Medication in Autism Spectrum Disorder

Dr Paramala J Santosh, MBBS, Dip NB (Psych), MD, PhD, FRCPsych
Visiting Reader, Developmental Neuropsychiatry & Psychopharmacology
Department of Child and Adolescent Psychiatry
PO85. Institute of Psychiatry, 16 De'Crespigny Park, London SE5 8AF
&
Head and Consultant Child & Adolescent Psychiatrist
Centre for Interventional Paediatric Psychopharmacology (CIPP)
Child and Adolescent Mental Health Services
Michael Rutter Centre, Maudsley Hospital, De'Crespigny Park, London SE5 8AZ

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Abstract

Medication can reduce the impact of interfering symptoms, improving the lives of individuals with autism spectrum disorder (ASD) and their families. Although there are no widely-accepted medications for treating the core symptoms of ASD, clinical trials have provided evidence for efficacy and tolerability of medication used for treating comorbid psychiatric conditions. A number of these have a good evidence base, including stimulant medication for the features of attention deficit hyperactivity disorder and risperidone for improving behaviour. Treatment with psychopharmacological agents should only be undertaken after a careful assessment to ensure that any psychiatric symptoms are not the result of underlying physical disorders and to determine which symptoms should be targeted. The aim is to choose and adjust medication that achieves maximum benefit with minimum adverse effects.

Background

Autism spectrum disorder (ASD) can present with a variety of neuropsychiatric, emotional and behavioural problems. Neurochemical and functional imaging studies have identified abnormalities in neurotransmitters and brain structure (1-4). No standard medication is effective in treating the core social-communication deficit in ASD, although some interesting experimental work in this area is emerging. The main focus of pharmacotherapy is to alleviate or reduce specific symptoms or behaviours, such as the features of attention deficit hyperactivity disorder (ADHD), aggression, anxiety, depression, mood lability, withdrawal, repetitive stereotyped, ritualised or self-injurious behaviours and occasionally psychotic or catatonic symptoms. The target symptoms should be selected carefully and measured before the start of treatment so that response can be monitored accurately. Before psychotropic medication is considered, a full history should be taken, including an account of any medication used in the past, together with the response, the past medical history and detailed family history. Careful note should be taken of any individual or family history of medical problems that might increase the risk of prescribing specific drugs. Children and adults with ASD and accompanying psychiatric symptomatology require a multidisciplinary/multimodal management approach, of which medication can be an important part. (Also see other papers in this issue, particularly the paper on practical management.) Symptoms such as inattention, impulsivity, hyperactivity, tics, obsessions and psychosis may respond largely to medication alone. Symptoms such as aggression, rituals, self-injury, anxiety and depression are likely to require both medication and other forms of management. Symptoms that are unlikely to respond to medication and need specific remediation include skill deficits in academic or social domains (5). (Other conditions that occur commonly in people with ASD and may be associated with behavioural disturbance, such as constipation and epilepsy, should be treated with appropriate medication. Also see paper on epilepsy in this issue.)

Effective dosing with minimum side-effects (EDMS) strategy

The "effective dose with minimum side effects" is the dose with which acceptable improvement of symptoms with minimal adverse effects is achieved. Medication should usually be initiated in small doses (typically one-eighth to one-sixth of the final anticipated dose), increasing about every five half-lives of the drug; in practice, for many drugs, this is three to seven days, with certain exceptions. It may require 4-6 weeks of titration to identify the EDMS. This strategy needs to be discussed fully with the family and patient. Feedback from the family, to assess both the beneficial and adverse effects, is essential.

Assessing co-occurring disorders in ASD

A comprehensive diagnostic evaluation for co-occurring disorders is an essential first step in planning treatment. Underlying medical conditions must be excluded first. It is common for abnormal behaviour in ASD to arise from unrecognised physical conditions that cause pain or discomfort, for example dental abscess, ear infections, constipation or heartburn. A full and thorough physical examination should be performed in any individual with ASD who has developed a recent change in behaviour. Anxiety disorders (especially social anxiety disorder), depression, sleep disorders, ADHD and oppositional defiant disorder (ODD) are common in ASD. Occasionally psychotic disorders or catatonia may occur.

