

The role of drugs in the treatment of autism

SUMMARY

The prevalence of autism spectrum disorder is increasing. It usually presents in childhood with abnormal behaviour and development.

The diagnosis can be difficult. There are often comorbidities which can cause confusion.

Non-drug treatments are first line. Drug treatment is not effective for the core symptoms of autism spectrum disorder. However, drugs may have a role in managing comorbidities and related symptoms, such as irritability and aggression.

Anxiety is a common comorbidity. Cognitive behaviour therapy can be effective, but in some cases selective serotonin reuptake inhibitors may have a role.

Most patients have problems sleeping, but drugs are not usually used to treat sleep disorders in children.

Antipsychotics, such as risperidone, may be considered for irritability and aggression. Clonidine is first line for children with Tourette syndrome. Patients need regular monitoring because of the adverse effects of these drugs.

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Introduction

The number of people with autism spectrum disorder is growing throughout the western world, partly due to changes in diagnostic methods and criteria.¹ In 2018 there were 205,200 Australians with autism, a 25.1% increase from the 164,000 with the condition in 2015.²

The symptoms usually begin in early childhood with the child experiencing problems with social skills, speech and behaviour. Comorbidities are common.

The challenges in managing the disorder are wide and varied. They include:

- communicating with those who have poor speech and language skills
- differentiating the clinical features of autism spectrum disorder from the symptoms of emerging or current mental illness
- determining a treatment plan that addresses very challenging symptoms such as aggression, agitation, impulsivity and obsessions
- avoiding polypharmacy where possible, while also treating a range of mental illnesses.

Many of the drugs prescribed in autism spectrum disorder have limited supporting evidence and some have significant adverse effects so monitoring is required. The impact of drug therapy on the patient and their family must be taken into account.³

Pathophysiology

The current hypotheses propose that autism spectrum disorder is caused by, at least in part, dopamine

signalling abnormalities in the brain.⁴ This impacts on the prefrontal cortex and the mesocorticolimbic circuit⁵ which affect behaviour and emotional regulation.

There have been many other postulated neurotransmitter-related causes.⁵ These include reduced GABAergic gene expression, increases in glutamate transport proteins, and serotonin transporter gene polymorphisms. Dopamine, glutamate and serotonin have therefore been considered as targets for drug treatment.

Comorbidity

Studies show a high rate of comorbid mental illness in autism spectrum disorder. In one study 74% of young people with autism spectrum disorder had at least five comorbidities.⁶ Another study reported comorbidity rates of:

- 28% for attention deficit hyperactivity disorder (ADHD)
- 20% for anxiety disorders
- 13% for sleep–wake disorders
- 12% for disruptive, impulse-control and conduct disorders
- 11% for depressive disorders
- 9% for obsessive compulsive disorder
- 5% for bipolar disorders
- 4% for schizophrenia spectrum disorders.⁷

It is important to remember that a deterioration in behaviour may not be directly related to the disorder. For example, it may be triggered by an underlying physical illness.

Non-drug treatment

Non-drug therapies are first-line interventions, particularly for children under seven or eight years of age, to try and assist with their developmental trajectory. The strategies that are used include psychology-based therapy with cognitive behaviour therapy, narrative therapy, schema therapy and positive behaviour support.³ Occupational therapy can assist with fine and gross motor skills, interoception skills and social skills.⁸

Drug-treatment strategies

Drugs may be added to augment non-drug therapies or to help with comorbidities. Historically, the most common drugs used for autism spectrum disorder were antipsychotics such as haloperidol.⁹ As diagnostic definitions were clarified, modern drugs, including atypical antipsychotics, were studied in children with psychiatric diagnoses.¹⁰

There have been many small studies, case reports and open-label trials in children with autism spectrum disorder.¹¹ It is important to focus on a low starting dose and a slow increase to reach the best, but lowest, dose for each patient. The Centre for Interventional Paediatric Psychopharmacology and Rare Diseases in the UK suggests that drug treatment begins with small doses (usually an eighth to a sixth of the typical dose), increasing after about 5–6 half-lives of the drug. For most drugs used in Australia that is an increase every three to seven days. A longer titration time is needed for fluoxetine because its active metabolite, norfluoxetine, has a half-life of 9–14-days.¹²

A large concern for all doctors looking after patients with autism spectrum disorder is the risk of polypharmacy. In one study polypharmacy was seen in 34% of the patients who received drug treatment.¹³ However, patients often present with symptoms suggestive of changes in different systems of the brain and it may not be possible to use one drug to treat all the symptoms.

