# Differences in Side-effects in Autism

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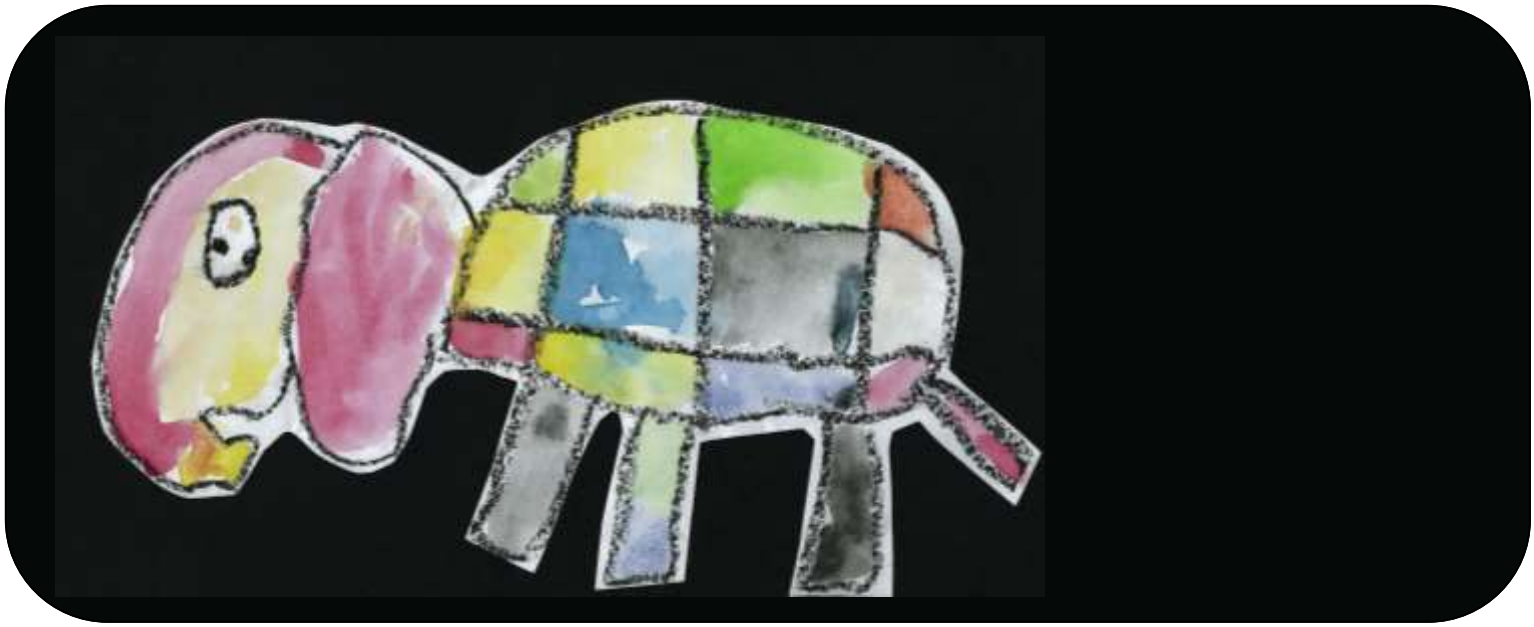
## Introduction

This article is written based on my training experience working in the Neurodevelopmental Psychiatry Team, at the Children's Hospital at Westmead. I came to appreciate that children with autism (ASD) with and without intellectual disability (ID) have different responses to medications to those found in the mainstream population. For those seen in the clinic, their level of behavioural/psychiatric disturbance was often so severe that other non-pharmacological approaches did not make any impact. Hence, I learned to consider a broader range of medications. As a registrar, my role included providing regular telephone follow up which gave me clinical experience on the need for attentive support for introducing medications. I met many cases in the Emergency Department, where case management had not progressed or was worse as a result of unexpected side effects. A search of the literature confirms the observation that young people with ASD/ID have a much higher rate of side effects and a lower rate of therapeutic success than a mainstream population. This article presents brief clinical case-scenarios of reported side effects and asks the reader to predict the medication used.