There is a remarkable lack of diagnostic instruments that have been adapted to assess co-occurring disorders specifically in people with ASD. The Centre for Interventional Paediatric Psychopharmacology (CIPP) identifies and diagnoses each co-occurring condition in ASD, by ensuring that the 'core' domain of the disorder is present, e.g. obsessions for diagnosing obsessive-compulsive disorder (OCD); symptoms reach 'thresholds' used in classificatory systems and are developmentally inappropriate; symptoms are NOT 'double counted' (e.g., hyperactivity in ADHD and for hypomania); each disorder produces additional impairment and checking that onset and course of the disorders are not indistinguishable and identical; and using multiple sources of information to ascertain the above criteria.

Adapting prescribing to suit ASD

The cognitive rigidity and abnormal sensory experiences in ASD can lead to individuals with this disorder insisting on taking tablets only of one colour, shape or size. They may refuse treatment because of the odour, consistency or taste of the medication. These issues need to be managed carefully and sensitively, in a way that is tailored to the individual. The medication may need to be given as a liquid or to be mixed with yoghurt, custard, orange juice (according to the stability of the medication) or even as tablets placed within a small piece of banana. Each service should have a policy on covert administration of medication when medication is administered by carers or staff, particularly in residential provision; this will usually involve multiagency agreement. The Mental Capacity Act will need to be considered for those aged 16 years and above. The individual may be trained to swallow tablets using reinforcement techniques, if necessary. Unusual dietary habits, such as excessive drinking of cranberry juice or grapefruit juice may have implications for dosing of medication because these may inhibit liver enzymes, slowing the rate of metabolism and increasing the blood level of some medication.

The art of prescribing medication

Patients and parents respond better when they feel understood, accept why treatment is necessary and are in agreement with the prescriber regarding the need for treatment. Rewards that the family experience from medication include improvements in symptoms, school performance and family relationships. The level of parental stress can also be decreased. Identified 'costs' include the impact of adverse effects, social stigma, lack of response, fear of addiction and fear of changing the child's personality (6). A trusting relationship between medical staff and the family is likely to have a positive effect on adherence.

The approach will depend on the age of the patient. Medication is not generally the preferred therapeutic management for pre-school children; psychosocial treatment is preferred. Teenagers usually want to feel involved in any decision-making (6). Again, policy and practice should be consistent with the Mental Capacity Act.

It is important to use a good system of outcome monitoring. There are web-based healthcare monitoring systems such as HealthTracker™ that monitor symptoms (including sensitive symptoms such as suicidality), adverse effects, quality of life and patient experience (7). Common measures that help to improve the response of both patient and parents are shown in Box 1.

Strategies to improve treatment response in Patients and Parents (Box 1)

- Collaborating with parents, patients, schools and care-providers, and providing a clear explanation of the diagnosis and the role of medication – developing a shared understanding of diagnosis and treatment between clinician, parents, patient and school leads to improved concordance.
- Setting realistic expectations and documenting what improvement is expected with the treatment.
- Providing clear information using information sheets, websites etc.
- Prioritise and perform multi-source monitoring (including school) of target symptoms.
- Parents and patients (when possible) opting in for treatment after weighing pros and cons as opposed to being told what to do.
- Start with small doses and identify the Effective Dose with Minimum Side-effects (EDMS).
- Willingness on part of clinician to change or stop the treatment if the expected outcome is not achieved.

Symptom-based pharmacotherapy in ASD

The choice of medication should be guided by functional analysis and an understanding of the target symptoms (8). Pharmacological management of symptoms is not a cure for ASD but can provide relief and allow patients to benefit more from educational, vocational and community-based programmes.

Some of the available evidence is presented in the following sections and summarised in Table 1 shown on the next page.

