Psychopharmacology (2012) 223:357–360
DOI 10.1007/s00213-012-2723-z

ORIGINAL INVESTIGATION

Aripiprazole in the treatment of challenging behaviour in adults with autism spectrum disorder

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Received: 7 February 2012 / Accepted: 9 April 2012 / Published online: 26 April 2012

Abstract
Background Autism spectrum disorders (ASD) are associated with repetitive behaviours and often also with hyperactivity, aggression, self-injurious behaviour, irritability and lability of mood. There is emerging evidence that aripiprazole, an antipsychotic with partial agonist dopaminergic effect, may be effective in the treatment of these challenging behaviours. Nevertheless, there is little evidence for their efficacy in adults with ASD.
Objectives The aim of this article is to present preliminary data on the use of aripiprazole in the treatment of challenging behaviour in the setting of ASD.
Methods We present a consecutive series of five inpatients of normal intelligence with challenging behaviour associated with ASD, diagnosed according to ICD-10 criteria, which was resistant to treatment with other medical and behavioural interventions and which was treated with aripiprazole.
Results Four out of five patients were classified as "much improved" or "very much improved" according to the Clinical Global Impression–Improvement scale. Aripiprazole caused akathisia, at a dose of 30 mg in the one patient who was not classified as a responder but was otherwise well tolerated.
Conclusions This is the first case series of adults with ASD presenting with challenging behaviour who have been treated with aripiprazole. While the results are promising, controlled trials are required to confirm the findings.

Keywords Autism · Autism spectrum disorders · Behavioural disorders · Antipsychotics · Aripiprazole · Neuropsychiatry

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Introduction

Autistic spectrum disorders (ASD) include autism, Asperger's syndrome and the pervasive developmental disorders (PDD). The prevalence of ASD is estimated to be over 60 per 10,000 (Fombonne 2009) and the estimated annual cost of autism in UK is approximately £1 billion (Jarbrink and Knapp 2001). Many of these costs are due to the management of challenging behaviours such as hyperactivity, aggression, self-injurious behaviour, irritability, lability of mood and repetitive behaviours (Malone and Waheed 2009; Matson et al. 2011). Medication is a valuable adjunct in the treatment of the behavioural symptoms of ASD and may help increase the efficacy of psychosocial interventions. The most compelling evidence for the efficacy of pharmacological treatment of behavioural symptoms in ASD is for antipsychotic drugs (McDougle et al. 2008). Aripiprazole is a novel antipsychotic with potent partial agonism at dopamine D2 receptors in addition to properties as a 5HT1A

agonist and 5HT2 antagonist (Burris et al. 2002). Numerous studies have reported efficacy of aripiprazole in the treatment of challenging behaviours in children and adolescents with ASD (Stigler et al. 2004; Marcus et al. 2009; Masi et al. 2009; Owen et al. 2009; Stigler et al. 2009) and aripiprazole is approved in USA for irritability associated with autism in children, but evidence in adults is limited (Staller 2003).

The first case series on the use of aripiprazole in the treatment of challenging behaviour in PDD was by Stigler and colleagues (Stigler et al. 2004) who reported their clinical experience of five children diagnosed with PDD and exhibiting aggression, self-injurious behaviour, hyperactivity and agitation and treated with aripiprazole. All five of their patients were classified as responders, defined as a Clinical Global Impression–Improvement (CGI-I) score of 1 or 2. In 2009, Stigler et al. (2009) published a prospective, open-label study of the use of aripiprazole to treat irritability in 22 children with PDD of whom 88 % were classified as responders according to the CGI-I score. Masi et al. (2009) published a retrospective study of 34 children with PDD and severely challenging behaviour treated with aripiprazole and classified almost a third (32.4 %) of their cohort as "much improved" or "very much improved" according to the CGI-I score. Owen et al. (2009) compared the efficacy of aripiprazole and placebo in the treatment of challenging behaviour in a cohort of 98 children with autistic disorder in a double blind, randomised trial and reported a significant decrease in the irritability subscale of the Aberrant Behaviour Checklist and a significantly greater improvement in mean CGI-I scores following 8 weeks of treatment with aripiprazole. In a double blind, randomised, placebo controlled trial, Marcus et al. (2009) compared the efficacy of aripiprazole and placebo in the treatment of challenging behaviour in a cohort of 218 children and adolescents aged 6–17 years diagnosed with autistic disorder. All patients taking aripiprazole demonstrated significant improvement according to a caregiver-rated ABC irritability, stereotypy and hyperactivity subscale scores and significantly greater improvement in CGI-I scores compared to placebo. Quality of life measures were also significantly more improved in the aripiprazole groups.

