AUTISM

Risperidone in autism therapy and its efficacy

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Michael Rimmington
Behaviour therapist at The iMap Centre, Cheshire, doctoral candidate at Salford University, Manchester, England

Correspondence
info@cheshire-autism.co.uk

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Abstract

This article explores the use of the atypical antipsychotic drug, risperidone. It will identify its core features and chemical properties and compare it with other commonly available interventions in its use with people with autism spectrum conditions (ASC). Common and rarer side effects of risperidone are explored. The discontinuation trials of two students with ASC are examined. Data were collected on the students' daily arousal levels to monitor any changes following discontinuation. The results showed a significant increase in the time student A spent at optimum arousal, while student B showed a clear movement away from his optimum arousal level and into a state of higher arousal. The different outcomes suggest that risperidone may have beneficial effects for some people but not for others. The use of antipsychotic medication may have short-term benefits but must be reviewed regularly and appropriate behavioural intervention programmes should always be considered as an alternative treatment to pharmacological interventions.

Keywords

autism, behaviour that challenges, learning disabilities, medication, risperidone

PEOPLE LIVING with autism spectrum conditions (ASC) typically find difficulties in social communication and interaction (Frith 2003, Volkmar and Pauls 2003, Wing 2003), display restricted or repetitive patterns of behaviour (MacDonald et al 2007, Leekam et al 2011, American Psychiatric Association 2013) often with associated sensory differences (Bogdashina 2003, Kern et al 2006, Matsushima and Kato 2013). These problems can lead to escalation of the person's anxiety levels (Bellini 2006, Gillott and Standen 2007, Trembath et al 2012) and patterns of behaviour that challenge (Farmer and Aman 2011, Hattier et al 2011, Hill et al 2014).

There are therapies claiming to alleviate some of the symptoms of ASC. Some follow a biological path (Shaw 1998) and include such approaches as the use of vitamin and mineral supplements (Adams et al 2011, Cannell 2013, Saad et al 2016) or the implementation of a gluten or casein-free diet, the latter of which has been shown in recent studies to have little efficacy (Mulloy et al 2010, Johnson et al 2011, Hyman et al 2016). Other treatments aim to alleviate the communication issues (Bondy and Frost 1994, Goldstein 2002, Frith et al 2010) or the social problems inherent with ASC (Gray and Leigh White 2002, Radley et al 2015, Deckers et al 2016). Some interventions opt for a behavioural methodology (LaVigna and Willis 2012, Rimmington 2016); Schreibman (2000) claims that behavioural approaches are the most empirically effective. If these and other routes prove unsuccessful then the parent of the child, the multidisciplinary team and, most importantly, the child may try a psychopharmacological intervention (West et al 2009, Elvins and Green 2010, Canitano and Scandurra 2011); one drug commonly shown to be effective in those on the autism spectrum is a medication called risperidone (Pandina et al 2007, Ghaeli et al 2014, Levine et al 2016).

Development and use of risperidone

In December 1993 risperidone was first granted approval for use by the US Federal Drug Administration (FDA); it was developed by Ortho-McNeil-Janssen, a division of the pharmaceutical company Johnson & Johnson. In 1994 it was released for use in people with schizophrenia under the trade name of Risperidal. The drug is now available as tablets, liquid and a slow-release depot injection into the gluteal muscle. Since then it has been approved for use in children and adults with schizophrenia, short-term usage

for episodes of mania in bipolar disorder and for people with ASC. By 1996 Risperidal accounted for nearly 17% of all new antipsychotic prescriptions by psychiatrists in the US (Raleigh 1996). In October 2006 the FDA approved risperidone to be used specifically for the treatment of 'irritability' in young children and adolescents with ASC. Irritability in this case was defined by the Aberrant Behaviour Checklist (ABC) (Aman et al 1985). The ABC is a 58-item, five-factor, third-party rating scale whose subscales are identified as follows:

1. Irritability, agitation, crying.
2. Lethargy, social withdrawal.
3. Stereotypic behaviour.
4. Hyperactivity, non-compliance.
5. Inappropriate speech.