**Case 1.** A 14-year-old girl with a history of high functioning ASD, anxiety and previous suicidal attempts with overdoses was brought to the Emergency Department (ED) due to panic attacks which were lasting from 5 minutes to 5 hours. During those episodes, the patient described feeling shaky, palpitations, twitching, hyperventilating, akathisia, restlessness and her mind was foggy. These episodes had started within a week from commencing on a medication for anxiety; what was the medication?

**Case 1 Outcome:** Patient commenced on fluoxetine 10mg 22 days prior to presentation to ED; 6 days into starting the medication she started experiencing the panic attacks and was initially unable to sleep or eat. Four days later, the medication was ceased, but symptoms were slow to recede. The patient was discharged from ED with the community mental health team follow-up. A week following discharge she was commenced on another selective serotonin reuptake inhibitor (SSRI), escitalopram, with a similar outcome of exacerbation of panic attacks again, and the medication was gradually weaned and ceased two weeks later.

SSRI's are activating antidepressants that are used for the treatment of restrictive, repetitive behaviours and interests, depression, anxiety and obsessive-compulsive disorder (OCD) (Williamson and Martin, 2012), (Beasley and Potvin, 1993). Due to treatment-emergent adverse effects, about 30% of neurotypical people discontinue treatment within the first month (Kaplan, 1997). SSRI use is associated with increased anxiety, nervousness, agitation and insomnia, which occur in up to 10-15% of fluoxetine-treated neurotypical patients (Chouinard, 1985, Plewes *et al* 1997, Chouinard *et al* 1999 and Gram, 1994). On com-



mencement of fluoxetine for anxiety or depression, new emergent agitation can develop in 9.2% within the first two weeks of treatment (Chouinard *et al,* 1999). Even though akathisia is a rare side effect of SSRI, a small proportion of patients have reported developing a feeling of inner restlessness and inability to stay still (Gram, 1994) (Walsh and Dinan, 2001). Activation has been described in doses between 5 and 40 mg/ day (Beasley and Potvinm 1993).

There are reports of fluoxetine-induced hypomania without any risk factor for bipolar disease within 3-5 weeks of treatment (Chavan, 1992; Aggarwal *et al,* 2011; Diler and Avci, 1999 and Go *et al,* 1998). Following the cessation of treatment hypomanic symptoms usually subside within 14 days (Chavan, 1992). In a cohort of 40 neurotypical youths treated for OCD and mood disorders, 30% of patients developed manic or hypomanic symptoms at fluoxetine doses as low as 10mg daily (Go *et al,* 1998). This can be more difficult to distinguish due to limited communication skills in ASD.

In comparison, side effects of hyperactivity, restlessness and agitation have been reported in up to 20-40% of patients with ASD and in 25% of patients with ID without ASD (Cook, 1992; DeLong *et al,* 1998; DeLong *et al,* 2002). This is 2-4 times as frequent when compared with neurotypical patients.

**Case 2.** A 13-year-old young man with autism (level 3) and moderate ID was brought for review due to concerns about aggressive behaviour. He was described to have a happy and caring nature, but also hyperactive, anxious, obsessive and rigid. His pediatrician had started him on a medication that helped for a short period of time, but then despite increasing doses did not improve his symptoms and caused increased weight gain of 30 kgs to 90 kg within five months of treatment. What was the treatment?

**Case 2 Outcome.** He was treated with risperidone, which was started as he entered puberty but behaviour worsened despite the gradual increase of dosing. This augmented dose caused increased appetite and weight gain. We found that hyperactivity and irritability were not the primary co-morbid problems for which risperidone was given, but anxiety, obsessions and rigidity with secondary aggression due to inability to control the situations was more likely.