The results of an open-label study of the use of aripiprazole in the treatment of behavioural disturbance in 12 patients, aged between 6 and 25 years, with fragile X syndrome and PDD by Erickson et al. (2011) report significant improvement, as measured by reduction in Clinical Global Impression–severity scores, in 10 (87 %) of their cohort.

Objectives

The aim of this article was to present preliminary data on the use of aripiprazole in the treatment of challenging behaviour in adults with autism spectrum disorders.

Methods

We report a consecutive series of five patients with normal IQ range who were admitted over a period of 12 months to an inpatient unit specialising in the treatment of behavioural disorders in adults with ASD. The unit is located in London, UK and receives referrals from all over the country. Diagnosis of ASD was made using the Autism Diagnostic Interview–Revised and Autism Diagnostic Observation Schedule (Lord et al. 1994) and supported by clinical assessment by trained clinical staff in a dedicated outpatient clinic or upon admission to hospital. Informed consent was obtained directly from all patients. Improvement, or deterioration, was retrospectively measured using the CGI-I checklist (Guy 1976) by the treating consultant.

Results

Patient A

Patient A is a 27-year-old man with autism who had a history of ideas of reference, paranoia, compulsive exercise and physical aggression. Over the course of admission, patient A had been prescribed risperidone, olanzapine, sodium valproate and lithium without significant therapeutic benefit. Clozapine led to some improvement in mood, paranoia and aggression and was augmented with aripiprazole 10 mg per day which led to a further improvement. When clozapine was discontinued due to neutropenia, aripiprazole was increased to 30 mg per day and resulted, over the course of the next month, in a notable and consistent improvement in compulsive behaviours, social interaction and mood. Four months after starting aripiprazole, patient A was discharged to a residential care facility with a view to eventually entering into full time work. His improvement was equivalent to a CGI-I score of 1 (very much improved).

Patient B

Patient B is a 20-year-old woman with Asperger's syndrome with a history of symptoms of irritability, agitation, insomnia and sudden outbursts of verbal and physical aggression. Patient B had, in the past, been prescribed olanzapine, risperidone, quetiapine, lithium and sodium valproate without any sustained improvement.

Following commencement of aripiprazole 10 mg per day, there was a rapid (within 2 weeks) and sustained improvement in patient B's level of arousal and agitation, and the number of aggressive outbursts reduced from a frequency of two to three per week, to a frequency of fewer than one per month. She was also consistently more engaged with nursing staff, with other patients on the ward and with occupational activities. Soon

afterwards she was discharged to a residential care home. Her improvement was equivalent to a CGI-I score of 1 (very much improved).

Patient C

Patient C is a 35-year-old man with autism and obsessive compulsive disorder who has been in the care of psychiatric services almost continuously since the age of 17. He presented with periods of agitation, self-harm, obsessive persecutory rumination and obsessional thoughts of harm to others. Patient A had been prescribed venlafaxine, fluoxetine, lithium, carbamazepine, quetiapine, sodium valproate, olanzapine and lamotrigine with little improvement in mental state. Clomipramine led to an improvement in obsessional symptoms and mood. The addition of aripiprazole 20 mg was associated, over the course of the 6-week period during which the dose of medication was increased, with an overall reduction in the frequency of episodes of increased arousal and challenging behaviour such as damaging property and self-harm. His improvement corresponds to a CGI-I score of 2 (much improved).

