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Article

Aripiprazole in youth with intellectual disabilities: A retrospective chart study

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Abstract

A retrospective chart study of patients on open-label aripiprazole treatment was conducted in the Netherlands to add to the knowledge of aripiprazole in children and young adults with mild and borderline intellectual disabilities (IDs). Fifty-three youths, mean age 14.7 $\pm$ 3.4 years and mean IQ 64.5 $\pm$13.8, were included. Treatment responders were defined as "much improved" or "very much improved" based on the Clinical Global Impression -Improvement scale. For 83% of the patients, disruptive behavior was the main target symptom. The overall response rate was 30% after 1–4 weeks and 69% after 5–8 weeks. The 5–8 weeks responders showed a response rate of 64% at 22–26 weeks. Mild adverse events were observed in 53% of the patients of which fatigue and weight gain were the most common. Seven patients (13.2%) discontinued because of adverse events. In 53 children and young adults with mild and borderline IDs, aripiprazole was effective in both the short and the long term. No serious adverse events were observed.

Keywords

aripiprazole, youth, intellectual, disabilities, child

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Introduction

Children and young adults with intellectual disabilities (IDs) are characterized by a relatively high incidence of disruptive behavior such as severe aggression, hyperactivity, and self-injury (Marcus et al., 2009; McDougle et al., 2003). In Europe, risperidone is registered for the short-term symptomatic treatment of conduct disorder in children and young adults with ID (Hellings et al., 2011). However, in particular considerable weight gain, as part of the metabolic syndrome that may lead to type 2 diabetes and cardiovascular morbidity, may limit its use (Hellings et al., 2011; McIntyre et al., 2001; Wevers, 2016). For this reason, several newer antipsychotic drugs have been introduced (Marder et al., 2003; Posey et al., 2008; Shapiro et al., 2003). Of these agents aripiprazole, which is a partial D2 and 5-HT1A agonist, and a 5-HT2A antagonist (Burris et al., 2002; Etminan et al., 2016; Stigler et al., 2009), is of special interest because of its favorable side effect profile, as it leads to less weight gain and does not affect prolactin levels, associated with side effects such as menstrual disturbances, infertility, loss of libido, erectile dysfunction and male gynecomastia (Byerly et al., 2008; Hellings et al., 2010; Trives et al., 2013; Wevers, 2016). In Europe, aripiprazole is only registered in youth from 13 years onwards for the treatment of mild to severe manic episodes in bipolar disorder (Pharmacotherapeutic Compass (PC), 2017). First reports on the short-term safety and efficacy in children and young adults with ID are promising (Hellings et al., 2011; Masi et al., 2009; Stigler et al., 2009) but need replication. Therefore, the aim of this retrospective chart study was to investigate treatment effects including side effects, in children and young adults with ID using aripiprazole. A secondary aim was to explore factors as gender, age and IQ associated with clinical effects.

Methods

This was a retrospective clinical chart study where electronic patient files were used in children and young adults with ID who had received aripiprazole treatment in two child- and adolescent outpatient clinics in the Netherlands, namely, the Bascule located in Amsterdam and Accare located in Groningen, both representing a mixed rural and urban population.

Our sample consisted of 53 children and young adults aged 8 to 21 years with an IQ below 85, previously measured by using the Wechsler Intelligence Scale for Children (WISC IQ test), who started aripiprazole treatment between January 2014 and June 2017. In the Netherlands, mental health-care services do not distinguish between people with a mild ID and people with a borderline ID. They also follow youths until 21. We therefore used the IQ range of 50–85 and the upper age limit of 21 to align with clinical practice. Descriptive statistics such as psychiatric diagnoses, comorbidity, target symptoms, and other concurrent psychotropic—and somatic medications—were performed. Also, treatment duration, dosage on different measurement moments, adverse events, and reason for discontinuation were evaluated. At baseline, target severity was assessed by using the Clinical Global Impression-Severity scale (CGI-S scale) and improvement of target symptoms during study was assessed by using the Clinical Global Impression-Improvement scale (CGI-I scale). Both CGI scales were retrospectively determined based on clinical manifestations noted by the physicians. Treatment responders between 1–4 weeks and 5–8 weeks of treatment were defined as "much improved" or "very much improved" based on the CGI-I. An estimate of long-term treatment respondence was created by evaluating the 5–8 weeks responders at 22–26 weeks. We used time intervals (4 and 8 weeks for short-term effects and 26 weeks for long-term effects) as clinicians did not use a fixed visit schedule.

