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REVIEW

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Psychopharmacological management of obsessive–compulsive behaviour in children and adolescents with autism spectrum disorders: a narrative review

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Abstract

In children and adolescents, autism spectrum disorders (ASD) and obsessive–compulsive disorders (OCD) may share similar features, such as deficits in social communication, repetitive behaviours and presence of obsession and compulsion. Studies have shown that children with OCD may exhibit the presence of ASD traits. Up to date research shows that selective serotonin reuptake inhibitors are commonly used to treat OCD, while treatment options for ASD are limited. A literature search was performed using the PubMed database and retrieving relevant papers up to December 2022. This review includes 9 case reports and 8 randomized controlled trials. The main psychopharmacological drugs used include antidepressants and antipsychotics. This review shows that the management of OCD behaviours in individuals with ASD and related conditions is of complex nature and pharmacological interventions may not be an effective method in managing this group of patients. Hence, more comprehensive research and deeper knowledge is important in optimizing pharmacological management for patients with OCD behaviours with underlying ASD.

Keywords Psychopharmacology, Autism spectrum disorders, Obsessive–compulsive disorders

Introduction

Autism spectrum disorders (ASDs) are commonly referred to as a group of neurodevelopmental disorders that can cause significant impairment in terms of social, communication and behaviour [1]. According to The Diagnostic and Statistical Manual (DSM-5), the core features of ASD are described as persistent deficits in social communication and social interaction across multiple occasions, and repetitive, restricted patterns of activities, interests and behaviour [2]. On the other hand, obsessive–compulsive disorder (OCD) is a condition characterized by distressing symptoms including repetition, intrusive thoughts or obsession, and time-consuming rituals or compulsions [3]. According to the DSM-5, core features of OCD include the presence of compulsions, obsessions or both [2].

In children and adolescents, both conditions may overlap as they share similar clinical characteristics such as inflexibility and symptoms of repetitive or stereotyped behaviours [4]. This overlap is demonstrated in research conducted by Ivarsson and Melin, which aimed to assess the prevalence of autistic traits in paediatric obsessive–compulsive disorder [5]. Paediatric patients with OCD (n = 109), according to DSM-IV criteria, were studied using parent ratings of the Autistic Symptom/Syndrome Questionnaire (ASST) to assess the presence of ASD symptoms as a continuous trait [5]. Furthermore, the study also indicated that autism ASD traits are quite

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common in OCD-patients as symptom scores were highest in cases with co morbid ASD [5]. In another study done by Stewart and colleagues, the aim of the study was to determine whether ASD traits indicated by the Social and Responsiveness Scale (SRS) and Social Communication Questionnaire (SCQ) were elevated in young children with OCD and to determine if ASD traits were associated with OCD severity[4]. Results show that higher scores were found on the SRS, but not the SCQ. For the SRS, 36.2% of the sample had a T-score of 60 or greater, whereas only 2.4% of the sample met clinical cutoffs for the SCQ [4]. This could be due to the SRS capturing the overlap between features of OCD and ASD such as impaired social reciprocity, language deficits and stereotypy [4].

Apart from clinical features, autism spectrum disorder with comorbid OCD also share common features in terms of treatment and brain pathophysiology [6]. Stereotypy routines and rituals that are frequent in ASD which many of these behaviours are identical to those seen in OCD could be due to the underlying mechanism which is due to disruption in serotonergic pathways in OCD and ASD [7]. Apart from that, serotonin (5-HT) receptor and 5-hydroxytryptamine (serotonin) receptor 1D (5-HT1D) sensitivity may play a role in affecting the behavioural domain within autism repetitive behaviours [8]. Hence, antidepressants, especially selective serotonin reuptake inhibitors, works as the 1st line pharmacological treatment of choice for most patients with OCD [9]. However, not many medications are truly effective in the treatment of autism spectrum disorders [10]. Therefore, this systematic review aims to investigate the available data on the pharmacological management of OCD in children and adolescent with ASD.