The Table outlines the drugs that may be considered for specific indications.^{14–17} Antipsychotic drugs should only be started by a psychiatrist or paediatrician or in consultation with one. For all antipsychotics ongoing monitoring is required. If possible, monitor weight, fasting lipids, blood glucose, prolactin and liver function every six months with more frequent monitoring at the start of treatment at one month and three months.

Anxiety and depression

Anxiety is one of the most common comorbidities with autism. There are links to difficulties with social communication and therefore the internal discomfort that can be experienced when in groups, going to new environments and when

experiencing change. Talking-based therapies, in particular cognitive behaviour therapy, have good supporting evidence.¹⁸ These techniques are harder to use in children and adults with a severe autism spectrum disorder who find working in a therapeutic relationship and speaking to a therapist about distressing feelings to be intolerable. Drugs have a role when anxiety is interfering in the functional life of a child, such as avoiding school, losing friendships or ceasing activities that were previously enjoyable.

The first-line drugs are selective serotonin reuptake inhibitors (SSRIs) such as sertraline, fluoxetine and fluvoxamine.¹⁹ The onset adverse effects of fluvoxamine,²⁰ which include agitation and anxiety, limit its use as a first-line drug. It is often used after a failed trial of sertraline or fluoxetine.

To provide the low doses required for some SSRIs, a compounding chemist may be needed to prepare a low-concentration liquid form.

Sertraline, fluoxetine and fluvoxamine can be used for depressive disorders, however there are less research data from children with autism spectrum disorder and a mood disorder. Treatment is considered on a case-by-case basis after specialist assessment.³ There is the risk for increased suicidal thinking occurring when using SSRIs. The harm–benefit ratio for each patient needs to be considered as well as monitoring for an increase in suicidal thinking in the first two weeks of treatment.¹¹

Mood lability

Children with autism spectrum disorder who present with externalising behaviours, which are behaviours that are targeted toward the external environment when distressed such as physical aggression, threats and destroying property, often have a labile mood. They also often have learning disorders, poor self-regulation and behavioural problems at school.

Sodium valproate can be helpful with aggression and is also used to treat irritability and mood lability.²¹

There are insufficient data to indicate the use of other mood stabilisers. Sodium valproate has many adverse effects including nausea, poor attention, skin reactions including Stevens-Johnson syndrome, and liver toxicity. It is best avoided in females because of its teratogenicity and has also been associated with polycystic ovary syndrome.

Tics and Tourette syndrome

Clonidine is the first-line treatment for tics and Tourette syndrome. There is evidence that atypical antipsychotics such as aripiprazole can also be used for treatment. Aripiprazole reduces the symptoms of Tourette syndrome, and can be used when there

Table Drugs that can be considered for comorbidities in children with autism^{14-17,27}

