Progress in Neuro-Psychopharmacology & Biological Psychiatry 37 (2012) 128–131

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Switching to aripiprazole in subjects with Pervasive Developmental Disorders showing tolerability issues with risperidone

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ARTICLE INFO

Article history:
Received 17 October 2011
Received in revised form 12 December 2011
Accepted 29 December 2011
Available online 8 January 2012

Keywords:
Aripiprazole
Behavioral symptoms
Pervasive Developmental Disorders (PDD)
Risperidone
Tolerability issues

ABSTRACT

Background: Subjects with Pervasive Developmental Disorders (PDD) often exhibit behavioral symptoms such as aggressiveness and irritability, which are targets of psychopharmacologic intervention. This retrospective study was designed to examine children and adolescents with PDD experiencing tolerability issues with risperidone treatment, and thereby assess the efficacy and tolerability of switching to aripiprazole.
Methods: This naturalistic study included 23 subjects with PDD (16 males, 7 females, age range 9–24 years, mean age 15.1 ± 3.9 years) diagnosed according to DSM-IV criteria and followed up for 14.9 ± 8.4 weeks after switching to aripiprazole from risperidone. Outcome measures were the Clinical Global Impression-Severity (CGI-S) and CGI Improvement (CGI-I) scales.
Results: The mean CGI-S scores of pre-aripiprazole treatment and post-aripiprazole treatment were, respectively 4.7 ± 1.4 and 4.6 ± 1.3. Mean maintenance dosages of risperidone and aripiprazole were, respectively, 0.7 ± 0.5 mg/day and 2.8 ± 1.3 mg/day. The mean CGI-I score, which shows the difference induced by switching from risperidone to aripiprazole, was 3.4 ± 0.8 for the whole sample, suggesting that the efficacy of risperidone for treating behavioral problems of PDD was maintained by aripiprazole. Some improvement of safety/tolerability issues such as increased appetite, somnolence, hyperprolactinemia, and amenorrhea occurred after switching to aripiprazole.
Conclusion: Results show that switching to aripiprazole might be generally well tolerated and might constitute an alternative treatment for subjects with PDD who experience tolerability issues with risperidone treatment. Additional long-term controlled studies of PDD subjects should be undertaken to evaluate the efficacy and safety of switching to aripiprazole from other antipsychotics.

1. Introduction

Pervasive Developmental Disorder (PDD) is a chronic developmental disorder in which disturbances in the development of the central nervous system impair a person's social, cognitive, and communicative competence (Myers, 2007). In addition, many patients with PDD exhibit behavioral symptoms such as hyperactivity, aggressiveness, irritability, impulsivity, mood disturbance, and self-injurious behavior (Leskovec et al., 2008). Though behavioral therapies are clearly the main interventions for these behavioral symptoms, psychopharmacologic intervention is also often needed from early childhood, which result in longer-term use of psychotropic medications (West et al., 2009). Thereby, it is important to choose generally safe and well-tolerated medications considering the possibility that continuous tolerability issues might have negative impact for the health of child and adolescent subjects with PDD.

Various psychotropic medications are currently used to treat a range of symptoms associated with PDD, including aggression, repetitive behaviors, low tolerance for frustration, and hyperactivity (McPheeters et al., 2011). Antipsychotics, including risperidone and the conventionally used agent haloperidol, are the most commonly used class of agents for treating patients with PDD (Lemmon et al., 2011; Levy and Hyman, 2005). Several reports have described that risperidone is well tolerated and effective in treating behavioral symptoms associated with PDD in children (McDougle et al., 2005; Shea et al., 2004). Nevertheless, a few PDD patients develop adverse events including extrapyramidal side effects, weight gain, transient sedation, galactorrhea, amenorrhea, and gynecomastia (Barnard et al., 2002; Canitano and Scandurra, 2008).

Abbreviations: DSM, Diagnosis and Statistical Manual of Mental Disorders; CGI, Clinical Global Impression; PDD, Pervasive Developmental Disorders.

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doi:10.1016/j.pnpbp.2011.12.015

Aripiprazole, an atypical antipsychotic agent, is a potent partial agonist at D2 and 5-HT1A receptors and a potent antagonist at 5-HT2A receptors (Hirose et al., 2004; Jordan et al., 2002). As with other antipsychotics, aripiprazole has been shown to be efficacious and generally well tolerated in children and adolescents with schizophrenia or bipolar mania (Biederman et al., 2005, 2007; Findling et al., 2008a, 2008b). According to the recent two large randomized controlled trials, which were conducted to evaluate the efficacy and safety of aripiprazole in the treatment of maladaptive behaviors in children and adolescents with PDD, aripiprazole was efficacious for irritability and was generally safe and well-tolerated (Marcus et al., 2009; Owen et al., 2009). Furthermore, in contrast to other atypical antipsychotics, aripiprazole is associated with minimal weight gain and has minimal negative influence on metabolic and neuroendocrine parameters (Casey et al., 2003; Naber and Lambert, 2004). Aripiprazole and risperidone have been approved by the U.S. Food and Drug Administration (FDA) for treating pediatric patients with irritability associated with autistic disorder (Prinseton et al., 2009; Titusville, 2009). Hence, switching from risperidone to aripiprazole might be an efficacious option, especially in patients with PDD experiencing insufficient efficacy or tolerability issues with risperidone treatment. However, no report in the relevant literature describes a study assessing the efficacy and tolerability of switching to aripiprazole in children and adolescents with PDD receiving risperidone treatment. We describe our retrospective clinical experience using aripiprazole switched from risperidone in children and adolescents with PDD, who were treated naturalistically in a routine clinical setting.