Table 1

Treatment of coexistent conditions in ASD	Medication	Evidence/comments
Irritability, aggression and challenging behaviour	Risperidone	• Has a specific licence for behavioural disturbance in ASD • Effective and well tolerated (McCracken et al., 2002) • Effectiveness established for 12 months (RUPP Autism network, 2005) • Weight gain and hyperprolactinaemia are common adverse effects
	Aripiprazole	• Generally well tolerated, significant improvement in aggression, self-injury and irritability (Owen et al., 2009, Marcus et al., 2009) • Periodic assessment required to determine continued need
	Olanzapine Clozapine Ziprasidone	• Limited evidence and significant adverse effect profile make them unsuitable for routine use in ASD
	Haloperidol	• Limited to the most treatment-refractory cases due to high risk of extrapyramidal adverse effects
	Lorazepam	• Sometimes used in acute situation but not recommended for long-term use
Attention Deficit Hyperactivity Disorder (ADHD)	Methylphenidate	• 1 in 2 children with ASD and ADHD improved; 2 in 3 children with ADHD without ASD improved (Santosh et al., 2006) • 40% to 50% response rate in children with ASD, hyperactivity and intellectual disability (Simonoff et al, 2013) • Effect size 0.5 in ASD and ADHD (RUPP, 2005)
	Dextroamphetamine	• No significant improvement (Campbell et al., 1972)
	Levoamphetamine	• Minimal positive effect (Campbell et al., 1976)
	Lisdexamphetamine	• Prodrug of dexamfetamine • No specific studies in children with ASD currently available
	Atomoxetine	• Improvement noted in hyperactivity but not in cognitive problems/inattention or the oppositional scales (Harfterkamp et al, 2012)
	Clonidine	• Some benefits in treating irritability, stereotypy, hyperactivity
	Guanfacine	• Reduction in hyperactivity reported (Scahill et al., 2006)
	Imipramine	• Not licensed for ADHD, should only be used in those who are non-responsive to stimulants, atomoxetine and alpha$_2$ adrenergic agonists because of possible cardiac adverse effects
Social disability	Risperidone	• Results are open to interpretation, social engagement might increase as anxiety/irritability is decreased by medication
Repetitive behaviours and circumscribed interests	Serotonergic drugs	• No difference in response rates compared to placebo (Williams et al, 2013) and should not be used for this purpose • Genuine obsessive or compulsive symptoms might be expected to respond to pharmacotherapy
Anxiety and depression	Selective Serotonin Reuptake Inhibitors (SSRIs)	• SSRI response may be atypical as brain serotonin reported to be raised in people with ASD • Fluoxetine can be justified in ASD and severe depression
	Propranolol	• Used for treating anxiety with somatic symptoms, particularly in children with intellectual disability
Mood lability and bipolar disorder	Sodium valproate Carbamazepine Lamotrigine Atypical antipsychotics	• Valproate reduces irritability and aggression in children with ASD (Hollander et al., 2001) • Risperidone and aripiprazole useful in reducing mood dysregulation along with irritability and aggression (McCracken et al. 2002, Krieger et al. 2011, Findling et al. 2014)
Core social communication impairment	There are no routine, widely-accepted pharmacological treatments for the core social-communication impairments in ASD, although some interesting research results have been emerging.	

A. Treatment of irritability, aggression and challenging behaviour

Many treatments have been studied for irritability, aggression and challenging behaviour. Risperidone has a specific licence for behavioural disturbance in ASD.

Aripiprazole

Aripiprazole is a dopamine modulator and a serotonin 5-HT1A agonist, partial dopamine D2 agonist

and a 5-HT2A antagonist. An initial case series (9), and two large double-blind, randomised, placebo-controlled 8-week studies involving over 300 children (10;11) concluded that aripiprazole was generally well tolerated in children and adolescents with ASD. There were significant improvements in aggression, self-injury and irritability. No major safety issues were identified. In a recent study, 85 patients randomised to a placebo-controlled aripiprazole discontinuation study did not show a difference in time to relapse between aripiprazole and placebo (12). Kaplan-Meier relapse rates at week 16 were 35% for aripiprazole and 52% for placebo (hazard ratio [HR] = 0.57; number needed to treat [NNT] = 6). In this study, although there was no statistically significant difference between aripiprazole and placebo in time to relapse during maintenance therapy, the HR and NNT suggested some patients might benefit from maintenance treatment. Patients receiving aripiprazole should be reassessed periodically to determine the continued need for treatment.