Because most data were available between 5 weeks and 8 weeks of treatment, associations between treatment response and gender, age, and IQ were calculated for this interval. χ^2 tests and

Table 1. Baseline characteristics.

Characteristics	Participants ($n = 53$)
Age, mean (SD) in years	14.7 (3.4)
Sex, *n* (%)	
Female	14 (26.4)
Male	39 (73.6)
IQ, mean (SD)	64.5 (13.8)
Principal diagnosis DSM-IV-TR, *n* (%)	
ASD	36 (67.9)
ADHD	10 (18.9)
Psychoses	2 (3.8)
Other	5 (9.4)
Target symptom, *n* (%)	
Disruptive behavior	44 (83.0)
ADHD	3 (5.7)
Psychosis	2 (3.8)
Anxiety/depression	1 (1.9)
Repetitive/compulsive behavior	3 (5.7)
CGI-S at baseline, *n* (%)	
Moderately ill	5 (9.6)
Markedly ill	32 (61.5)
Severely ill	15 (28.8)
Other concurrent psychotropic medication, *n* (%)	
Stimulant	16 (30.2)
Antipsychotic	2 (3.8)
Clonidine	2 (3.8)
Concurrent somatic medication, *n* (%)	
Anticonvulsant	2 (3.8)
Analgesic	3 (5.7)
Other	4 (7.6)
Previous use of risperidone, *n* (%)	
Yes	41 (77.4)
No	8 (15.1)
Unclear	4 (7.5)

ASD: autism spectrum disorder; ADHD: attention-deficit hyperactivity disorder; CGI-S: Clinical Global Impression-Severity; SD: standard deviation.

independent *t*-tests were performed by using the SPSS statistical program, version 24. p values of $<.05$ were used to indicate the statistical significance. As this was a chart study, no ethical approval was required as per Dutch law.

Results

A total of 53 children and young adults of which 39 males and 14 females (mean age 14.7 $\pm$ 3.4 years; range 8–21 years) with an IQ below 85 (mean IQ 64.5 $\pm$ 13.8) were included. Baseline characteristics are summarized in Table 1. The majority of patients (68%) had a primary diagnosis of autism spectrum disorder (ASD). Of these patients with ASD, one third had a comorbid

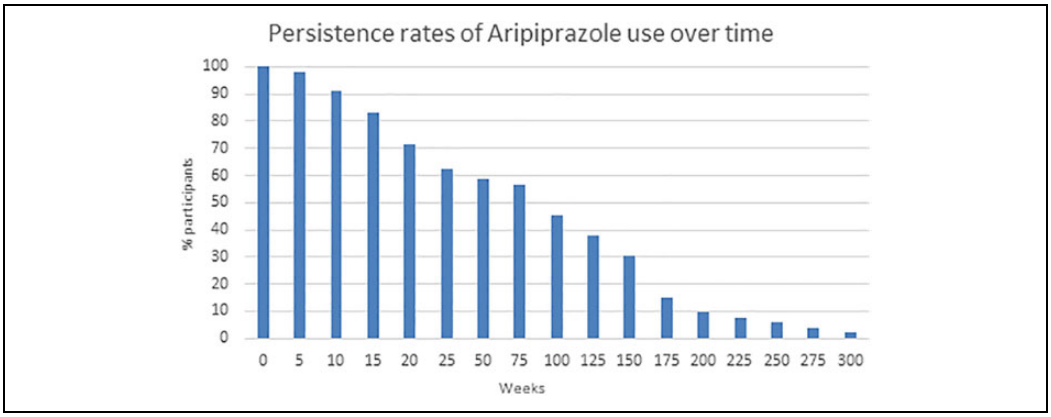

Figure 1. Persistence rates of aripiprazole use over time. The average treatment duration was 80 ± 73 weeks.

diagnosis of attention-deficit hyperactivity disorder (ADHD). In 15 patients (28%) somatic comorbidity was present, such as Down syndrome, epilepsy, Fragile X syndrome, and a few other rare syndromes. This also included disorders such as kidney disease, B-thalassemia, constipation, premenstrual syndrome, and alopecia areata that had been previously diagnosed by different physicians.