Drug	Dose	Half-life	Best indication	Common adverse effects in young people
Sertraline	Start 0.5 mg/kg, up to 2 mg/kg. Gradual dose increases are recommended. Common dose range is 50-200 mg a day. Alternatively: <ul style="list-style-type: none"> • over 6 years – start at 25 mg and increase to 50 mg after 1 week then by 25 mg monthly • 6-18 years – maximum dose 200 mg a day. 	27 hours	Anxiety disorders, particularly generalised anxiety disorder	In younger children agitation, labile mood. Risk of increased suicidal thinking Withdrawal symptoms if the dose is not tapered off slowly
Fluoxetine	Start 0.5 mg/kg, up to 1 mg/kg. Average dose for 7-12 years – 20-30 mg a day. 12 years and over with eating disorders or obsessive compulsive disorder – up to 60 mg may be needed. The maximum dose for other diagnoses is 40 mg a day. Alternatively: <ul style="list-style-type: none"> • under 12 years – start at 5 mg and increase by 5 mg monthly to a maximum of 30 mg • 12 years and over – the maximum dose is 40 mg for major depression and 60 mg for obsessive compulsive disorder. 	Active metabolite norfluoxetine 9-14 days	Depression, obsessive compulsive disorder, eating disorder symptoms including avoidant restrictive food intake disorder	Nausea, headaches, agitation, insomnia Tablets have a strong aversive flavour Risk of increased suicidal thinking
Fluvoxamine	0.5 mg/kg up to 2 mg/kg. Maximum dose generally 150 mg (divided doses once 100 mg a day is given). Alternatively: <ul style="list-style-type: none"> • over 8 years – start at 25 mg and increase by 25 mg monthly. 	15.6 hours	Obsessive compulsive disorder, significant anxiety disorders	Agitation, restlessness, onset and offset adverse effects when starting and weaning Risk of increased suicidal thinking
Sodium valproate	5 mg/kg once a day for 2 weeks then increase if needed for mood, up to maximum of 20 mg/kg (divided doses once over 200 mg a day).	8-20 hours	Can help with mood lability and aggression particularly in those with comorbid intellectual impairment	Nausea, metallic taste, fatigue, weight gain, poor attention, Stevens-Johnson syndrome, liver toxicity Sevenfold increase in polycystic ovary syndrome Need to monitor blood concentrations, but many children with autism spectrum disorder cannot tolerate venepuncture
Risperidone	Over 5 years and below 20 kg – 0.25 mg once daily for 3 days, then increase to 0.5 mg daily. If necessary, increase by 0.25 mg every 2 weeks. Usual range 0.5-1.5 mg daily. Over 5 years and over 20 kg – 0.5 mg once daily for 3 days, then increase to 1 mg daily. If necessary, increase daily dose by 0.5 mg every 2 weeks. Usual range 1-2.5 mg daily, maximum 3 mg daily.	3-20 hours	Used in autism spectrum disorder, approved by Therapeutic Goods Administration, best for agitation, aggression, impulsivity	Weight gain, increased appetite including hoarding of food at times

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Table Drugs that can be considered for comorbidities in children with autism^{14-17,27} (continued)

Drug	Dose	Half-life	Best indication	Common adverse effects in young people
Aripiprazole	6-18 years - 2.5 mg once daily for 1 week, then 5 mg once daily. If necessary, increase daily dose in 5 mg increments at intervals of at least a week, to a maximum of 15 mg once daily.	75 hours	Agitation, irritability	Less weight gain than risperidone but little sedation and can be an activating drug
Olanzapine	13-18 years if under 40 kg - 2.5 mg at night, maximum dose 5 mg. 13-18 years if over 40 kg - up to 5 mg at night, maximum dose 10 mg.	21-54 hours	Aggression and mood lability when risperidone, aripiprazole and sodium valproate have not been effective	Significant sedation, weight gain and hypersalivation
Quetiapine	Over 13 years old and under 40 kg - 25 mg at night, increase to 25 mg twice a day (or 50 mg long-acting) if tolerated, maximum dose 50 mg a day. Over 13 years old and over 40 kg - 25 mg at night and increase up to maximum dose 100 mg a day if tolerated.	7-12 hours		
Atomoxetine	0.5 mg/kg a day increasing after at least 3 days. Maximum 1.2-1.4 mg/kg a day or 100 mg, whichever is lower.	17 hours	ADHD, slightly better results for inattention	Nausea, fatigue ²⁷
Methylphenidate	Under 12 years - 5 mg twice a day. Over 12 years - 10 mg twice a day. Maximum 60 mg daily.	Children: 2.5 hours Adults: 3.5 hours	ADHD	Weight loss, poor weight gain, palpitations, agitation
Dexamfetamine	6-12 years - start at 2.5 mg daily and increase at weekly intervals. Usual maximum is 20 mg in 2 divided doses. Over 12 years - 5 mg every morning, daily dose may be increased by 5 mg at weekly intervals until optimal response. Maximum 40 mg a day.	12 hours	ADHD	Weight loss, poor weight gain, palpitations, agitation
Lisdexamfetamine	6-18 years - 30 mg once each morning - if necessary, increase the daily dose by 20 mg at intervals of at least a week. Maximum 70 mg daily.			
Guanfacine	Starting dose of 1 mg. Under 11 years - increase to maximum of 4 mg a day. Over 11 years - increase to maximum of 7 mg a day.	10-30 hours	ADHD	Fatigue, weight gain ²⁷