Risperidone

Risperidone has been one of the most extensively-studied medications for aggressive and challenging behaviours in children with autism. The Research Units of Paediatric Psychopharmacology (RUPP) autism network conducted an 8-week double-blind, placebo-controlled trial in 101 children and adolescents with autism and showed that risperidone was effective and well tolerated for the treatment of tantrums, aggression or self-injurious behaviour (13). Of the risperidone-treated subjects, 69% were categorised as treatment responders compared with 12% of the placebo group. Risperidone also led to greater reduction in social withdrawal, stereotypies, hyperactivity and inappropriate speech.

Double-blind discontinuation of risperidone was carried out after 4 months of open-label treatment. 62.5% of subjects randomised to placebo had significant worsening of symptoms compared with 12.5% who continued on risperidone, indicating that the medication was only effective as long as the patient was taking it (14). Similar findings have been reported in other controlled studies (15-17).

A randomised, placebo-controlled, double-blind study by Nagaraj et al., (18) which included children as young as 2 years, showed that, based on ratings on the Childhood Autism Rating Scale and Children's Global Assessment Scale, risperidone was highly effective in this group ($p<0.001$ and $p=0.035$, respectively).

A double-blind, placebo-controlled trial of pentoxifylline added to risperidone showed that this combination might have synergistic effects in the treatment of behavioural problems of children with autism (19). Based on the immune-dysfunction hypothesis, pentoxifylline has been used in children with autism (20;21).

Other antipsychotics

Hollander et al., (22) in an 8-week, double-blind, placebo-controlled pilot study in children and adolescents with pervasive developmental disorder, found a 50% response in the CGI-I (clinical global impression of improvement) with olanzapine, compared with a 20% response with placebo.

Small open-label studies or case series have reported that quetiapine (23;24), ziprasidone (25), and clozapine (26;27) might help to improve irritability and hyperactivity in ASD. However, definitive studies are lacking. The significant adverse-effect profiles of olanzapine (metabolic syndrome), clozapine (neutropenia) and ziprasidone (potential QTc-interval prolongation) make them unsuitable for routine use in ASD.

Anderson et al., (28) in a double-blind, placebo-controlled trial of haloperidol published in 1984, reported a statistically significant reduction in hyperactivity, aggression and temper outbursts. The use of haloperidol is now limited to only the most treatment-refractory cases because of the high risk of extrapyramidal side effects.

Other typical antipsychotics studied include chlorpromazine, trifluoperazine, thioxanthine, trifluperidol, fluphenazime and molindone (17).

Benzodiazepines
Benzodiazepine drugs such as lorazepam are sometimes used in the acute situation to calm aggression but disinhibition can result, with a worsening of behaviour, implying that the situation needs to be monitored very carefully. They are not recommended for long-term use because of the possibility of tolerance and adverse effects.

B. Treatment of ADHD features

Methylphenidate
Methylphenidate has been the most studied among the psychostimulants. A large open-label study showed that 1 in 2 children with ASD plus ADHD improved with stimulant treatment while 2 in 3 children with ADHD without ASD improved (29). The RUPP Autism Network (30) in a double-blind, placebo-controlled trial of methylphenidate in 72 children with autism and hyperactivity, most of whom also had intellectual disability (ID) (mean IQ 62.6, range 16-135), demonstrated an effect size of 0.5 and more adverse effects. A large randomised clinical trial of methylphenidate in children with intellectual disability and hyperactivity by Simonoff et al. (31) more definitively confirmed findings previously reported from smaller studies. This sample, selected for ID, but coincidentally including autism in a third of the sample, demonstrated a similar effect size of about 0.5, suggesting a medium effect widely in the intellectual and developmental disability population, with a 40-50% response rate.

Amphetamines
Amphetamines have been used to treat ADHD in children with ASD but recent studies are lacking. Two studies conducted in the early seventies did not show any statistically significant results. In a placebo-controlled crossover study of 16 children (32), dextroamphetamine yielded no significant improvement. A double-blind crossover trial of levoamphetamine in 12 children, showed only a minimal positive effect (33).

Lisdexamphetamine, dexamfetamine coupled to L-lysine, is a prodrug of dexamfetamine. It has the advantage that tablets can be dispersed in water and has a longer duration of action than dexamfetamine. However, no specific studies in children with autism are yet available.