Risperidone is an atypical or second-generation antipsychotic medication. Atypicals are sometimes preferable to typical or first-generation antipsychotics, such as low potency chlorpromazine or the higher potency haliperidol, due to there being a reduced risk of extra-pyramidal symptoms (EPS) (Min et al 1993, Hughes et al 2002) with less need for anti-Parkinsonian medication (Vijay and Chandrashekar 2005). Although some studies have shown that at dopamine D2 receptor occupancy levels of greater than 60%, risperidone does not appear to protect against the risk of EPS (Kapur et al 1995, Knable et al 1997). The 66th edition of the British National Formulary (BNF) (Joint Formulary Committee 2013) states that common extrapyramidal side effects for antipsychotic medication include tardive dyskinesia (involuntary movements of the tongue, jaw and face), akathisia (restlessness), Parkinsonian symptoms (tremor) and dystonia (abnormal face and body movements). It must also be noted that some of the previous studies were conducted to compare the efficacy of other antipsychotics versus risperidone in the treatment of schizophrenia and not in ASC.

Side effects

Risperidone is not without documented side effects of its own and those listed in the 66th edition of the BNF (Joint Formulary Committee 2013) are highlighted in Table 1. King et al (2003) found that in their study group of 51 children and adolescents using risperidone, nearly half displayed some form of negative side effects including EPS, sedation or weight gain. Martin et al (2004) also concluded that chronic risperidone use in children with ASC tended to cause weight gain excessive of normal developmental levels. In a 63-subject six-month study, they also recognised that excessive weight gain in the first month of use was a strong predictor of continuing weight gain over the remainder of the study, recommending that clinicians may look to alternative therapies if a significant weight gain was observed during the first month. More recent studies by Alan and Kultur (2015) and Wink et al (2014) also confirm the link between risperidone and weight gain.

Risperidone is an atypical or second-generation antipsychotic medication

Raised prolactin levels

One side effect of risperidone is increased prolactin levels or hyperprolactinaemia (Hariharan and Mohsin 2002, Maguire 2002, Buhagiar and Cassar 2008). Elevated prolactin levels can cause several short-term effects such as amenorrhea (absence of a menstrual cycle), galactorrhea (excessive lactation), gynecomastia (over-developed male mammary glands) and sexual dysfunction, and longer-term problems such as decreased bone density and a higher risk of certain cancers (Maguire 2002).

Hariharan and Mohsin (2002) report on a case of galactorrhea, amenorrhea and excessive weight gain in a 43-year-old female with chronic schizophrenia. These symptoms manifested after six months with a 2mg/day dosage of risperidone. Tests showed highly elevated prolactin levels. A discontinuation programme was affected replacing risperidone for quetiapine. The galactorrhea ceased after one week, menstruation returned after three

weeks and there was a dramatic decrease in prolactin levels over the following three months (from 53.4 to 4.4ng/mL).

A similar case was reported by Mabini et al (2000) involving a 38-year-old male who displayed highly elevated prolactin levels, galactorrhea and gynecomastia 14 days after taking risperidone. The symptoms readily decreased after discontinuation. Documentation of such cases may be rare but Maguire (2002) hypothesises that this may be due to the sensitive nature of the symptoms and advises that clinicians should always ask about such things when people are taking antipsychotics such as risperidone. Bryson et al (2003) warn of the higher incidence of seizures when using traditional antipsychotic and atypical antipsychotic medications in the management of autism. Koch-Stoecker (2002) also describes the risk of non-epilepsy drug-induced seizures from typical and atypical neuroleptics, but finds risperidone as a negligible or low seizure risk.

Chemical properties and actions

Risperidone is a benzisoxazole derivative; it is chemically different to most atypical neuroleptics. Its effectiveness is due to the site-specific inhibition of receptors found in the hypothalamus. The hypothalamus acts to regulate physiologic functions such as hunger and thirst, sleep, temperature regulation, sex drive, mood and the release of other hormones in the body (Montagna 2006, Braine 2009). Risperidone possesses high blocking properties of the 5-hydroxytryptamine (5-HT) and dopamine (D2) receptor sites, but with a much greater affinity for the 5-HT site over the D2 receptor sites, while still retaining good anti-dopaminergic properties (Hariharan and Mohsin 2002). Risperidone also binds to α1 and α2 adrenergic receptor sites and to the histaminergic (H1) receptor sites, but with much less affinity (Min et al 1993).