ADHD attention deficit hyperactivity disorder

is little response to psychological interventions or when there is a contraindication or no response to clonidine.²² Aripiprazole may be better tolerated than clonidine.²³

Irritability and aggression

Aggression is one of the most common sources of concern for parents of children with autism spectrum disorder. It can cause large interruptions in their schooling, relationships, their ability to leave the home and it can greatly disrupt a family.

Often antipsychotics such as aripiprazole and risperidone have been used to help treat irritability and problem behaviours in children and adolescents with autism spectrum disorder.^{24,25} In Australia, risperidone is approved by the Therapeutic Goods Administration for irritability and aggression in autism in patients under 18 years of age. However, the risks with risperidone include weight gain, elevated lipids, blood glucose and prolactin, and interruption of puberty. Aripiprazole has been used in other countries, in particular the USA, as it causes less weight gain and has less effect on prolactin. It is not as sedating as risperidone and this can cause difficulties for families if they have been using risperidone to settle night-time aggression and to improve sleep.

Before prescribing, record height, weight, menarche and regularity of menstruation, blood glucose, fasting lipids and prolactin. Monitor these again after one month and then six-monthly. An increase in prolactin or the development of abnormal muscle movements requires the drug dose to be lowered and a review of the antipsychotic therapy.

At present, due to small sample sizes and open-label studies, there is insufficient evidence to show that antipsychotics such as olanzapine, quetiapine, ziprasidone or clozapine are effective in autism spectrum disorder.^{10,11} There is also little evidence that older antipsychotics, antiepileptic drugs and glutaminergic modulators (such as ketamine and memantine) are helpful in managing aggression.²⁵ Sodium valproate can be tried if antipsychotics are not effective or the patient cannot tolerate them.²¹

For some patients with a poor response to risperidone and aripiprazole, off-label use of an alternate antipsychotic can be considered.²⁶

Attention deficit hyperactivity disorder

ADHD is a common comorbidity with autism spectrum disorder.^{7,27} The drugs used in treatment are the same as those used for ADHD alone, namely methylphenidate, dexamfetamine, guanfacine and atomoxetine.²⁷ Stimulant treatment improves the

symptoms of ADHD in patients with autism spectrum disorder. Atomoxetine can assist with inattentive ADHD and patients with comorbid anxiety symptoms. The adverse effects include nausea and fatigue.²⁸

Insomnia

Insomnia and sleep disorders affect close to 80% of people with autism spectrum disorder, and often present as a sleep onset disorder. Behavioural management is the mainstay of treatment.

There are few drugs that are useful for sleep disorders in children. Benzodiazepines are not recommended. Antipsychotics should also be avoided because of their high risk of adverse effects. Melatonin is often used to manage sleep disorders in children, partly because it is available over-the-counter in overseas countries. It has a low risk of adverse effects and dependency.²⁹ Clonidine in low dose (50–200 microgram at night) has also been used, in particular when the insomnia is secondary to stimulant treatment.¹¹

Conclusion

Many patients and families seek medical-based intervention for the core symptoms of autism spectrum disorder including social and emotional skills, rigid thinking and poor theory of mind. For these features of autism spectrum disorder non-drug treatments are first line and are focused on psychology input, social skills groups, peer mentors, and support in education and employment.

Assistance with managing aggression and irritable behaviours may be obtained by using risperidone or aripiprazole, with risperidone having the most research-based data at present. There is little evidence for the use of other antipsychotics or glutaminergic drugs such as ketamine and memantine.

The most common comorbidity is anxiety and SSRIs can be helpful. The possibility of comorbid ADHD is important to consider. Comorbid ADHD can be treated with the same drugs as ADHD alone and for some patients it can be used with an antipsychotic to manage hyperactivity, inattention and aggression.