Patient D

Patient D is a 22-year-old man with a diagnosis of Asperger's syndrome who was admitted to our unit following deterioration over the preceding 6 months in his level of social and educational functioning and the onset of motor symptoms such as response latency, posturing and muscular rigidity. A diagnosis was made of catatonia in the setting of an autism spectrum disorder and patient D was commenced on a reducing dose of lorazepam. The dose was reduced over the course of the next 2 months and after this time there was a noticeable improvement in his mobility and spontaneity. The addition of aripiprazole at a dose of 7.5 mg per day was associated with further improvement, over the course of the following month, from his baseline level of functioning in terms of reciprocity and spontaneity. His improvement on aripiprazole corresponds to a CGI-I score of 1 (very much improved).

Patient E

Patient E is a 21-year-old man who was transferred to the unit with a diagnosis of ASD and schizophrenia. At the time of admission, he presented with hallucinations, thought broadcast and somatic passivity despite being on 40 mg of olanzapine per day. Due to significant residual symptoms, his medication was switched to aripiprazole 30 mg which led to a marked worsening of hallucinations and passivity phenomena. Patient E also experienced severe akathisia on doses of aripiprazole above 20 mg. The deterioration of symptoms on aripiprazole corresponds to a CGI-I score of 6 (much worse).

Discussion

This is the first case series of adults with ASD treated with aripiprazole. In the cases described above, our patients had proven refractory to prior pharmacotherapy. Aripiprazole was well tolerated and led to a lasting improvement in mental state in all cases apart from patient E. Patient E experienced severe akathisia at doses above 20 mg per day. The only other reported side effect was mild restlessness reported by patient C. Aripiprazole was not discontinued or reduced in this case, at the patient's request, as he found the medication beneficial at a dose of 20 mg.

Dose range in our series was 7.5–30 mg per day (mean dose 19.5 mg). Two patients (patients B and C) presented with episodic challenging behaviour and lability of mood, two patients presented with obsessional ruminations and persecutory thoughts (patients A and C) and one patient presented predominantly with abnormality of movement (patient D). While it is possible that, in these cases, the efficacy of aripiprazole is a reflection of the fact that it functions as, respectively, a mood stabiliser, antipsychotic and a recognised treatment for catatonia, it is also possible that the improvement may be due to a specific property of aripiprazole which is relevant in autism. Such a property is suggested by the studies we have reviewed above. Moreover, there is evidence that aripiprazole has more affinity than other antipsychotic drugs for brain regions which are implicated in autism, in particular the mesocortex and corpus striatum (Brambilla et al. 2003; McAlonan et al. 2005; Langen et al. 2007; Grunder et al. 2008). Interestingly, in Masi and Cosenza's series (Masi et al. 2009) of children with pervasive developmental disorders and severely challenging behaviour treated with aripiprazole, they found that non-responders were younger than responders by about 3 years which may reflect the consistently differing neuroanatomical findings in children versus adults with autism spectrum disorders (Schumann et al. 2009; Courchesne et al. 2010).

There are a number of limitations to this study. This is a small case series of inpatient from a tertiary referral unit specialising in the treatment of challenging behaviour in patients with ASD and so it may not be possible to generalise these findings to patients in the community. The lack of a control group in case series makes it difficult to draw firm conclusions regarding efficacy. As discussed above, the efficacy of aripiprazole in these cases may be attributable to its effect on instability of mood, paranoia and catatonia, rather than a specific effect in ASD.

Conclusions

There are minimal data and a lack of national guidelines providing guidance for the treatment of challenging behaviour in adults with ASD. Our experience suggests that aripiprazole may be particularly effective in this group for the treatment of a variety of challenging behaviours that occur in the context of ASD. Further, randomised controlled trials are needed to inform optimum care of this patient group.

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