

37 - Pharmacological treatment of core ASD symptom

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Prescribing in children and adolescents CHAPTER 5 Autism spectrum disorder (ASD) in children and adolescents Autism spectrum disorder is a complex condition characterised by core deficits in social communication development and behaviour (stereotypies and/or restricted and unusual patterns of interests) as well as sensory difficulties. ICD-11 now matches DSM-5 in removing the subtypes of autism (e.g. the term Asperger's syndrome has been discontinued). In addition, ICD-11 distinguishes between ASD with or without intellectual development. DSM-5 recommends recording whether or not there is accompanying intellectual impairment. The heterogeneity of ASD poses assessment and treatment challenges. Co-occurring mental health conditions are highly prevalent in ASD with 69–79% of individuals experiencing at least one in their lifetime.^{2,3} These include attention deficit hyperactivity disorder (ADHD), disruptive behavioural disorders, anxiety and obsessive compulsive and mood disorders. Other associated problems include intellectual disability, epilepsy, sleep disturbance, self-harm, irritability and aggression towards others. Associated neurodevelopmental, medical and psychiatric disorders complicate the symptom profile and affect overall outcome. Evaluating and optimally treating co-occurring conditions and/or associated problem behaviours are, therefore, essential. Currently there are no validated or licensed pharmacological treatments that alleviate core ASD symptoms.^{4,5} Targeting problem behaviours and comorbid psychiatric conditions with pharmacological interventions is, however, common practice. Pharmacotherapies are commonly used in individuals with ASD as adjuncts to psychological interventions. The evidence to date^{4,6} shows reasonable efficacy of risperidone and aripiprazole for irritability and aggression; supports the use of methylphenidate, atomoxetine and guanfacine for ADHD and melatonin for sleep problems; but shows limited efficacy of SSRIs for anxiety, depression and repetitive behaviours. The evidence for antiepileptics remains inconsistent. There is a potential role for $\alpha 2$ agonists, cholinergic agonists, glutamatergic agents, gamma-aminobutyric acid (GABA) agonists and oxytocin but these require further investigation.^{4,6}

Individuals with ASD are likely to experience more severe adverse effects than typically developing individuals.⁴⁻⁶ Therefore, achieving an effective dose with minimum adverse effects can be a challenging task. Treatment should be initiated in small doses and increased about every five half-lives of the drug, and it may take 4-6 weeks of titration to determine the therapeutic dose for each individual case.⁷ Excluding any medical conditions, the presence of pain or any other physical discomfort such as gastro-esophageal reflux must be a priority before managing problem behaviour with psychotropic drugs. A comprehensive physical examination should be part of standard practice. The efficacy and adverse effects associated with pharmacotherapy in individuals with ASD should be systematically monitored in view of their impaired communication and the increased propensity for more adverse effects. Standardised behaviour rating scales and adverse effect checklists are essential tools in monitoring progress.⁸ Pharmacological treatment of core ASD symptoms Evidence from clinical trials to date has not demonstrated clear efficacy of any psychotropic agent in routinely treating core symptoms of ASD.^{4,6}

606 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 Restricted repetitive behaviours and interests (RRBIs) RRBIs are distressing and disruptive to functioning and therefore an important treatment target to improve overall outcomes in ASD.⁹ Behavioural therapies should be used as first line. When RRBIs are severe with significant impact on functioning and/or pose risks to others or self then pharmacotherapy can be considered. A Cochrane review (last updated in 2013) found 'no evidence of effect of SSRIs on reducing RRBIs in children and emerging evidence of harm' although there are data that support their use in adults.¹⁰ A 2022 meta-analysis of 16 studies demonstrated a small effect size for antidepressants in treating restricted and repetitive behaviours. Subgroup analyses indicated that clomipramine had a higher efficacy than SSRIs and adults had a better response than adolescents and children.¹¹ Risperidone is probably effective in reducing RRBIs in children who have high levels of irritability or aggression¹² (any specific efficacy for repetitive behaviours is doubtful). Reductions in stereotypical behaviours have also been reported¹³⁻¹⁶ albeit in studies with methodological limitations.⁶ A 2020 meta-analysis of studies on a wide range of currently available pharmacological agents showed evidence supporting only antipsychotic medication,¹⁷ whereas another recent meta-analysis of nine studies found no evidence for any pharmacological agent in reducing RRBIs.¹⁸ Overall, given the profile of adverse effects of dopamine-blocking agents, consensus guidance from the British Association for Psychopharmacology⁶ rightly cautions against their routine use for the treatment of RRBIs. If they are used, they should be prescribed in small doses and as part of a carefully considered, time-limited and monitored overall treatment plan. Social and communication impairment Currently, no drug has been consistently shown to improve the core social and communication impairments in ASD.⁷ Risperidone may have a secondary effect through improvement in irritability.¹⁹ Analysis of data from two multicentre trials suggested that risperidone was effective for the treatment of social disability in children with ASD.²⁰ Glutamatergic drugs and oxytocin looked promising.²¹ However, two meta-analyses and two recent double-blind placebo-controlled trials suggested that oxytocin has no significant effect on social communication.²²⁻²⁵ Larger studies with better methodology are needed.^{23,26} Sulforaphane has shown mixed results with both positive and negative trials.²⁷⁻²⁹ Insulin growth factor 1 (IGF-1)³⁰ awaits further work to prove its efficacy in modifying ASD core symptoms, as do glutamatergic agents.³¹⁻³³ Acetylcysteine³⁴ is probably not effective. Three small double-blind placebo-controlled trials using folinic acid for language impairment look encouraging.³⁵ There is growing but inconsistent evidence for dietary interventions reducing ASD core symptoms.^{36,37} The targeting of the gut microbiome, including probiotic treatment and faecal microbiota transplants, has drawn much interest.³⁸ However, there is little evidence to

support the use of nutritional supplements or dietary therapies for children with ASD³⁶ or indeed any relationship between maternal food intake and child's diet and the development of ASD/symptoms severity.³⁷

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