In 44 children and young adults (83%), disruptive behavior was the target symptom for aripiprazole treatment. In addition, other target symptoms were ADHD symptoms, psychotic symptoms, anxiety/depression, and repetitive/compulsive behavior. It appeared that 41 out of 53 patients (77%) used risperidone before starting aripiprazole treatment, 45% of these 41 patients had discontinued risperidone treatment because of insufficient efficacy, 27% discontinued because of weight gain, and the remaining patients (12%) had discontinued because of both insufficient treatment effect and weight gain. The average aripiprazole treatment duration was 80 ± 73 weeks (range, 3 to 287 weeks) (see Figure 1). Mean daily aripiprazole doses were 3.6 ± 2.3 mg (range, 0.3–10 mg) at 1–4 weeks and 5.0 ± 4.2 mg (range, 1–20 mg) at 5–8 weeks. At 22–26 weeks, the mean daily dose was 5.6 ± 4.1 mg (range, 1–20 mg). Existing medications were kept stable. Sixteen patients (30%) received stimulants, other medications are detailed in Table 1. None of the concomitant somatic drugs have known drug interactions with aripiprazole.

Between weeks 1–4 and 5–8, response rates were 30% and 69%, respectively (see Figure 2). Non responders were 36% between 1–4 weeks and 18% between 5–8 weeks. Thirty four percent of the participants had no evaluation between 1–4 weeks, and between 5–8 weeks, this percentage was 15%. No significant differences were found between treatment response and gender ($\chi^2(1) = 0.114$, $p = 0.736$), age ($t(43) = -0.463$, $p = 0.910$) and IQ ($t(38) = 0.107$, $p = 0.156$).

Five to eight weeks responders ($n = 36$) showed a response rate of 64% at 22–26 weeks of treatment with a mean daily dose of 5.6 ± 4.1 mg (range, 1–10 mg) at 22–26 weeks (Figure 3).

At endpoint, 37 patients (69.8%) discontinued aripiprazole treatment because of various reasons (Table 2). Seven patients (13.2%) discontinued treatment because of adverse events of which three because of fatigue at, respectively, 12, 26, and 76 weeks, one patient because of abdominal pain at 8 weeks and one patient discontinued because of apathy at 10 weeks. Additionally, one patient

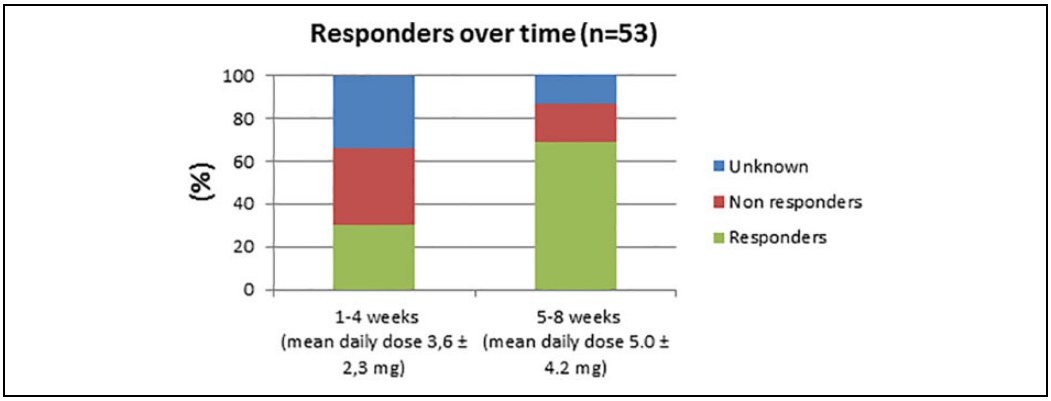

Figure 2. Treatment responders between 1 week and 4 weeks (30%) and between 5 weeks and 8 weeks (69%).