Risperidone was approved by FDA in children for 6-16 years in 2007 for management of irritability associated with ASD (Williamson and Martin, 2012). For example, risperidone has been shown to reduce irritability by 57%, and this benefit maintained at 6 months

(McCracken *et al,* 2002). However, treatment is associated with hyperprolactinemia and weight gain (Anderson *et al,* 2007; Aman *et al,* 2 005), which are worse in children than adults (Taylor, Paton and Kapur, 2015). Additional side effects reported in children with ASD were fatigue, drowsiness, dizziness, enuresis and drooling (McCracken *et al,* 2002). Extrapyramidal side-effects (EPS) were no more common than in placebo group (Aman, 2015); nevertheless, clinicians are noted often not to treat EPS with anticholinergics, but rather cease the medication. There is a growing appreciation that in the long term, major tranquillisers cause obesity and cardiometabolic syndrome, which is a contributor to premature mortality. Accordingly, long-term medication needs to be considered judiciously.

**Case 3.** A teen boy with ASD (level 3) and moderate ID was reviewed for aggressive behaviour in relation to rigidity, OCD and anxiety. During the initial assessment, he had been treated with a medication that improved his obsessive behaviours but contributed to the patient's significant melt-downs, anxiety and self-harm. What was the medication?

**Case 3 Outcome.** Both Case 1 and 3 demonstrate behavioural activation whilst using SSRI. Patient 3 was treated with fluoxetine of 40 mg per day with no improvement of his symptoms, except some of his obsessions resurfaced when the medication was withdrawn. On cessation of fluoxetine, his behaviour gradually improved but did not resolve.

Fluoxetine is shown to be more effective in older adolescents and adults compared to children (Williamson and Martin, 2012; Taylor, Paton and Kapur, 2015), and a strong correlation of fluoxetine efficacy has been seen with the family history of major affective disorder such as bipolar disorder or major depression. Study by DeLong and colleagues (2002) of children with idiopathic ASD treated with fluoxetine (0.15-0.5mg/kg) for the duration of 5-76 months showed excellent response in 17%, good response in 52%, fair response in 8% and poor response in 23% (DeLong, 2002). In this study, behavioural activation, hyperactivity, irritability, aggressiveness and agitation were primary factors for fluoxetine intolerance. These symptoms were sometimes seen almost immediately, but at times, a few weeks to months after 'successful treatment (DeLong *et al*, 1998; DeLong *et al*,2002).

**Case 4.** A 17-year-old girl with autism (level 3) and moderate ID with features of anxiety presented to our clinic. She had been treated with risperidone and fluoxetine, neither of which had improved her symptoms and therefore fluoxetine was ceased. At the time of initial review, she was managed on a small dose of risperidone. Due to on-going anxiety, self-harm and aggression towards caregivers, she was commenced on another medication which significantly improved her anxiety and rigidity leading to a cessation of further meltdowns. Since starting the new medication, she was energetic, elevated and happy at the time, but had significant problems with sleep initiation. What was the medication?

**Case 4 Outcome.** This patient commenced on propranolol with almost miraculous improvement in her anxiety and aggression. When she was faced with new and anxiety-provoking situations, she was able to self-regulate without aggression. At the same time, she was unable to go to sleep which had become an even more significant problem than before.

Propranolol is a beta-1 adrenergic receptor blocker that has anxiolytic effects but has been shown to improve emotional, behavioural and autonomic dysregulation symptoms in ASD (Sagar-Ouriaghli *et al,* 2018). Unfortunately to-date the exact mechanism in violence and aggression is not clearly established, but it is theorised that anger involves an explosive release of adrenalin from the adrenal glands. Melatonin secretion at the same time is implicated by the beta 1-adrenoreceptors as well (Munoz-Hoyos *et al,* 2001). Sleep disturbance, of difficulty with initiation and maintenance, has been shown to be caused by reduced production of melatonin through specific inhibition of beta-1 adrenergic receptors by propranolol (Stoschitzky *et al,* 1999).

**Case 5.** A late-teen with a history of level 3 autism, moderate ID and obesity presented with aggression mainly associated with food requests. Initially, risperidone did work, but with difficulty managing his appetite and learned aggressive behaviour. The trial of treatment with another obesogenic medication increased these symptoms.

**Case 5 Outcome.** This patient was commenced on olanzapine and thereafter paliperidone depot injections, in an attempt to reduce and cease the olanzapine. Despite the medications, his aggressive behaviour continued.