Methods

A literature search was performed using the PubMed database and retrieving relevant papers up to September 2023. Search strategy was ((autism) OR (Asperger's syndrome) OR (pervasive developmental disorder)) AND ((obsessive-compulsive) OR (repetitive)). Additional studies of interest were retrieved from the reference list of selected articles. The titles and abstracts of all studies were first screened for their eligibility to be included in this review. A full-text manuscript was then examined to assess the eligibility when the decision cannot be made based on the title and abstract solely. The eligibility criteria for inclusion were case reports or controlled trials and patients who had psychopharmacotherapy for obsessive–compulsive behaviours in children and adolescent with ASD. For case report, the relevant data were collected including patients' age, gender, psychiatric comorbidities, clinical presentations, management, and clinical response. For controlled trials, the relevant data were collected including sample size, study duration, age, treatment given, results and adverse effects. Figure 1 shows the flow diagram of studies selection.

Clinical cases in literature

The search yielded 9 case reports reporting OCD in ASD with psychopharmacological management [11–19]. In the 9 cases that were included in this review, the mean age of the patients was 14.4 ± 3 years old and 77.78% (7/9) were male. 66.67% (6/9) patients were diagnosed with ASD and 33.33% (3/9) patients were diagnosed with Asperger's syndrome. 55.56% (5/9) patients received a diagnosis of OCD. Majority of the patients 77.78% (7/9) presented with other psychiatric comorbidities which include major depressive disorder (MDD), generalized anxiety disorder (GAD), non-verbal learning disability (NVLD), attention deficit hyperactivity disorders (ADHD), disruptive mood dysregulation disorder (DMDD), anorexia nervosa, and Tourette disorder. Antidepressants was used in 77.78% (7/9) patients to manage the obsessive–compulsive behaviours which include fluoxetine (4 patients), paroxetine (1 patient), sertraline (1 patient) and mirtazapine (1 patient). Antipsychotics was used in 55.56% (5/9) patients to manage the obsessive–compulsive behaviours which include aripiprazole (3 patients), risperidone (1 patient) and olanzapine (1 patient). Melatonin is used in one of the patients. The findings of case reports are summarized in Table 1.

Randomized control trials

The search yielded 8 randomized controlled trials (RCT) investigating psychopharmacological management of OCD in ASD [20–27]. The findings of RCT are summarized in Table 2. In the 8 RCTs that were included in this review, 5 RCTs were on antidepressants, 2 RCTs were on antipsychotics and 1 RCTs was on anxiolytics. 2 RCTs on fluoxetine showed improvements of Yale Brown Obsessive–Compulsive Scale (Y-BOCS) while the rest showed no significant improvements. RCT on risperidone showed significant improvement of Children's Yale Brown Obsessive–Compulsive Scale (CY-BOCS) scores but olanzapine had no significant improvement. Furthermore, RCT on anxiolytic buspirone also showed no significant improvement.

Medications use in ASD and OCD

The current available pharmacological treatment options of ASD target the symptoms of ASD and comorbid conditions such as alleviating stereotypies, irritability, hyperactivity, anxiety, obsessions, aggression, and self-injurious behaviour rather than directed primary to the core symptoms of ASD [28]. Pharmacological