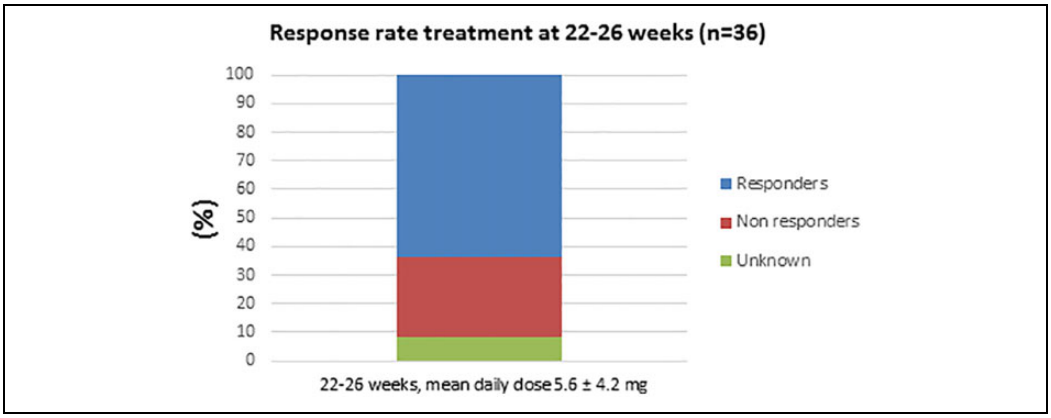

Figure 3. Treatment responders between 5 weeks and 8 weeks ($n = 36$) have been evaluated over time. The response rate between 22 weeks and 26 weeks of treatment was 64%.

Table 2. Reason discontinuation within study period (January 2014–June 2017; $n = 37$).

Treatment condition at endpoint study	Participants, *n* (%)
Discontinued because of insufficient effect	12 (22.6)
Treatment taken over by other institution	10 (18.9)
Discontinued because of side effects	7 (13.2)
Discontinued because of prolonged treatment effect	5 (9.4)
Other (migration, unknown reason)	3 (5.7)

discontinued aripiprazole treatment because of constipation and overflow diarrhea at 15 weeks and one patient discontinued because of weight gain at 42 weeks of treatment. Mild side effects were observed during treatment in 39.8% of all patients (Table 3).

Table 3. Adverse events as noted by physicians ($n = 53$).

Adverse events	Participants, *n* (%)
Fatigue	12 (22.6)
Weight gain	3 (5.7)
Urinary incontinence	2 (3.8)
Nausea/vomiting	2 (3.8)
Movement disorders (tics and tremor)	2 (3.8)
Constipation and overflow diarrhea	1 (1.9)
Increased appetite	1 (1.9)
Decreased appetite	1 (1.9)
Pain in limbs	1 (1.9)
Priapism	1 (1.9)
Abdominal pain	1 (1.9)
Apathy	1 (1.9)

Baseline weight measurements were available from 47 patients (89%) with a mean weight of 52.5 $\pm$ 20.5 kg. Between 1 week and 4 weeks of treatment, weight measurements were available from 9 patients (17%) where the mean weight was 56.2 $\pm$ 18.5 kg. Three patients showed considerable weight gain between 1 week and 4 weeks, namely 2 kg in 1 patient and 3 kg in 2 patients. From 9 patients (17%), weight measurements were available between 5 weeks and 8 weeks with a mean weight of 45.7 $\pm$ 18.2 kg. Between 5 weeks and 8 weeks of treatment, one patient gained 1.5 kg and 2 patients gained more than 3 kg.

