



Children and autism

Part 1 – recognition and pharmacological management

BACKGROUND

Autism is a neurodevelopmental disorder characterised by complex aetiology, variable presentation and widely divergent outcomes. It is clear that an individual's intrinsic genetic susceptibility, health, nutritional status and environmental exposures all contribute to the aetiology of autism.

OBJECTIVE

This article aims to assist the general practitioner in recognising and managing a child with an autistic disorder.

DISCUSSION

Screening for autism by the GP can lead to referral for a formal diagnosis, enabling much needed support at an early stage of development, which can improve outcomes for the individual. Currently, evidence for psychotropic use and awareness of adverse effects in young people with autism is limited. Antipsychotic medications are increasingly used in people with autism and the importance of monitoring for adverse effects is paramount. Primary strategies for dealing with children with autism are understanding, environmental modification and behavioural interventions. Combined with these, pharmacological interventions may have benefits for children with autism with extreme or challenging behaviours.

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Case study

Megan presents distraught because her 2.5 year old son Blake has just been diagnosed with an autism spectrum disorder. About 6 months ago Blake had become extremely distressed in the surgery for no apparent reason. At the time, Megan expressed concern to you about Blake's development, particularly that he appeared to have 'lost language'. You remembered that at 18 months of age when you vaccinated Blake he was regularly and appropriately using single words and starting to combine words, but at the time of his second birthday he was rarely speaking. Furthermore, where he had previously been affectionate and engaging, he had become distant and difficult to engage. At the time you told Megan that Blake's changes may simply have been due to the birth of her second child when Blake was aged 20 months, but you wrote a referral to a paediatrician because you were concerned about Blake's deviation from his previous developmental path.

The paediatrician was immediately concerned; he engaged a speech pathologist to start therapy with Blake and ordered a range of blood tests, an electroencephalogram (EEG), a magnetic resonance image (MRI) of the brain and referred him to the multidisciplinary team at the local autism association. Results of these investigations resulted in Blake receiving a diagnosis of autistic disorder (AD).

Although in some ways relieved to have a diagnosis and keen to commence an intervention program, Megan is clearly devastated. She is overwhelmed by the amount of information she has been given by health professionals and information discovered for herself on the internet. She asks you what causes autism and for your advice about managing autism with pharmacological, complementary medicines and dietary interventions.

What is autism?

Autism is a life long, complex neurological developmental disorder. It typically develops during the first 3 years of life and is characterised by a triad of deficits in language/communication, social skills and behavioural repertoire.¹ In recent years, the definition and criteria for diagnosing

autism has been revised and broadened to include milder and more common forms of the disorder.² Autistic disorder (AD) is classified in the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) as one of five related pervasive developmental disorders (PDDs).³ The remaining four PDDs are pervasive developmental disorder not otherwise specified (PDD-NOS), Asperger syndrome, childhood disintegrative disorder and Rett disorder.

Clinical presentation varies between these distinct diagnoses, however all PDDs demonstrate the characteristic triad of core deficits. Approximately 75% of those with AD have concurrent intellectual disability.⁴ Autistic spectrum disorder (ASD) is an umbrella term that is used to represent a broad heterogeneous disorder by collectively grouping AD, Asperger syndrome and PDD-NOS.²

Diagnosis of autistic disorder

Diagnosis of AD typically occurs when a child is approximately 2–4 years of age. Diagnosis is subjective and based on a cluster of behaviours observed clinically as there is currently no laboratory test to diagnose autism. The DSM-IV outlines criteria for the diagnosis of AD and related PDDs.³

Prevalence

A review of epidemiological studies estimated the prevalence of AD to be 13 per 10 000 and the broader spectrum of PDD to be about 60–65 per 10 000.⁵ This is much higher than that reported by studies published between the mid 1960s and mid 1970s, which estimated that 4 per 10 000 of the population had AD. Autistic disorder is about four times more prevalent in boys and does not seem influenced by racial or ethnic status and occurs across the socioeconomic spectrum with similar frequencies.⁶ Epidemiological findings have caused debates about a possible 'epidemic' of autism.⁷ However the apparent increase in prevalence may simply reflect a broadening of the concept of ASD, an increase in public awareness and more inclusive diagnostic criteria.