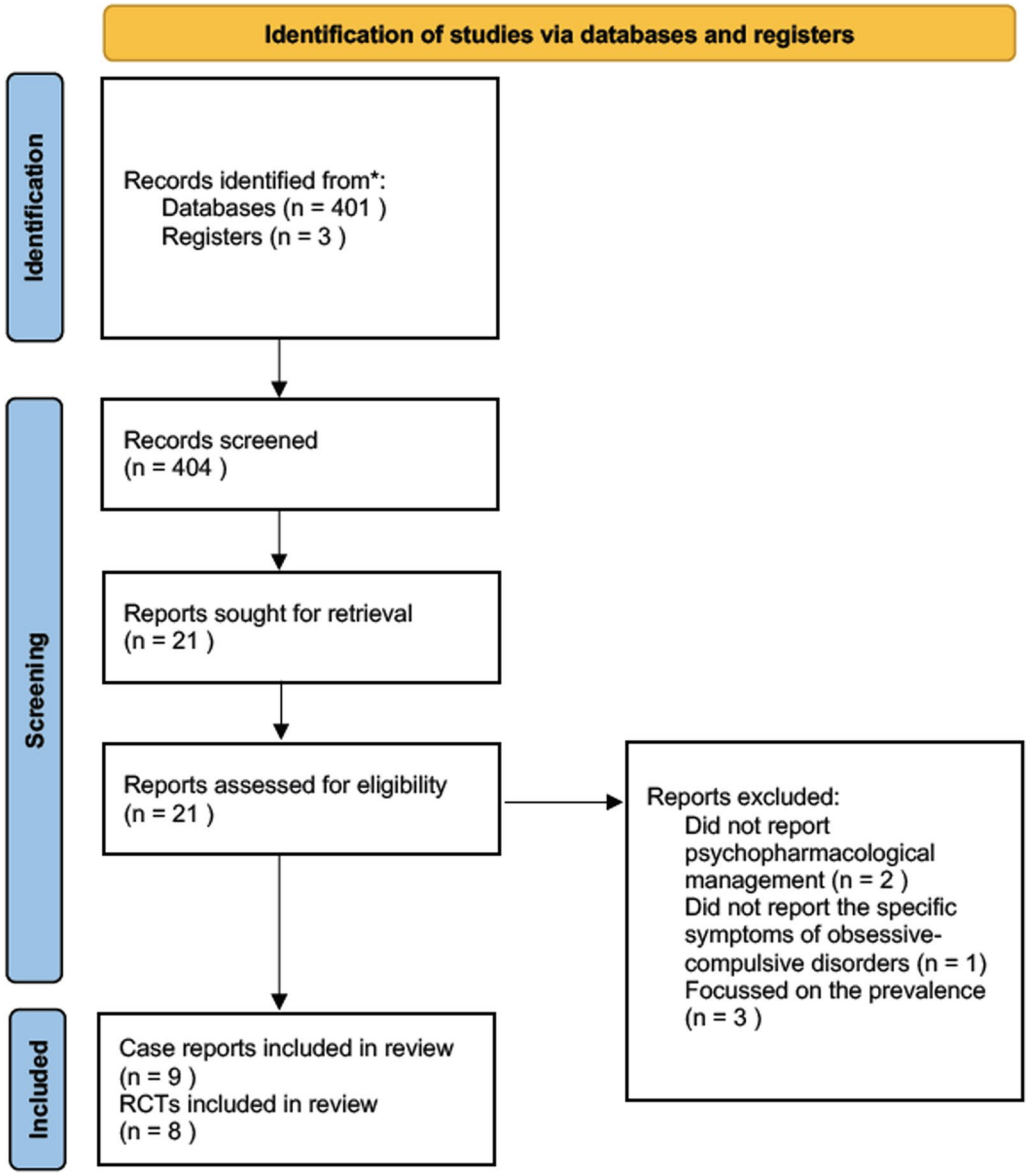

Fig. 1 Flow diagram of studies selection

management may be an effective management for child and adolescent patients with underlying ASD who have severe OCD symptoms and exacerbation [16]. For mild to moderate OCD, cognitive behavioural therapy (CBT) is the first line of treatment, whereas for moderate to severe OCD, selective serotonin reuptake inhibitors (SSRIs) are the first line of treatment [29]. Jassi and colleagues reported that young people with OCD and ASD were more likely to be treated with medication compared to young people with ASD only [30]. Similarly, Martin and colleagues also demonstrated that young people with OCD and ASD were more likely prescribed with sedatives, antidepressants, or antipsychotics compared to young people diagnosed with OCD and ASD only [31].