Olanzapine is indicated for the management of irritability in ASD (Taylor, Paton and Kapur, 2015) and has been shown to be effective in about 50% of the cases, but it doesn't improve aggression or repetitive behaviours (Hollander *et al,* 2006). At the same time, it causes significant weight gain, with a reported weight gain of 3.4 kg +/- 2.2kg in an 8-week study of 6 -14-year-old children with ASD. This reinforces the dictum that medication can only be used to treat symptoms that may predispose to aggression, and behavioural management including a safety plan is critical for aggression and violence (Dossetor, 2016). This is obviously easier to teach with a small child, but it is no less important with a large adolescent.

**Case 6.** A 9-year-old boy with autism, moderate ID and hyperactivity was commenced on treatment to manage his hyperactivity. However, this treatment caused dizziness, and he had become "out of control" every time after the medication was given.

**Case 6 Outcome.** Stimulants are indicated for the treatment of inattention, over-activity and impulsiveness. However, the efficacy in ASD is limited with the response rate being reported to be around 50% in children with autism (Research Units, 2005; Aman et al 1997). For example, only a quarter of patients have been shown to respond to the first stimulant trial, in comparison with 60-70% of neurotypical children. Furthermore, 57% of children with ASD showed adverse effects: 36% developed agitation, 14% depressed mood and 10% aggression (Stigler et al, 2004). Another study showed that 49% of children with ASD on treatment with methylphenidate showed side effects such as reduced appetite (37%), insomnia (26%), irritability (15%), tics (7%) and lethargy (7%) (Aman et al, 1997).This provides some explanation for why clonidine is the first line treatment of ADHD in ASD and/or ID in our clinical team.

**Case 7.** A pre-teen boy with autism, moderate ID and hyperactivity was commenced on treatment to manage his hyperactivity, but it was discontinued as it increased his irritability and in higher doses caused sedation.

**Case 7 Outcome.** As a second line treatment for hyperactivity, this young man was commenced on clonidine. Due to undesired symptoms, treatment was ceased, and his ongoing management of hyperactivity was effectively managed non-pharmacologically with organised activities – walking, running, and playing. Clonidine is indicated to be used to manage hyperarousal, hyperactivity, irritability, anxiety and insomnia in ASD (Doyle and McDougle, 2012). Treatment with clonidine has been shown to improve attention deficit, hyperactivity, mood instability, aggressiveness, sleep initiation and night awakening in children with ASD (Ming *et al,* 2008). Interestingly, if clonidine worked within the first week for sleep, the dose did not need to be increased in the first year. Main reported side effects were sedation, decreased activity, and paradoxical patient irritability (Ming *et al,* 2008), which may be explained by the patient fighting the sedative effect of the clonidine. Rarely reported side effects to include pallor, tachycardia, hypotension and depression. This case illustrates that there is no single answer for ADHD in autism.

**Case 8.** A 12-year-old boy with autism level 3 and epilepsy was already treated with sodium valproate. His main problems on presentation were anxiety and meltdowns lasting for hours in relation to indecisiveness. He was commenced on a medication which improved his anxiety and therefore meltdowns but also concentration. However, it caused increased appetite, increased seizure activity requiring augmentation of sodium valproate dose and initially slight drowsiness which could have been because of the medication or increased seizure activity.

**Case 8 Outcome.** This young man was commenced on aripiprazole (Abilify) with good effect on his anxiety and therefore also a significant improvement of his meltdowns which prior to treatment caused problems in daily living.