Aetiology

The exact cause of AD is unknown and it appears to have diverse aetiologies. Approximately 6–10% of affected children have

a medical condition that might have lead to AD (eg. fragile X syndrome, tuberous sclerosis and neurofibromatosis) leaving 90% of cases to be idiopathic.⁵ It appears that genetic predisposition plays a key role in the aetiology of autism although environmental influences are also implicated.⁴ Evidence for the key role genetics plays in autism stems from twin studies where it is reported that there is a 60 and 92% concordance for AD and ASD in monozygotic (identical) twins respectively versus 0 and 10% in dizygotic (nonidentical) twins respectively.^{8,9} The sibling recurrence rate is reported to be 3–7% and the heritability, approximately 90%.² Numerous biochemical abnormalities are theorised to occur in autism including the impairment of sulfoxidation and sulfation leading to compromised liver detoxification ability, copper-zinc imbalance, oxidative stress and intestinal hyperpermeability which can result in exorphin (opioid) intoxication.¹⁰ There is also evidence to suggest the immune system plays a role in the aetiology of autism¹⁰ and that autistic symptoms may be due to immune deficiency, autoimmunity or abnormal immunologic response to infections.¹¹ There are many theories linking autism and immunisation, however there is no scientific evidence to support causality. Numerous epidemiological studies conducted around the world have discounted a connection between immunisation and the development of autism.^{12,13}

Red flags for autism spectrum disorder

As the general practitioner is often the first port of call in the health care system, it is important for GPs to be aware of the developmental red flags in young children that require further investigation if one or more are present. Red flags for autism and related disorders are outlined in *Table 1*.

Management

Children with autism have the same health care needs as children without a disability and benefit from the same nutrition, health promotion and disease prevention activities. Nearly all children will gain varying degrees of benefit from intensive and early intervention, including educational and behavioural

therapy^{15,16} as well as rehabilitative therapies such as speech pathology, physiotherapy and occupational therapy. In addition, they may have health care needs specific to conditions that coexist such as epilepsy. This article, and an accompanying article in the next issue of *Australian Family Physician*, will concentrate on the pharmacological, dietary and complementary therapies used to mitigate the manifestations of autism. In order for GPs to support the child and their family it is crucial they know about behavioural/speech/psychological therapies in autism, however such discussion is beyond the scope of these articles.

Conventional medications

Some children may benefit from the use of pharmacological interventions. When deemed appropriate, medications should generally be initiated by a specialist such as a developmental paediatrician, child neurologist or child psychiatrist. However, GPs may be asked about pharmacological agents used to influence the behaviour of autism and should have an awareness of the potential benefits, limitations and adverse effects. Our understanding of the use of medications in autism is somewhat limited due to the dramatically varying signs and symptoms present in young children with autism, the lack of reliable instruments to measure the effects of medications, the dearth of double blind studies, and the short term duration of pharmacological trials. It has been reported that children with autism have quantitative abnormalities in serotonin, dopamine, opioid, and the gamma-aminobutyric acid neurotransmitter systems. Consequently, pharmacological interventions have included selective serotonin reuptake inhibitors (SSRIs), psychostimulants and antipsychotics. A range of antihistamines and anxiolytics have also been used. The distressing characteristics of the disorder, to both the individual and the parent/carer, make finding pharmacological treatments to reduce autistic symptoms and therefore improve quality of life, of utmost importance.¹⁷ The primary strategies that influence the behaviour of children with autism are understanding, environmental modification

Table 1. Red flags for autism and related disorders¹⁴

- A plateau or regression in development (particularly language or social skills) not typically associated with a regression in physical development
- Speech and language delay (ie. no single words by 2 years), or stereotypical use of language such as repetition or jargon
- A lack of, or reduced social eye contact
- Failure to orient to name
- Failure to 'cuddle in' or lift their arms up to be picked up by parent or caregiver
- Failure to point or use gestures such as showing to engage parent (or caregiver) to share an experience or an object of interest
- Lack of interactive and/or functional play – that is child does not use toys as they should be used but focuses on a particular part of the toy
- Lack of interest in peers
- Unusual preoccupations; may be with parts of objects or interests such as trains or water
- Resistance to change
- Unusual body movements such as hand flapping or twisting, rocking, spinning, pacing, toe walking, unusual sensory interests (eg. over or under reacting to sound and pain, mouthing objects, feeling textures)

and behavioural interventions. However, combined with developmental, educational and behavioural therapies, medications can be helpful in the overall management of autism.¹⁸

Young people with ASD may present with maladaptive behaviours such as aggression, tantrums and impulsivity, which may severely limit their social and developmental progress.¹⁹