Polypharmacy should be avoided if possible but comorbid conditions need to be addressed. However, the use of an atypical antipsychotic for aggression and irritability, plus an SSRI for an anxiety disorder or drugs for ADHD, may be needed for patients with these common comorbidities. <

Conflict of interest: none declared



SELF-TEST QUESTIONS

True or false?

1. Dexamfetamine is the first-choice drug for managing the core symptoms of autism spectrum disorder.
2. Risperidone should not be used in patients with irritability, related to autism spectrum disorder, under the age of 18 years.

Answers on page 225

REFERENCES

- King M, Bearman P. Diagnostic change and the increased prevalence of autism. *Int J Epidemiol* 2009;38:1224-34. <https://doi.org/10.1093/ije/dyp261>
- Australian Bureau of Statistics. Autism in Australia. In: 4430.0 - Disability, ageing and carers, Australia: summary of findings, 2018. www.abs.gov.au/statistics/health/disability/disability-ageing-and-carers-australia-summary-findings/latest-release [cited 2020 Nov 1]
- Howes OD, Rogdaki M, Findon JL, Wichers RH, Charman T, King BH, et al. Autism spectrum disorder: consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. *J Psychopharmacol* 2018;32:3-29. <https://doi.org/10.1177/0269881117741766>
- Pavál D. A dopamine hypothesis of autism spectrum disorder. *Dev Neurosci* 2017;39:355-60. <https://doi.org/10.1159/000478725>
- Eissa N, Al-Houqani M, Sadeq A, Ojha SK, Sasse A, Sadek B. Current enlightenment about etiology and pharmacological treatment of autism spectrum disorder. *Front Neurosci* 2018;12:304. <https://doi.org/10.3389/fnins.2018.00304>
- Joshi G, Petty C, Wozniak J, Henin A, Fried R, Galdo M, et al. The heavy burden of psychiatric comorbidity in youth with autism spectrum disorders: a large comparative study of a psychiatrically referred population. *J Autism Dev Disord* 2010;40:1361-70. <https://doi.org/10.1007/s10803-010-0996-9>
- Lai MC, Kassee C, Besney R, Bonato S, Hull L, Mandy W, et al. Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. *Lancet Psychiatry* 2019;6:819-29. [https://doi.org/10.1016/S2215-0366\(19\)30289-5](https://doi.org/10.1016/S2215-0366(19)30289-5)
- National Institute for Health and Care Excellence (NICE). Autism spectrum disorder in under 19s: support and management. Clinical guideline CG170. 2013 Aug 28. <http://www.nice.org.uk/guidance/cg170> [cited 2020 Nov 1]
- Faretra G, Doohar L, Dowling J. Comparison of haloperidol and fluphenazine in disturbed children. *Am J Psychiatry* 1970;126:1670-3. <https://doi.org/10.1176/ajp.126.11.1670>
- Campbell M, Cueva JE. Psychopharmacology in child and adolescent psychiatry: a review of the past seven years. Part I. *J Am Acad Child Adolesc Psychiatry* 1995;34:1124-32. <https://doi.org/10.1097/00004583-199509000-00008>
- Hollander E, Phillips AT, Yeh CC. Targeted treatments for symptom domains in child and adolescent autism. *Lancet* 2003;362:732-4. [https://doi.org/10.1016/S0140-6736\(03\)14236-5](https://doi.org/10.1016/S0140-6736(03)14236-5)
- Santosh PJ, Singh J. Drug treatment of autism spectrum disorder and its comorbidities in children and adolescents. *BJPsych Adv* 2016;22:151-61. <https://doi.org/10.1192/apt.bp.115.014597>
- Murray ML, Hsia Y, Glaser K, Simonoff E, Murphy DG, Asherson PJ, et al. Pharmacological treatments prescribed to people with autism spectrum disorder (ASD) in primary health care. *Psychopharmacology (Berl)* 2014;231:1011-21. <https://doi.org/10.1007/s00213-013-3140-7>