2. Methods

2.1. Subjects

Our retrospective study was based on a clinical database of 23 outpatients (16 males, 7 females) with PDD, aged between 9 and 24 years (mean age, 15.1 ± 3.9 years), who had been referred to a specialty clinic for children at the Hiratani Child Development Clinic.

Subjects included 16 patients (69.6%) with autistic disorder, 3 patients (13.0%) with Asperger disorder, and 4 patients (17.4%) with pervasive developmental disorders not otherwise specified (PDD-NOS). The diagnosis of PDD was confirmed by a child psychiatrist (author M.H.) based on classifications in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR; American Psychiatric Association, 2000). Subjects with psychotic disorders or bipolar disorder were excluded. Subjects were also excluded if they had a history of drug or alcohol abuse. In addition, subjects with severe mental retardation for whom a definitive diagnosis of autism could not be made were excluded.

To treat a range of behavioral symptoms associated with PDD, including irritability, aggression, repetitive behaviors and hyperactivity, all subjects had received treatment with risperidone (mean maintenance dosage, 0.7 ± 0.5 mg/day) previously, which was interrupted rapidly and which was simultaneously switched to aripiprazole (mean maintenance dosage, 2.8 ± 1.3 mg/day) because of increased appetite and weight (11 patients), hyperprolactinemia (3 patients), somnolence (2 patients), amenorrhea (1 patient), or long-term safety (6 patients). The dosage of aripiprazole was titrated depending on the clinical outcome and occurrence of adverse effects, but was same as the starting dose during the treatment in most cases. Written informed consent to treatment was obtained from each participant's legal guardian (parents for all children in this report; legally appointed guardians for all adults). Subjects provided assent when able. Twelve subjects (52.1%) continued to receive concomitant psychotropic medications such as carbamazepine, methylphenidate, fluvoxamine, valproate sodium, and zolpidem. Medications except for risperidone and aripiprazole were unchanged during the switching period.

Our naturalistic study was retrospective. The patients could have discontinued medication including aripiprazole at any time when adverse effects occurred. The protocol used for this study was approved by the Institutional Review Board of the University of Fukui.

2.2. Behavioral Rating Scales

Each patient was assessed by the research team for behavioral symptoms before switching to aripiprazole and again after switching to aripiprazole (mean duration of aripiprazole treatment: 14.9 ± 8.4 weeks). The clinical course of the patients was monitored by child psychiatrists of our research team. The child psychiatrists involved in the diagnosis and treatment were highly experienced in managing children and adolescents with PDD. They had been properly trained in the use of the diagnostic instruments. Measures of severity before and after switching to aripiprazole were the following. To assess the severity of behavioral symptoms including irritability, aggression, self-injury, repetitive behaviors and hyperactivity, we used Clinical Global Impression-Severity (CGI-S) (DiLalla and Rogers, 1994): a single item that rates the severity of global symptomatology on a scale from 1 ('normal') to 7 ('extremely ill'). Clinical Global Impression-Improvement (CGI-I) (DiLalla and Rogers, 1994), a single item recorded at the end of the study rating behavior from 1 ('very much improved') to 7 ('very much worsened'), was also applied to compare the severity of global symptomatology before and after switching to aripiprazole. These instruments have been used extensively in psychopharmacological studies of children and adolescents with PDD (Masi et al., 2003; Nicolson et al., 1998; Zuddas et al., 2000).

2.3. Statistical analyses

Results of CGI-S scores are presented as mean ± SD differences. Potential differences between the CGI-S score of baseline (before taking risperidone) and that of risperidone treatment period and aripiprazole treatment period were calculated using Wilcoxon signed-rank tests and were considered significant at $P<.05$.

3. Results

Patient characteristics just before switching to aripiprazole are shown in Table 1. The mean CGI-S score of baseline (before taking risperidone), the endpoint of risperidone treatment period (just before switching to aripiprazole from risperidone), and the endpoint of aripiprazole treatment period (14.9 ± 8.4 weeks after switching to aripiprazole) were, respectively, 5.5 ± 1.2, 4.7 ± 1.4, and 4.6 ± 1.3

Table 1
Patient background.

Subject	n = 23
Age at examination (years)	
Mean ± SD	15.1 ± 3.9
Gender, n	
Male	16
Female	7
Diagnosis, n (%)	
Autistic disorder	16 (69.6)
Asperger disorder	3 (13.0)
PDD-NOS	4 (17.4)
Reason for switching to aripiprazole, n (%)	
Excessive appetite	11 (47.8)
Hyperprolactinemia	3 (13.0)
Somnolence	2 (8.7)
Amenorrhea	1 (4.3)
Long-term safety	6 (26.1)

PDD, pervasive developmental disorders; PDD-NOS, pervasive developmental disorders not otherwise specified.