms, including repetitive behaviors using CY-BOCS. No significant difference was found between levetiracetam and placebo groups in all the areas investigated in twenty patients with autism ranging from 5 to 17 years of age [137].

Also, some evidence in favor of valproate is available, with two studies by Hollander et al. [138,139], reporting a reduction in repetitive behaviors: in the first study in 13 autistic children, then in a larger population of 27 children and adolescents [139].

Schizophrenia spectrum disorders

Studies have shown that ASD and schizophrenia spectrum disorders (SSD) often co-occur, with a pooled prevalence of non-affective psychosis, such as schizophrenia, found to be 9.5% in a recent systematic review [140]. Previous studies reported inconsistent findings, with prevalence rates varying between 0% to 61.5% [141]. Comorbidity rates seem to be particularly high in case of early onset (EOS) or very early onset schizophrenia (VEOS). While autism is a life-long condition which can be detected by 2 years of age, schizophrenia usually occurs in young and middle adulthood. Nonetheless, the distinction between the two disorders still poses diagnostic challenges. Indeed, ASD and schizophrenia present a significant overlap in symptoms presentation. Many shared genetic, environmental, and neurobiological factors, as well as similar levels of neuropsychological impairment, have been described [142].

Moreover, some studies reported that autism-like features, along with other developmental abnormalities, frequently precede the onset of schizophrenia, particularly the childhood-onset type [143]. Interestingly, a recent study suggests that worse prognosis in early onset-psychosis may be due to the frequent co-occurrence with pre-morbid autism [144]. Moreover, psychotic symptoms may be difficult to evaluate in patients with poor communication and cognitive abilities. Regarding sex differences in SSD in ASD, limited research and inconsistent findings preclude definitive conclusions [145].

Despite the frequent co-occurrence of ASD and SSD and the widespread use of antipsychotics in ASD, there is a dearth of studies specifically assessing the effectiveness of these medications on psychotic symptoms in ASD [146]. Therefore, the clinical management of schizophrenia in ASD is still uncertain, and current strategies are based on data derived from neurotypical samples.

Regarding antipsychotic safety and tolerability in ASD, a recent systematic review [147] found metabolic disturbances as the most common side effect of antipsychotics in patients with neurodevelopmental disorders. Other reported side effects include sedation, prolactin increase, sexual dysfunctions, neurological and behavioral disorders, cardiological and hematological side effects. It's worth noting that autistic children may be particularly susceptible to extrapyramidal side effects of first-generation antipsychotics.

Bipolar disorder

Latest evidence on frequency of bipolar disorder in ASD population reported an estimated prevalence ranging between 5-8% [148]. Many factors affect the diagnosis: characteristic ASD symptoms (such as abstract thinking difficulties, limited emotional expression, poor verbal and nonverbal communication skills) significantly limit the ability to identify the main symptoms of affective disorders in this group of patients. Bipolar disorder seems to be the major comorbidity for mood disorder in adolescents and young adults with high-functioning ASD [149]. Young patients with both bipolar disorder and ASD exhibit typical BD mood symptoms but with earlier onset, mixed symptoms presentation, and additive functional impairments. Significant amelioration of clinical symptoms occurred over time, suggesting that early recognition and treatment of mood disorders in youth with ASD may improve clinical outcomes [150]. Targets of the treatment are symptoms such as irritability and self injurious behavior disorder. It is important to emphasize that there are a limited number of controlled trials regarding the use of psycho-pharmacological interventions in this population.

Lithium

Lithium is primarily used as a maintenance drug in the treatment of bipolar disorder to stabilize mood and prevent manic episodes. A retrospective chart review by Mintz et al. examined the use of extended and immediate release lithium carbonate in both young and adult patients with ASD. It found that 73.7% of patients with ASD and concomitant maladaptive behaviors experienced "improvement" (CGI-I rating ≤ 3) with the addition of lithium to their treatment regimen. Those with comorbid "ADHD" phenotype were most predictive of an efficacious response [151]. Thus lithium carbonate seems to be a viable, efficacious and well tolerated alternative to various neuroleptics and other psychotropic medications for use as a mood stabilizer for patients with ASD.

Antiepileptics drugs

Valproate is an anticonvulsant drug used as a mood stabilizer. As reported above a RCT by Hollander et al. showed divalproex effect on improving irritability without a specific comorbidity of bipolar disorder [152].

Conclusions

The current evidence-based management of ASD in children relies primarily on behavioral interventions to address the core symptoms of the condition, while pharmacological treatments are mainly used to manage co-occurring conditions associated with ASD. Despite the widespread use in clinical practice of psychopharmacological treatments in this population, robust evidence on the efficacy and tolerability is very scarce. The strongest evidence is about the use of risperidone and aripiprazole for controlling irritability and aggression, while the use of other antipsychotic drugs is not supported by similar strong evidence and is limited by possible side effects, with metabolic disturbance being the most common. In sleep disorders, there is sufficient evidence for the efficacy of melatonin to increase total sleep time and to reduce sleep-onset latency. When it comes to addressing comorbid neurodevelopmental problems, methylphenidate has shown to be effective in treating ADHD symptoms in children with ASD, although this group is known to be less responsive than ADHD without ASD and at a higher risk of experiencing adverse effects. Furthermore, there is currently no specific evidence available about treatments for tics and Tourette Syndrome in ASD. Controlled studies specifically designed to evaluate the effectiveness of treatments for anxiety and mood disorders, such as unipolar depression and bipolar disorder, in individuals with ASD are currently lacking. In addition, clinicians must exercise caution when administering antidepressants to individuals with ASD, especially in pediatric populations, as they may be at a higher risk of side effects, particularly behavioral activation. Regarding OCD, fluoxetine and fluvoxamine have demonstrated some efficacy in reducing OCD symptoms in individuals with ASD. However, clinicians must be careful when interpreting these findings due to limited validated measures for assessing OCD in ASD and the difficulties in differentiating between the two conditions. When it comes to pharmacological approaches for SSDs in individuals with ASD, the evidence is significantly limited. As a result, management primarily relies on evidence derived from studies on neurotypical individuals. Therefore, to fill the gaps in knowledge, future research should prioritize conducting randomized controlled trials with larger sample sizes in ASD population and using validated measures to assess comorbidities.

Conflict of interest statement

In the last two years, B.V. has received consultant fees or honoraria from Medice, Menarini, Angelini, and Alkermes Pharmaceuticals; C.D. has received consultant fees from Roche and Lundbeck. The remaining authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

Conceptualization, CD, VV, IS. and BV; methodology, BV and CD; writing-original draft preparation CD, IS and VV; writing-review and editing, CD, IS, VV and BV; supervision, BV. All authors have read and agreed to the published version of the manuscript.

Ethical consideration

Not applicable.

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