SSRIs and psychostimulant medications

Children with autism may have significant symptoms of hyperactivity and inattention and may respond to psychostimulants. In one study, methylphenidate was efficacious in treating hyperactivity associated with PDDs, but the magnitude of response was less than that seen in typically developing children with attention deficit hyperactivity disorder (ADHD).²⁰ Children with autism can also display severe ritualistic and obsessive compulsive behaviours as well as anxiety and depression. Treatment of these symptoms with pharmacotherapy has not been well studied in ASDs. Limited information with SSRIs suggest adults may have a better response than children, and that children may have more troublesome adverse effects that require more cautious dosing strategies.^{21–23} The use of SSRIs in children and adolescents is topical because of their reported potential to increase suicidal thoughts and impulses in young people.²⁴

Antipsychotics

The efficacy of antipsychotics in young people with ASD has been studied for over 20 years.²⁵ Anderson^{26, 27} demonstrated the effectiveness of haloperidol in the treatment of behavioural disturbances in young people with ASD. Many conventional antipsychotics have approval for children with severe behavioural disorders but not specifically for use in autism (eg. haloperidol, chlorpromazine, trifluoperazine, pericyazine). Furthermore, haloperidol and other associated conventional antipsychotics have a high tendency for extra pyramidal side effects which may include withdrawal and tardive dyskinesia, which reduces their acceptance and limits their use.²⁵

Recent research has focused on examining the effectiveness of atypical antipsychotics in treatment of behavioural difficulties that occur in children and adolescents with autism. Risperidone has been shown to be beneficial in children and adolescents with autism in whom destructive behaviours (eg. aggression, impulsivity and self injurious behaviours) are prominent.²⁸ Shea²⁵ was able to demonstrate the efficacy of risperidone in AD and other PDDs in reducing negative behaviours. However, most subjects had a diagnosis of autistic disorder (70%), therefore interpreting efficacy in the other forms of PDDs is limited.

In addition, risperidone has been demonstrated to be beneficial in young patients with AD in a 2 month double blind placebo controlled trial, followed by a 4 month open label continuation study.²⁹ Due to the short duration of trials with risperidone in ASD, it is important to be cognisant that its long term efficacy and safety is still largely unknown.²⁵

Risperidone is the only antipsychotic that has been approved by the Therapeutic Drugs Administration (TGA) for the treatment of behavioural disorders associated with autism in children and adolescents. The recommended daily doses are weight specified: 0.5–1.5 mg for weight <20 kg and 1.0–2.5 mg for weight >20 kg. Risperidone became available through the Pharmaceutical Benefits Scheme (PBS) for the management of symptoms of autism from 1 April 2007.

In contrast, no other atypical antipsychotic is at present approved for the treatment of behavioural disorders in children. Currently, there are only a small number of open label published studies of other atypical antipsychotics, such as olanzapine and quetiapine, with some studies not demonstrating efficacy in paediatric patients with ASDs.²⁵ Newly marketed atypical antipsychotics such as aripiprazole warrant prescribing with extra caution due to inexperience with use in all populations.³⁰

Antipsychotics have the potential to cause many side effects including: weight gain, diabetes, dyslipidaemia and extra pyramidal side effects. Sedation is another adverse effect that can have a negative impact on cognition. Sedative effects may make a child easier to manage but this should never be exploited. Improved patient monitoring has the potential to result in earlier detection of side effects that could, without identification and intervention, result in impaired health of the patient. As antipsychotics have long term safety concerns it is important that monitoring for adverse effects and physical health is undertaken in young people prescribed antipsychotics.³¹ It is crucial that careful consideration be given to the risks versus the benefits when prescribing antipsychotics for children with autism.

Given that psychostimulants, SSRIs and antipsychotics only address the symptoms of autism, and not its underlying causes, Levy

and Hyman¹¹ hypothesise this is the reason why many parents and carers of children with autism turn to complementary and alternative medicines (CAMs) in an attempt to mitigate the manifestations of their child's condition.¹¹ The use of CAMs in the management of autism is discussed in Part 2 of this article in the next issue of *Australian Family Physician*.

Conclusion

Pharmacological interventions may have benefits in a child with autism who has extreme and/or challenging behaviours. In particular, there is a role for psychostimulants in some children with coexisting ADHD, and SSRIs may be helpful in children with obsessions/compulsions. Drug initiation and stabilisation is best undertaken by a developmental paediatrician, child neurologist or child psychiatrist.

An understanding of the difficulties a child with autism faces informs the ways GPs can structure interactions and the environment to decrease their anxiety and distress, and support the development of positive behaviours. For children with autism, as is the case for all children with a disability, a primary focus is the provision of support and assistance to parents in order to minimise negative impacts of the disability on the family and to enable them to support their child's development so they can reach their full potential.

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