Antidepressants

SSRIs are use in the management of OCD in ASD, as several studies have shown that 22 to 28% of the patients with ASD have an increased blood serotonin levels compared to normal individuals [32]. Depletion of tryptophan, which is a precursor of serotonin, leads to decrease in plasma tryptophan levels and exacerbate the symptoms in individuals with ASD [33]. Excess accumulation of serotonin in the platelets, due to increased serotonin

Table 1 Cases reporting psychopharmacological management of obsessive–compulsive disorder in autism spectrum disorder

Ref	Age	Diagnosis	Clinical features	Medical	Clinical response
Sasayama 2009	15 years old female	OCD, Asperger's disorder	She presented with severe contamination fears and contamination-related checking behaviours. Y-BOCS score was 40	Paroxetine titrated up to 60 mg/d	Her contamination fears had reduced. Her Y-BOCS score at 6 months after initiation of paroxetine was 14
Celik 2011	15 years old male	Asperger's syndrome	He was presented with obsessive thoughts of feeling guilty about his homosexual thoughts and masturbation and pre-occupation of stock farming. He also had compulsion to count stones. Y-BOCS score was 31 (compulsion score: 14, obsession score: 17)	Aripiprazole 5 mg/day and titrated up to 10 mg/day after 2 weeks	He had reduced in his obsessive thoughts and compulsions and improved in his speech and social reciprocity. Y-BOCS score was 13 (compulsion score: 7, obsession score: 6);
Bernhardt 2011	15 years old male	OCD, Tourette disorder, Asperger's disorder	He presented with intrusive and persistent thoughts that drove him to check and tap nearby objects. Clinical Global Impression (CGI)-Severity (S) score was 5 (markedly ill)	Fluoxetine 60 mg/d, aripiprazole 1 mg/d, memantine 10 mg/d	He had decreased in his desire to perform rituals and reduced intrusive, disturbing thoughts. (CGI-I) score = 2 [much improved]). He no longer felt the need to perform rituals at school, and as a result, his grades improved
Cawkwell 2016	16 years old female	ASD, OCD, MDD, GAD, NVLD	She was admitted to the hospital due to obsessions and fears about contamination and about her identity being stolen. The obsessive thoughts led to worsening agitation, anxiety, and suicidal ideations	Medication upon admission: ziprasidone 80 mg, bupropion XL 300 mg, and lamotrigine 250 mg Treatment during hospitalization: risperidone 0.25 mg b.i.d titrated up to 3 mg at night and 1 mg in the morning. Fluoxetine 10 mg titrated up to 20 mg to target OCD	She was able to read a book by herself and to conduct prolonged conversations without being interrupted by her obsessions
Hendriksen 2016	9 years old male	Duchenne muscular dystrophy, ASD	He was presented with panic attacks and severe compulsions such as writing numbers on pages, arranging colour pencils in sequence of rainbow, saying "peanut butter" 10 times before taking medication and taking 10 sips of water afterwards	Medication upon presentation: prednisolone 0,75 mg/kg/day (10 days on/10 days off) Medication started: Fluoxetine 5 mg/day and gradually titrated up to 20 mg/day	Diminished in compulsion acts markedly diminished, improved personal–social and school functioning, and he was more cheerful
Akbas 2018	11 years old male	ASD	He presented with refusal to eat for past 12 days with ritualistic behaviour of touching his hands to his head and then to plate of food	Aripiprazole 5 mg/day and mirtazapine 15 mg/day	The repetitive behaviours decreased gradually and started to eat and drink during upon first week of treatment

Table 1 (continued)

Ref	Age	Diagnosis	Clinical features	Medical	Clinical response
Lu 2018	18 years old male	ASD, OCD, anorexia nervosa	He was presented with severe eating disorders with a BMI of 13.8 due to spending multiple hours a day inspecting each bite of food for contamination and had profound exacerbation of his stereotypes during meals	Fluoxetine was started and titrated to 120 mg daily	He had improvement in his OCD behaviour and weight gain with BMI of 19.1 during discharge
Gray 2021	13 years old male	ASD, ADHD, DMDD, OCD, anxiety, depression	He was presented to the emergency department with decrease oral intake due to worsening anxiety and obsessive thoughts of fear of contaminated surfaces and objects	Medication upon admission: oxcarbazepine, risperidone, clonidine Treatment during hospitalization: sertraline 50 mg with gradual titrated up to 200 mg, olanzapine 5 mg, with the addition of Ativan 0.5 mg three times a day as needed for anxiety	He was less irritable and more social with staff and participated in group sessions with increased oral intake
Poyraz Fındık 2021	18 years old male	ASD, ADHD	He presented collecting feathers from clothes initially followed by repetitive tearing his clothes for the last 1 year	Previous medication: aripiprazole 20 mg/day, risperidone (1 mg/day) Treatment: Risperidone was discontinued, aripiprazole was continued, and melatonin 3 mg/day was started	He has sudden reduction in his clothes tearing behaviour,