Atomoxetine
Three open-label studies have suggested that atomoxetine may be effective in children and adolescents with ASD for symptomatic treatment of hyperactivity, impulsivity and oppositionality (34-36). A double-blind, placebo-controlled trial involving 97 patients aged 6 to 17 years with ADHD and ASD treated with 1.2mg/kg/day atomoxetine or placebo for 8 weeks showed some improvement on ADHD-RS (ADHD rating scale) scores. In school they examined between-group differences in the CTRS-RS (Conners teacher rating scale) and found that only the hyperactivity score was statistically significantly improved; there were no statistically significant differences in the Cognitive Problems/ Inattention or the Oppositional subscales. There was also no difference between the percentage of children on atomoxetine and placebo who improved 'much' or 'very much' on the CGI-I (37).

Clonidine
Clonidine is an alpha2 adrenergic agonist that is useful in ASD with ADHD and also in Tourette syndrome. Two small double-blind, placebo-controlled crossover trials in the early nineties reported some benefits with clonidine in treating irritability, stereotypy, hyperactivity, inappropriate speech and oppositional behaviour in children with autism; sedation and fatigue were listed as adverse effects (38;39).

Guanfacine
Guanfacine is another alpha2 adrenergic agonist. A retrospective case-note analysis of 80 patients (40) and an 8-week prospective open trial of guanfacine in children with ASD (41) reported a reduction in hyperactivity. Sedation, constipation and headache were the most reported adverse effects; the latter study also reported increased irritability, aggressiveness, sleep disruption and decreased appetite.

Imipramine
Imipramine is one of the older antidepressant drugs that has been used for the treatment of ADHD but should only be used in those who are non-responsive to stimulants, atomoxetine and alpha2 adrenergic agonists because of its cardiac side-effects. It does not have a licence for this indication.

C. Treatment of Social Disability

There is growing interest in measuring social disability as a core element of ASD in medication trials. A secondary analysis has been carried out using the Aberrant Behavior Checklist Social Withdrawal subscale using data from two multi-site, randomised trials with risperidone. Study 1 was a double-blind investigation of 52 subjects assigned to placebo and 49 subjects to risperidone. Study 2 was a comparative investigation of 49 subjects assigned to risperidone only and 75 subjects assigned to risperidone plus parent training. After 8 weeks of treatment, all active treatments were superior to placebo (effect sizes ranging from 0.42 to 0.65) (42). These results are open to interpretation. If, for example, anxiety is decreased by risperidone, the degree of social engagement might be expected to increase. Whether the results were a direct or indirect consequence of the medication remains open to question.

D.Treatment of Repetitive Behaviours and Circumscribed Interests

Patients with ASD exhibit perseverative or repetitive behaviours, which may produce impairments. When endeavours are made to stop these repetitive or self-stimulatory occupations, patients may exhibit challenging behaviours. These behaviours have to be differentiated from obsessions and compulsions occurring in patients with obsessive compulsive disorder (OCD). Despite many small studies suggesting that serotonergic drugs may help reduce the repetitive behaviours in ASD (43-46) a recent Cochrane review has clearly concluded that response rates are no different for these medicines compared to placebo (47) and that they should not be used.

Obsessions and compulsions that interfere with the life of the individual and cause him or her distress should be distinguished from excessively preferred ideas or behaviours. Genuine obsessive or compulsive symptoms might be expected to respond better to pharmacotherapy and this is supported, at least anecdotally, by clinical experience. In contrast, excessively preferred ideas or activities would not be expected to respond.

E. Treatment of Anxiety and Depression

There is considerable evidence that children and adolescents with ASD are at increased risk of anxiety and anxiety disorders. A meta-analysis revealed that about 39.6% of young people with ASD had at least one comorbid anxiety disorder (48).

SSRIs
With respect to pharmacological interventions, the usual treatment in typically-developing populations is selective serotonin reuptake inhibitors (SSRIs). However, brain serotonin has been reported as being raised in people with ASD and consequently the response to SSRIs may be atypical. More generally, treatment trials have been confined to children of average cognitive ability, typically with an IQ greater than 80. Fluoxetine can be justified when a child with ASD is severely depressed. Anecdotally, sertraline and citalopram have been used to manage severe anxiety disorders in this group. There is a clear need for evaluation of both psychological and pharmacological approaches to treating anxiety in individuals with ASD.