Discussion

In this retrospective clinical chart study, we found in a sample of 53 children and young adults with mild and borderline ID, aripiprazole treatment was effective in reducing disruptive behavior in almost one-third of the patients between 1 week and 4 weeks and in more than two-thirds of the patients between 5 weeks and 8 weeks. These findings are consistent with those reported by Marcus et al., 2009, who reported a response rate of 56% in a group of 53 children with a diagnosis of autistic disorder. Added here, current study findings are also in line with previous research by Ichikawa et al. (2017) and Owen et al. (2009), who showed a statistically significant greater improvement in mean clinician-rated CGI-I scores. In the current study, respectively, 36% and 18% of the patients were nonresponders between 1–4 weeks and 5–8 weeks.

To evaluate long-term effects in the 5–8 weeks responders, a response rate between 22 weeks and 26 weeks was created, where 64% of the 5–8 weeks responders were also responders after 22–26 weeks of aripiprazole treatment. This implicates that in almost two-thirds of short-term responders, who continue on aripiprazole, long-term effectiveness can be expected. This is comparable with both short and long-term effectiveness that were found in studies on first line treatment with risperidone (Hellings et al., 2011; Wevers, 2016).

The mean dose of aripiprazole used in this study is within the range of doses used in other studies (Hellings et al., 2011) and in line with national and international guidelines on the use of aripiprazole (PC, 2017).

Adverse events were observed in 53% of the patients, of which fatigue and weight gain were the most common, which corresponds to previous research reported by Marcus et al. (2011). Within

this study, weight gain was highly variable, notably between −3 kg and 3 kg at week 5–8 and between −3 kg and 7 kg at week 22–26 where, respectively, 1.3 kg and 4 kg would be expected according to grow charts. One child with obesity at baseline stopped because of a weight gain of 14 kg in 42 weeks, where about 12 kg was to be expected. On the other side, in 7 visits even weight loss was recorded, which may be contributed to discontinuation of risperidone, which is known to cause considerable weight gain in children (Hellings et al., 2011; Wevers, 2016). The relatively mild weight gain associated with using aripiprazole in this study implicates that also in children and young adults with ID aripiprazole is less likely to induce weight gain. Overall, aripiprazole was well tolerated, and no severe adverse events have been noted. There was no significant association between treatment response between 5 weeks and 8 weeks and gender, age, and IQ.

Compared with previous research, this study contains a relatively large sample size of children and young adults with mild to borderline ID ($n = 53$) and multiple comorbid conditions which adds to the relative scarce data in this population. Interestingly, in 77% of the patients, it appeared that aripiprazole was prescribed after previous risperidone treatment was ineffective or discontinued because of side effects. This reflects the increasing use of aripiprazole in the Netherlands as a second-line treatment after risperidone. This on the one hand limits the generalizability of this study to youth who recently discontinued risperidone. On the other hand, this strongly adds to the knowledge on second-line treatments in this severely affected clinical population.

A major limitation of this study was the retrospective design which caused missing data or data that could not be processed. Additionally, the investigators had to rely on the accuracy of the notes of the clinicians obtained from nonstandardized consultations. For example, the CGI-I scale was retrospectively determined based on clinical manifestations noted by the physicians. However, the CGI-I scale scoring was a reliable measure, with a 100% agreement score between investigators in 20 randomly assessed visits. Furthermore, the design did not contain randomization, blinding, or a control group. In addition, possible confounding effects of concomitant behavioral treatments have not been taken into account. However, most behavioral treatments had largely taken place months before aripiprazole treatment was initiated and it is therefore unlikely that these had an effect on the observed treatment effects of aripiprazole.

Conclusion

In this retrospective explorative clinical chart study in 53 children and young adults with mild to borderline ID who were largely diagnosed with ASD, aripiprazole treatment was effective in 69% of the patients after 5–8 weeks of treatment. In 83% of the patients, disruptive behavior was the main target symptom. These responders showed a prolonged response rate of 64% up till 22–26 weeks. Most frequently reported adverse events were fatigue and weight gain. In one-tenth of the patients, this led to discontinuation, mainly because of fatigue. Weight gain was mild, suggesting that the lesser potential of aripiprazole for inducing weight gain also applies to children and young adults with mild to borderline IQ. Further randomized controlled studies are needed in this population.

Declaration of conflicting interests

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