OCD obsessive–compulsive disorder, *Y-BOCS* Yale–Brown Obsessive Compulsive Scale, *CGI* Clinical Global Impression, *ASD* autism spectrum disorder, *MDD* major depressive disorder; *GAD* generalized anxiety disorder; NVLD, non-verbal learning disorder, *DMDD* disruptive mood dysregulation disorder

Table 2 Randomized controlled trials reporting psychopharmacological management of obsessive–compulsive disorder in autism spectrum disorder

Study	Sample	Study duration	Age range	Treatment	Assessment scales	Results	Adverse effects reported
Hollander et al. 2005	20 intervention and 19 placebos	8 weeks	5–16	Fluoxetine (mean dosage: 9.9 ± 4.35 mg/d)	Y-BOCS	Reduced repetitive behaviours by CY-BOCS compulsion scale	Anxiety, insomnia, drowsiness, agitation, diarrhoea, anorexia, URI, weight gain
Wasserman et al. 2005	10 intervention and 10 placebos	10 weeks	5–17	Levetiracetam (mean dosage: 862.50 ± 279.19 mg/day)	CY-BOCS	No significant improvement	Agitation, aggression, hyperactivity, impulsivity, loss of appetite, self-harm, weight gain, weight loss
Hollander et al. 2006	6 intervention and 5 placebos	8 weeks	6–14	Olanzapine (mean dosage: 10 mg/d)	CY-BOCS	No significant improvement	Weight gain, rhinitis, constipation, insomnia, glazed eyes
King et al. 2009	73 intervention and 6 placebos	12 weeks	5–17	Citalopram (mean dosage: 16.5 mg/d)	CY-BOCS	No significant improvement	Increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypy, diarrhoea, insomnia, dry skin or pruritus
Kent et al	30 low-dose, 31 high-dose, 35 placebo		5–17	Risperidone (low-dose: 0.125 mg/day [20 to < 45 kg], 0.175 mg/day [> 45 kg] or high-dose: 1.25 mg/day [20 to < 45 kg], 1.75 mg/day [> 45 kg])	CY-BOCS	Improvement of CY-BOCS score significantly	Increased appetite, sedation, somnolence, weight gain
Chugani et al	54 low-dose, 55 high-dose, 57 placebo	24 weeks	2–6	Buspirone (low dose: 2.5 mg/Ml, high dose: 5 mg/Ml)	ADOS RBS	2.5 mg buspirone group showed significant improvement of ADOS RBS	Psychiatric, respiratory, general gastrointestinal, infections, neurological, nutrition, skin, renal and urinary, immune system, musculoskeletal, ear
Reddihough et al	75 intervention, 71 placebo	16 weeks	7.5–18	Fluoxetine (starting 4–6 mg/d, titrated up to 20–30 mg/d)	CYBOCS-PDD	Improvement of CYBOCS-PDD score significantly	mood disturbance, irritability, gastrointestinal problems such as nausea and diarrhoea, and sleep disorders
Herscu et al	78 intervention, 80 placebo	14 weeks	5–17	Fluoxetine (mean dose 11.8 mg/day)	CY-BOCS	No significant improvement	Insomnia, activation syndrome, agitation, upper respiratory tract infection, diarrhoea, vomiting