Propranolol
Propranolol is an older drug that has been used for treating anxiety with somatic symptoms, particularly in children with intellectual disability. A neuroimaging study suggested that it might have a positive influence on brain connectivity in children with ASD (49).

F. Treatment of Sleep Problems

Children and adolescents with ASD have sleep problems, particularly insomnia, at a higher rate than typically-developing children, ranging from 40% to 80% (50). Sleep problems in ASD might occur as a result of complex interactions between biological, psychological, social/environmental and family factors, including child-rearing practices that are not conducive to good sleep. Identifying and treating sleep disorders may result not only in improved sleep, but may also impact favourably on daytime behaviour and family functioning. Several studies have also demonstrated the effectiveness of behavioural interventions for sleep-onset and sleep-maintenance problems in these populations. When behavioural interventions are not effective or lead only to a partial response, pharmacological treatment options should be considered. Melatonin has been shown in randomised trials to help initiation of sleep in neurodevelopmental disorders including ASD (51;52). However, it does not appear to be very effective in maintaining sleep. Antihistamines, clonidine, trazodone and benzodiazepines have been used with little evidence in this population. (Also see papers in this issue on sleep and practical management.)

G. Treatment of Mood Lability and Bipolar Disorder in ASD

Mood stabilisers commonly used in ASD are sodium valproate, carbamazepine, lamotrigine and atypical antipsychotics. Epilepsy is a common comorbidity with ASD (see paper on autism and epilepsy in this issue). Antiepileptic drugs are also used to treat bipolar disorder, mood lability, impulsivity, irritability, aggressive behaviour and explosive rage. Several case reports and case series have suggested the efficacy of valproate for aggression in children and adults with mental retardation. An open-label study reported that valproate reduces irritability and aggression in children with ASD (53). In a double blind, placebo-controlled, parallel group design study, Hellings et al. found no significant differences between the treatment groups (54).

In a 12-week, double-blind, randomised, placebo-controlled trial of divalproex sodium compared with placebo, statistically significant improvements were reported for irritability and aggression in children with ASD (mean age 9.46+/-2.46, mean nonverbal IQ 63.3+/-23.9) (55). 62.5% of divalproex subjects vs 9% of placebo subjects were responders (CGI-irritability OR: 16.7) on the ABC-Irritability subscale. There was a trend for responders to have higher valproate blood levels compared with non-responders. Larger sample follow-up studies are warranted.

Case series are available for lithium carbonate (56). Little structured evaluation of carbamazepine or lamotrigine has taken place. Atypical antipsychotics such as risperidone and aripiprazole have been useful in reducing mood dysregulation along with irritability and aggression (12;13;57).

Self-injurious behaviour

Self-injurious behaviour can result in physical harm to the individual; it also often causes great distress to families and carers. Skilled behavioural management should usually be the first approach. There is an absence of good evidence for any specific pharmacological treatment. Risperidone may be of benefit through the reduction of irritability/anxiety. Although open-label studies of naltrexone have been conducted in people with autism and self-injurious behaviour, with some positive reports (58), a double-blind study in adults failed to show any benefit (59).

Core social communication impairment

There are no routine, widely-accepted pharmacological treatments for the core social-communication impairments in ASD, although some interesting research results have been emerging.

Investigation of the role of the glutamate system in the treatment of core social impairment in ASD has demonstrated promising, though mixed results. Use of piracetam is based on the hypothesis that autism is a hypoglutaminergic disorder. Piracetam is a positive modulator of AMPA-sensitive glutamate receptors. A double-blind, placebo-controlled trial of piracetam added to risperidone in

patients with ASD suggested that this combination might have increased synergistic positive effects in the treatment of behaviour, as measured by the Aberrant Behavior Checklist (60).

The desire to expand treatment options in this area of impairment has recently included the study of the neuropeptide oxytocin. Oxytocin plays a key role in social behaviour. In a double-blind, randomised placebo-controlled, crossover design study of 16 males aged 12 to 19 with autism or Asperger syndrome, administration of oxytocin nasal spray (18 or 24 IU) improved emotional recognition (61). In comparison with placebo, oxytocin administration (low and high doses) statistically significantly improved performance on the "Reading the Mind in the Eyes Task". This finding suggests the potential for earlier intervention and further evaluation of oxytocin nasal spray as a treatment to improve social communication and interaction in young people with ASD but large studies are necessary.