Although the exact mechanism is not yet fully understood, its therapeutic properties are thought to be due to the antagonistic activity at the 5-HT2 and D2 receptors (Buck 2008). It has also been claimed by Taketomo (2005) and Masi et al (2001) that it is the blockade of the 5-HT and D2 site that is thought to be responsible for the reduction in EPS with risperidone over other typical neuroleptics. Risperidone reverses the dopaminergic inhibition of prolactin production in the anterior pituitary (Hariharan and Mohsin 2002). A potential explanation for the commonly seen weight gain in atypical antipsychotic users (Wink et al 2014, Alan and Kultur 2015) is that leptin (a hormone secreted by adipocytes) exerts negative feedback on hypothalamic appetite regulation, which causes desensitisation of the leptin receptors and therefore feedback from the adipocytes is not detected by the brain's satiety centre (Martin et al 2004). However, in the same study, they also concluded that changes in serum leptin level could not reliably predict weight gain in risperidone users.

Behavioural approach

In 2005 McDougle et al studied 101 young people with ASC in an eight-week, double-blind placebo controlled trial, followed by a 16-week continuation period. All showed behavioural difficulties, such as aggression or self-injury. The subjects were initially assessed using the ABC and the Clinical Global Impression (CGI) improvement scale with a positive responder being defined as showing a 25% reduction in the ABC irritability subscale and much improved or better on the CGI scale. Of the subjects randomly assigned risperidone, 69% showed a positive response, as opposed to only 12% of those administered the placebo. Those people who were administered the placebo were then offered an eight-week open label trial of risperidone. Further to this, anyone showing a positive response in either the blind or open eight-week trials was invited to partake in a further 16-week continuation phase to help determine the maintenance of the improvement in the various aberrant behaviours. Three differing behavioural assessment scales were used to determine any behavioural changes:

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TABLE 1. Side effects of risperidone use

Side effects	Less common side effects	Rarely seen side effects
» Gastrointestinal disturbances. » Dry mouth. » Dyspnoea. » Drowsiness. » Asthenia. » Tremor. » Sleep disturbances. » Agitation. » Anxiety. » Headache. » Urinary incontinence. » Arthralgia. » Myalgia. » Abnormal vision. » Epistaxis. » Rash.	» Anorexia. » ECG Changes. » Hypoesthesia. » Impaired concentration. » Hyperprolactinaemia. » Sexual dysfunction. » Blood disorders. » Tinnitus. » Angioedema.	» Intestinal obstruction. » Pancreatitis. » Jaundice. » Seizures. » Hyponatraemia. » Abnormal temperature. » Oedema. » Priapism.

- A parent-rated modification of the Ritvo-Freeman Real Life Scale. (Freeman et al 1986).
- The Children's Yale Brown Obsessive Compulsive Scale (Scahill et al 1997).
- The Maladaptive Domain of Vineland's Adaptive Behaviour Scales (Sparrow et al 2005).

The results of this study show that risperidone is more effective than a placebo in three of the Ritvo-Freeman subscales – sensory motor behaviour, affectual reactions and sensory responses – but showed no significant difference over the placebo for the remaining two subscales – social relations and language. It also proved better than a placebo on the compulsive subscale of the Yale Brown scale and in the maladaptive behaviour domain of the Vineland scale. While no further improvements were found during the 16-week continuation phase the initial improvements were maintained.

Adetunji et al (2006) identify that the parent-based modified Ritvo-Freeman scale used in this study could have an inherent bias towards improvement and is therefore no more valid than the original scale and also that drug-induced fatigue – experienced by 59% of the subjects – and drug-induced drowsiness – experienced by 50% of the subjects – may have been responsible for a reduction in some of the behaviour. They also agree with Schreibman (2000) that the behavioural approach still has the greatest empirical efficacy when relating to autism therapy. In a similar study of 80 young people in an eight-week, double-blind placebo controlled study, Shea et al (2004) confirmed the findings of McDougle et al (2005) that risperidone proved consistently effective at relieving certain disruptive behavioural symptoms in children with ASC and other pervasive developmental disorders.