Y-BOCS Yale–Brown Obsessive Compulsive Scale, *CY-BOCS* Children's Yale-Brown Obsessive Compulsive Scale, *ADOS RBS* Autism Diagnostic Observation Schedule Repetitive Behaviors Scale, *CYBOCS-PDD* Children's Yale-Brown Obsessive Compulsive Scales modified for pervasive developmental disorders

transporter on the platelet membrane, results in hyperserotonemia in ASD patients [34, 35]. On the other hand, some studies have demonstrated that low levels of serotonin in children with ASD during early brain development, due to decrease serotonin production in the frontal cortex or decrease in tryptophan metabolism [36, 37]. Positron emission tomography (PET) studies have shown decrease serotonin in the cerebrospinal fluid in ASD children less than 5 years old [36]. Furthermore, the metabolic profile of lymphoblastoid cell lines from ASD patients has demonstrated a deficiency in enzyme responsible for the conversion of tryptophan to serotonin [37]. Serotonin dysregulation in ASD patients is associated with symptoms of anxiety and repetitive behaviours [38].Therefore, SSRIs, which block the reuptake of serotonin, may be effective in reversing the dysregulation of serotonin that caused hyperserotonemia in ASD patients [36]. Furthermore, glutamate dysregulation is also implicated in OCD where magnetic resonance imaging (MRI) of patients with OCD demonstrated increased in glutamate levels in caudate regions of the brain [39]. The glutamate levels in the caudate region decreased significantly after treatment with SSRIs and are associated with improved OCD severity and symptoms [39]. In addition, ASD individuals also demonstrated dysregulation of the glutamate system, which include increased glutamate levels in the blood and brain and disequilibrium of glutamate receptor 6 gene [40, 41].

SSRI fluoxetine has shown to be effective in reducing the severity and frequencies of restricted and repetitive behaviour in ASD patients [42]. Several clinical trials have demonstrated improvement in CY-BOCS compulsion scale with low-dose fluoxetine in ASDs patients [20, 26, 27]. Low-dose fluoxetine is generally well-tolerated and favourable safety profile, and the dosage should be titrated if there is presence of side effects such as irritability, hyperactivity, impulsivity, aggression, and sleep disturbances [42]. Children and adolescents weighing less than 30 kg should be prescribed a maximum of 20 mg, and 30 mg for those weighing more than 40 kg, as higher doses are associated with side effects [43]. Sertraline has also been used in OCD in ASD adolescents and demonstrated the efficacy in reducing the symptoms [16]. Two clinical trials reported a significant decrease in self-injury, aggression, and repetitive behaviours in adults with ASD treated with sertraline of dosage ranged from 25–200 mg/day with minimal side effects [44, 45]. A case series in children with ASD aged 6 to 12 years showed decrease in the symptoms such as anxiety, irritability, agitation and panic [46]. However, a randomized control trial demonstrated that low-dose sertraline (2.5–5.0 mg/d) showed no difference in expressive language, cognitive and adaptive functioning compared to placebos [47]. Nevertheless, some patient showed improvement in CGI-I with sertraline and the lack of efficacy in the RCT may be due to the heterogenous developmental trajectories and behavioural manifestations [47]. Furthermore, three case reports have demonstrated that paroxetine treatment is effective in ASD by reducing the symptoms of stereotypies, OCD, anxiety, self-harm, and temper tantrums with variable minimum effective dosage from 10 to 40 mg/day [42].

Some children response to fluoxetine at lower dose of 4 to 8 mg/day but other children required higher dose of 15 to 40 mg/day for effective response [42]. Some studies showed that fluoxetine and citalopram are not effective for obsessive–compulsive behaviour which may be due to inadequate dosage used in the clinical trials [23, 27]. Clinical trials have demonstrated that a dosage of 20 to 60 mg/day is required to decrease CY-BOCS scores in OCD of non-ASD children and adolescents [48, 49]. The response to SSRI in different children with ASD may be due to the interactions between genetic and environmental factors [50]. A study also demonstrated that fluvoxamine which is a SSRI is more effective in ASD patients with long allele of serotonin transporter gene promoter region polymorphism (5-HTTLPR) [51]. Similarly, the 5-HTTLPR polymorphic repeat at *SLC6A4* gene promoter region showed a positive response to escitalopram with an improvement of Aberrant Behavior Checklist (ABC) Irritability Subscale in ASD patients [52]. However, another study conducted by Najjar and colleagues did not showed an association between the clinical response of escitalopram and serotonin transporter (SLC6A4) and serotonin-2A receptor (HTR2A) genes in ASD patients [53]. The response of SSRI in ASD patients with OCD is variable with different optimal dosages, tolerability, and efficacy of reducing symptoms [42]. Furthermore, some studies might have encountered limitations associated with the application of CY-BOCS-PDD in individuals with ASD to gauges improvements of obsessive–compulsive symptoms which can be pleasurable or distressing that impair daily function given the wide spectrum of repetitive behaviours observed in individuals with ASD [54]. Besides that, trials show that SSRIs are effective in adults with ASD, suggesting the possibility that SSRIs may yield greater benefits and improved tolerance in post-pubertal individuals with ASD [54].