There have been reports of specialist treatment with specific medication for neurogenetic syndromes such as Fragile X with acamprosate (62) and Rett syndrome with insulin growth factor (63) but further evidence is required before such treatments can be recommended.

Important adverse effects of psychotropic medication

- Hyperprolactinaemia is very common with risperidone and other D2 blockers such as sulpiride and amisulpride. It can also occur with high-dose typical antipsychotics such as haloperidol. Aripiprazole, on the other hand, produces hypoprolactinaemia. 49% of 56 boys treated with an antipsychotic (mostly risperidone) developed hyperprolactinaemia, which was associated with low bone mineral density compared to boys who did not develop hyperprolactinaemia, although the difference, compared with a group who were not treated with antipsychotic medication, did not reach statistical significance (64).
- Weight gain is the most troublesome adverse effect of antipsychotics. Metabolic syndrome is the co-occurrence of being overweight, hypertension, hyperlipidaemia and hyperglycaemia. Weight gain is greatest for clozapine and olanzapine and it is least for ziprasidone and aripiprazole (65). It is important to provide patients and families with information about medication-induced weight gain and to educate them about metabolic syndrome, diet and weight monitoring. Recommending regular exercise and strict dietary regulation should be an integral part of management. Implementing healthy eating for the whole family may be the only way of succeeding in the aim of having the index child follow a healthy diet.
- Extrapyramidal adverse effects are more common with typical antipsychotics or high doses of atypical antipsychotics.
- Serotonergic drugs are more likely to produce behavioural activation in children than adults.
- QTc-interval prolongation can occur with a variety of psychotropic medications when used in those with pre-existing cardiac problems.

Pharmacological Preparation for Medical or Surgical Interventions in ASD

The medical safety of people with ASD and learning disability should not be compromised because of the potential difficulty of carrying out investigations such as MRI scans, nor should other essential procedures be neglected. Sedation may be necessary. Oral midazolam can be effective for minor procedures. General anaesthesia is often necessary for longer procedures, such as MRI scans. Melatonin can be used as a sedative for EEG investigations and a higher dose of risperidone can be used on a once-only basis for specific procedures such as minor dental work. If melatonin or risperidone are used in this way, it is wise to have a "dry run" when the medication is administered at least a week or two before the procedure while the child is being closely observed by parents or other carers, to determine whether the selected dose and type of sedation appears to be effective and to ensure that there are no unwanted effects.

Conclusions

The best evidence for the beneficial effect of pharmacological treatment for psychiatric conditions or symptoms associated with ASD is for methylphenidate in the treatment of the features of ADHD and for risperidone and aripiprazole in the treatment of irritability/behavioural disturbance. There is no routine treatment for the core social-communication features of ASD but some interesting studies have been carried out in this area, particularly with oxytocin and medications that target glutamatergic or GABAergic neurotransmitter systems.

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GP Comment.

What have I learned from this paper?

1. Individuals with ASD require a multidisciplinary/multimodal management approach, of which medication can be an important part. This excellent paper highlights the medications which have a good evidence base.

2. Before initiating any medication for a recent change in behaviour in any individual with ASD, it is essential to exclude a possible physical cause.

3. The target symptoms should be selected carefully and measured before the start of treatment so that response can be monitored accurately.

4. There is an excellent section on the art of prescribing medication in ASD, including the effective dosing with minimum side-effects (EDMS) strategy. Also Box I provides a helpful summary of common measures which improve the response of both patient and parents.

5. The table of medications highlights the good evidence base for methylphenidate for ADHD features; and risperidone for improving aggressive and challenging behaviour. There is no routine treatment for the core social-communication features of ASD.

6. To conclude, there is a need for further evaluation of both psychological and pharmacological approaches. It would be interesting to compare the effect on social disability of medication such as risperidone, versus parent training alone. It would also be interesting to compare the cost of different therapies.

I consider this is a highly informative, clear article which should be essential reading for all GPs.

Dr Anthea Robinson
GP at Moakes and Whipperley Medical Centres, Luton.

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