Discontinuation trials

The author would like to report on the discontinuation trials of two students who lived at a specialist residential school for young people with ASC. The discontinuations were scheduled as part of ongoing health planning by specialist medical practitioners and a multidisciplinary team including psychiatrists, parents and the centre nurse. The team deemed both discontinuations to be in the best interests of the two students as they had both been using risperidone for significant periods. The decision to discontinue was not instigated for the purposes of this article; the author was not part of the team or the decision-making process. Data were collected on the students' daily arousal levels to monitor any changes following discontinuation. With the agreement of the team the author was permitted to analyse the data collected.

Student A

This student was in his late teens at the time of the discontinuation. He had been using risperidone for more than three years at a dosage of 2mg per day (1mg twice per day). He displayed incidences of self-injury, for which the risperidone appeared to be of little help. Student A was taking no other medication before discontinuation. He was non-verbal and therefore unable to give his informed consent. He had become lethargic, choosing to spend most of his time in bed and becoming difficult to redirect onto activities he had previously appeared to enjoy. Prediscontinuation monitoring was carried out using an internal, observational emotional arousal scale which was linked to the student's positive behaviour support plan

Apparent emotional arousal level was measured by student A's staff member or teaching assistant using a five-point scale from hypoarousal to hyperarousal:

- Level 1 indicates hypoarousal: sleeping, lethargy, appearing uncooperative, refusing activities, negligible social interactions.
- Level 2 indicates optimum arousal: laughing, interacting, playing games and partaking in activities.
- Level 3 and above indicates hyperarousal: anything from crying, screaming and self-injury to slapping, hitting and attempting to bite members of staff.
- Level 4 or above requires some form of restrictive physical intervention for the safety of the student, the staff team or other students.

Emotional arousal level was monitored every 15 minutes from 8.30am to 7pm over a two-week period in both the residential and educational settings (Table 2).

TABLE 2. Arousal levels for student A before discontinuation

Arousal levels	% time at arousal
Level 1 Hypoarousal	31.12
Level 2 Optimum arousal level	29.76
Level 3	11.33
Level 4	14.62
Level 5 Hyperarousal	13.17

Discontinuation was commenced in early July at a rate of 0.25mg every three weeks over a 24-week period. The arousal levels of student A were re-monitored two weeks after the end of the discontinuation; the results are highlighted in Table 3.

The results show a significant increase in the time student A spent at optimum arousal, with corresponding decreases in all other arousal levels, except level three which showed a negligible increase. Supporting staff anecdotally reported that student A appeared brighter and more responsive, with a greater interest in activities. However, it must also be noted that as part of the ongoing health plan, as the risperidone was being discontinued, citalopram was being introduced. This may have affected the results of the arousal monitoring, although King et al (2009) found citalopram to be ineffective with children on the autism spectrum.

Student B

This student was in his early teens. He was generally calm but could display erratic mood swings and sometimes aggressive outbursts. He also had epilepsy and tended to experience a high number of seizures of differing manifestations. These could often be prolific and protracted in length so he was prescribed a rescue medication as required alongside two commonly used anti-epileptics. Student B had been prescribed risperidone for just under three years, at a dosage of 1mg (0.5mg twice per day).

The results from the student B discontinuation trial show the opposite to student A. The decision to discontinue his risperidone treatment was made by a multidisciplinary team, as he appeared generally calm, to minimise any potential side effects of long-term risperidone use. Student B was verbal and while he may have been able to verbally give his consent, he had been deemed to lack the mental capacity to make an informed decision about his medication. Before discontinuation there had been progress in student B's behaviour, with reports of increased attention in class, less incidences of aggression and a general improvement in his tolerance of staff and peers. Pre-discontinuation monitoring was completed following the same criteria as for student A (Table 4).

Student B followed a graduated discontinuation programme, removing 0.25mg from his daily dose every week for a period of four weeks. Monitoring was completed two weeks after complete cessation of the risperidone (Table 5).

Student B showed a clear movement away from his optimum arousal level and into a state of higher arousal, with a twofold increase in the time spent at arousal level 3 and a threefold increase spent at level 5. Supporting staff also anecdotally reported that his attention span and his ability to stay on task had both decreased and there was a noted increase in his aggressive behaviour. A decrease in seizure activity was also evident from an average of 11 a month down to seven a month, which correlates with evidence that antipsychotic medication reduces the seizure threshold of those with epilepsy (Bryson et al 2003).