Aripiprazole is a third-generation antipsychotic that has been approved by the FDA since 2009 for use in 6 -17-year-old children with autism who have irritability and stereotypies such as repetitive, purposeless actions (Hirsch and Pringsheim, 2016). Short-term intervention with Aripiprazole has also shown to improve hyperactivity in children and adolescents. Aripiprazole has a smaller effect on weight than risperidone; on risperidone, 76 % of subjects gained weight (mean +2.7 kg, range -3.3 to 8.1 kg) (Stigler *et al*, 2009) versus 1.13 kg on aripiprazole compared to placebo (Hirsch and Pringsheim, 2016; Ching and Pringsheim, 2012). A 14-week prospective trial in children with mild ASD, 5-17 years showed a 3-fold decrease of prolactin level (Stigler *et al*, 2009). The most common adverse events were mild tiredness (21 -56%), cough (48%), increased appetite (44%), nau-

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sea/vomiting (40%), rhinitis (40%), drooling (9%) and tremor (10%). There are rare reports that aripiprazole can reduce seizure threshold when there is underlying seizure disorder.

**Case 9.** A young teenager with autism, average intellect, bipolar type 1 and ADHD was commenced on treatment to improve arousal and aggression. He had refused oral treatment, and he was therefore started on intramuscular preparation of the same medication. The medication caused postural hypotension described as lightheadedness during exercise, tachycardia, increased tiredness and stiffness of lower limb muscles. What was the medication used?

**Case 9 Outcome.** This patient was commenced in intramuscular paliperidone with improved agitation and hyperarousal.

Paliperidone is a second-generation atypical antipsychotic with limited studies showing its effectiveness. Studies have shown an 84% response rate in improving irritability, but it has caused mild-to-moderate EPS (in 16%), an average weight gain of 2.2 kg and 8-fold prolactin increase (5.3 to 41.4 ng/mL) (Stigler *et al*, 2012). Furthermore, paliperidone can cause dizziness, sedation, hypotension and motor side effects (Taylor, Paton and Kapur, 2015). If there is concern about side effects, it is recommended to be patient allowing the patient to accommodate the medication. Anticholinergics like benztropine can be used to improve motor

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side effects, and early enrolment in lifestyle interventions for exercise and weight management with monitoring is recommended.

**In summary:**
Although psychotropic medications are less efficacious and have more side effects in young people with ASD, I found that patient persistence with a broader range of medications was helpful in the vast majority of cases. It is important to use safer medications rather than resort to major tranquillizers early in treatment. Warnings about the main side effects at the start of treatment and telephone support for other side effects is vital to maintain the confidence of the patient and parents and find the right combination of medications with minimal side effects. Further to establish the impact of each medication, it is important to change one medication at a time. Some medications, such as SSRI’s list large numbers of side effects that one seldom sees. It is valuable to warn patients and parents of common side effects, and suggest that if any other new symptoms arise, they should be in touch to review the importance of such symptoms.
SSRIs are more efficacious in adults and older adolescents for the treatment of repetitive behaviours and may exhibit behavioural activation frequently in children particularly with ID and ASD. Whereas activating side-effects are reported in 10-15% of neurotypical children, these are reported in up to 40% of children with ASD. SSRI’s can be valuable in some instances of co-morbid anxiety and depression, and where aggression is driven by the stereotypic rigidity of autism. We recommend using these medications with caution and titration of doses should be done more slowly.

Atypical antipsychotics are efficacious for the treatment of irritability in children, adolescents, and adults with ASD. It is a significant health inequity that aripiprazole is not approved on the Prescriber’s Benefit Scheme even though there is evidence of efficacy and fewer side effects than traditional major tranquillisers. Even though olanzapine and risperidone have been reported to work in about 50% of the time for irritability in ASD consideration of significant side effects should be paramount.

For hyperactivity and inattention, psychostimulants may be beneficial but are less efficacious and associated with more adverse effects compared to neurotypical individuals with ADHD. Unfortunately, the first trial of stimulants works in about 25% of cases with ASD in comparison with 60-70% of neurotypical children. Furthermore, the rate of side effects has been reported to be over 50% in children with ASD. Due to this, clonidine is a preferred first-line treatment for autism with ADHD and/or anxiety.

Although the literature helps guide choices, the only trial that matters is identifying if this medication actually helps in the case. Sometimes the constellation of symptoms may help select a medication choice, and sometimes the effects or side effects help further understand the nature of the presenting problem. Finally, psychotropic medication is only indicated for a comorbid psychiatric disorder, and not for the core symptoms of ASD or challenging behaviour.

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