Antipsychotics

Children and adolescents who have been diagnosed with both OCD and ASD has nearly three times more likely to prescribed with antipsychotics compared to those diagnosed with ASD or OCD alone [31]. Two antipsychotics which are risperidone and aripiprazole are approved by FDA for management of irritability in children and

adolescent with ASD [38]. Randomized-controlled trials have suggested that treatment with second-generation antipsychotics have potential to reduce repetitive and obsessive–compulsive behaviours in children with ASD [21, 24]. Risperidone acts as dopamine D2, noradrenergic α2, and serotonin 5-HT2 receptors antagonist [42]. High-dose risperidone in children with ASD is effective in managing of irritability symptoms and improving of obsessive–compulsive behaviour, but not in low-dose risperidone [24]. However, high-dose risperidone treatments in children with ASD have been associated with increase weight gain [24]. Aripiprazole acts as an antagonist in hyperdopaminergic regions or as a partial agonist in hypodopaminergic regions, primarily targeting dopamine D2 receptors [55]. Additionally, aripiprazole also acts as a partial agonist on serotonin 5-HT1A and 5-HT2C receptors and antagonist on serotonin 5HT2A receptors [55]. Aripiprazole shows positive outcomes for irritability and hyperactivity in 30–50% of children and adolescents with ASD [56]. However, approximately two-thirds of children on aripiprazole continue to exhibit residual symptoms or do not respond to aripiprazole, necessitating additional pharmacological therapies [56, 57]. Risperidone has a slightly higher efficacy and a higher risk of adverse effects when compared to aripiprazole. However, aripiprazole is effective and well-tolerated in children and adolescents who switch from risperidone due to adverse effects [58]. Therefore, it is imperative that ASD children requiring antipsychotic medications are administered the lowest effective dosage, particularly as they undergo growth and maturation, as higher doses are associated with a range of potentially severe adverse effects, including metabolic syndromes, sedation, tardive dyskinesia, and potential impacts on their growth [24].

Conclusion

Through this review, the findings from the case reports and randomized controlled trials shows that management of OCD behaviours in individuals with ASD and related conditions is of complex nature. Primarily, this review demonstrated the variability in the efficacy of pharmacological interventions within this patient cohort. Antidepressants such as SSRI, antipsychotics and anxiolytics have been used but the effectiveness varied, where some showed improvements while others did not, depending on the dosage, individual variability in response as well as potential side effects. Hence, more comprehensive research and deeper knowledge and understanding of the underlying pathophysiology of the condition is important in optimizing pharmacological management for patients with OCD behaviours with underlying ASD. Besides that, it is also important to note that non-pharmacological treatment that is individualized and tailored specifically for the patients such as cognitive behavioural therapy may be important in achieving better results and outcomes in the long run.

Abbreviations

ADHD	Attention deficit hyperactivity disorders
ASD	Autism spectrum disorders
ASSQ	Autistic Symptom/Syndrome Questionnaire
CY-BOCS	Children's Yale Brown Obsessive–Compulsive Scale
DMDD	Disruptive mood dysregulation disorder
DSM	Diagnostic and Statistical Manual
GAD	Generalized anxiety disorder
MDD	Major depressive disorder
MRI	Magnetic resonance imaging
NVLD	Nonverbal learning disability
OCD	Obsessive–compulsive disorder
PET	Positron emission tomography
RCT	Randomized control trials
SRS	Social and Responsiveness Scale
SSRI	Selective serotonin reuptake inhibitors
SCQ	Social Communication Questionnaire
Y-BOCS	Yale Brown Obsessive–Compulsive Scale

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Declarations

Ethics approval and consent to participate

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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