- US Food and Drug Administration. Drugs@FDA: FDA-approved drugs. www.accessdata.fda.gov/scripts/cder/daf [cited 2020 Nov 1]
- Stahl Online. The prescriber's guide. 6th ed. Cambridge: Cambridge University Press; 2020. https://stahlonline.cambridge.org/prescribers_guide.jsf [cited 2020 Nov 1]
- Shann F. Drug doses. 17th ed. Melbourne: Collective Pty Ltd; 2017.
- AMH Children's Dosing Companion. Adelaide: Australian Medicines Handbook; 2020. <https://childrens.amh.net.au> [cited 2020 Nov 1]
- Wood JJ, Drahota A, Sze K, Har K, Chiu A, Langer DA. Cognitive behavioral therapy for anxiety in children with autism spectrum disorders: a randomized, controlled trial. *J Child Psychol Psychiatry* 2009;50:224-34. <https://doi.org/10.1111/j.1469-7610.2008.01948.x>
- Nadeau J, Sulkowski ML, Ung D, Wood JJ, Lewin AB, Murphy TK, et al. Treatment of comorbid anxiety and autism spectrum disorders. *Neuropsychiatry (London)* 2011;1:567-78. <https://doi.org/10.2217/npv.11.62>
- Reinblatt SP, DosReis S, Walkup JT, Riddle MA. Activation adverse events induced by the selective serotonin reuptake inhibitor fluvoxamine in children and adolescents. *J Child Adolesc Psychopharmacol* 2009;19:119-26. <https://doi.org/10.1089/cap.2008.040>
- Hollander E, Chaplin W, Soorya L, Wasserman S, Novotny S, Rusoff J, et al. Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. *Neuropsychopharmacology* 2010;35:990-8. <https://doi.org/10.1038/npp.2009.202>
- Quezada J, Coffman KA. Current approaches and new developments in the pharmacological management of Tourette Syndrome. *CNS Drugs* 2018;32:33-45. <https://doi.org/10.1007/s40263-017-0486-0>
- Hollis C, Pennant M, Cuenca J, Glazebrook C, Kendall T, Whittington C, et al. Clinical effectiveness and patient perspectives of different treatment strategies for tics in children and adolescents with Tourette syndrome: a systematic review and qualitative analysis. *Health Technol Assess* 2016;20:1-450. <https://doi.org/10.3310/hta20040>
- Lake JK, Denton D, Lunsy Y, Shui AM, Veenstra-VanderWeele J, Anagnostou E. Medical conditions and demographic, service and clinical factors associated with atypical antipsychotic medication use among children with an autism spectrum disorder. *J Autism Dev Disord* 2017;47:1391-402. <https://doi.org/10.1007/s10803-017-3058-8>
- Fung LK, Mahajan R, Nozzolillo A, Bernal P, Krasner A, Jo B, et al. Pharmacologic treatment of severe irritability and problem behaviours in autism: a systematic review and meta-analysis. *Pediatrics* 2016;137 Suppl 2:S124-35. <https://doi.org/10.1542/peds.2015-2851K>
- Fitzpatrick SE, Srivorakiat L, Wink LK, Pedapati EV, Erickson CA. Aggression in autism spectrum disorder: presentation and treatment options. *Neuropsychiatr Dis Treat* 2016;12:1525-38. <https://doi.org/10.2147/ndt.s84585>
- Antshel KM, Russo N. Autism spectrum disorders and ADHD: overlapping phenomenology, diagnostic issues, and treatment considerations. *Curr Psychiatry Rep* 2019;21:34. <https://doi.org/10.1007/s11920-019-1020-5>
- Patra S, Nebhinani N, Viswanathan A, Kirubakaran R. Atomoxetine for attention deficit hyperactivity disorder in children and adolescents with autism: a systematic review and meta-analysis. *Autism Res* 2019;12:542-52. <https://doi.org/10.1002/aur.2059>
- Abdelgadir IS, Gordon MA, Akobeng AK. Melatonin for the management of sleep problems in children with neurodevelopmental disorders: a systematic review and meta-analysis. *Arch Dis Child* 2018;103:1155-62. <https://doi.org/10.1136/archdischild-2017-314181>