Following the negative effect on the arousal levels and behaviour of student B, the team agreed that risperidone was to be reintroduced at half the previous dosage (0.5mg daily). Eight weeks after reintroduction monitoring was recorded compliant with the previous criteria (Table 6). It shows the expected shift back towards optimum arousal. Also noted was a slight increase in seizure activity to eight a month.

This shows a return to the time spent at optimum arousal, with an eradication of the time spent in hyperarousal. However, the time student B spent at level 5 hyperarousal was always minimal, with or without risperidone intervention, and may have been missed during the brief two-week monitoring period. Student B had recently started a new class and he

TABLE 3. Arousal levels for student A two weeks after discontinuation

Arousal levels	% time at arousal
Level 1 Hypoarousal	14.57
Level 2 Optimum arousal level	52.16
Level 3	12.14
Level 4	11.76
Level 5 Hyperarousal	09.37

TABLE 4. Arousal levels for student B before discontinuation

Arousal levels	% time at arousal
Level 1 Hypoarousal	0.47
Level 2 Optimum arousal level	87.03
Level 3	6.13
Level 4	5.90
Level 5 Hyperarousal	0.47

appeared much more settled, which could also explain the sharp increase in the time spent at hypoarousal.

Discussion

Despite the small sample size, the two cases described suggest that risperidone may have beneficial effects for some people yet not for others, since discontinuation of risperidone has had very different outcomes for these students. On reviewing the published literature it is difficult to determine accurately the efficacy of risperidone for all people on the autism spectrum, although in double-blind trials risperidone has some efficacy over placebo (Shea et al 2004, McDougle 2005) and is advantageous over typical antipsychotics such as haloperidol (Hughes et al 2002, Vijay and Chandrashekar 2005). Risperidone is not, however, without its own group of potential side effects, with the risk of weight gain and the associated comorbidities of obesity, and the appearance of EPS at higher doses being the most significant of these.

For carers and clinicians the use of risperidone can be effective in reducing behaviours of concern in some people on the autism spectrum. By contrast, however, some studies have found that behavioural interventions are more effective in supporting behaviours that challenge (Schreibman 2000). Also, positive behaviour support models, such as those described by Gore et al (2013), are often regarded as more ethical since they focus on person-centred values which help the person develop their own coping mechanisms and aim to empower them over their lifetime and not just over the course of drug treatment.

However, behavioural intervention programmes can be complex and difficult to design appropriately without significant specialist support and can be an unavailable option to many parents and carers of people with autism (LaVigna and Willis 2012, Rimmington 2016).

TABLE 5. Arousal levels for student B two weeks after discontinuation

Arousal levels	% time at arousal
Level 1 Hypoarousal	0.49
Level 2 Optimum arousal level	79.36
Level 3	12.78
Level 4	5.90
Level 5 Hyperarousal	1.47

TABLE 6. Arousal levels for student B eight weeks before reintroduction

Arousal levels	% time at arousal
Level 1 Hypoarousal	5.71
Level 2 Optimum arousal level	86.67
Level 3	5.71
Level 4	1.90
Level 5 Hyperarousal	0.0

Conclusion

There are advantages to choosing behavioural intervention programmes over pharmacological therapies when supporting behaviours that challenge in people on the autism spectrum from an ethical and long-term perspective. However, the use of risperidone has benefits for some people, particularly where appropriate support for the development and implementation of behavioural intervention programmes is restricted or unavailable. However, it is important to acknowledge that people with autism are individuals who change over time. The use of antipsychotic medication may have short-term benefits but must be reviewed regularly and appropriate behavioural intervention programmes, which offer the person an opportunity to develop their own internalised coping mechanisms, should always be considered as an alternative treatment to pharmacological interventions. Any use of risperidone must be carefully monitored with regular discontinuation trials implemented by healthcare professionals.

Implications for practice

- The discontinuation of risperidone can have different effects on individuals.
- Carefully monitor and review any use of risperidone – discontinuation trials must be implemented by healthcare professionals.
- Offer behavioural intervention programmes if available and with appropriate support.

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