Letter to the Editor

Efficacy and Safety of Aripiprazole for Treatment of Irritability in Children with Autistic Disorder: An Open-Label Study

Dear Editor,

Autistic disorder is characterized by delay and deviance in the development of social interaction and communication as well as specific interests and repetitive restricted behaviors. Symptoms of the disorder are chronic and they are manifested before the age of 3 years. In addition to these symptoms, severe irritability such as aggression, tantrum, mood swings, and self-injury are sometimes seen among these patients. Such symptoms further disrupt an individual's performance and cause many problems for the patient and family.[1] Treatment of autistic disorder mainly includes behavioral and educational interventions. Pharmacological treatments are also used for controlling behavioral symptoms that cause considerable impairment in performance and do not respond to behavioral interventions. The effective pharmacological treatment for such symptoms improves response rate to behavioral and educational interventions in autism.[2]

Aripiprazole was approved in 2009 for treating behavioral problems at the ages of 6-17 years.[3] Aripiprazole's mechanism of action is different from other antipsychotics. This drug is a D2 partial agonist; that is, it acts as an antagonist and an agonist in hyper dopaminergic state and hypo dopaminergic state, respectively. The drug is also a 5HT1A partial agonist and has high affinity to 5HT2C, 5HT2A, and H1 receptors.[4] Aripiprazole is the only antipsychotic drug that reduces prolactin levels. Aripiprazole-induced weight gain is little and has a few impacts on glucose and lipids.[5]

Most studies on controlling aggression in autism were carried out at the ages above 6 years and there are limited data at pre-school ages. However, there are also behavioral problems at these ages and they sometimes limit educational interventions. With respect to the importance of early treatment, it seems necessary to conduct studies on the effective and safe drugs to reduce behavioral problems in this age group. This study was designed as an open-label trial for a total duration of 8 weeks, aimed at evaluating effectiveness, safety, and tolerability of Aripiprazole in 3 to 6 years old children with autistic disorder and behavioral problems such as irritability, aggression, agitation, and self-injury. The study was conducted in Akhavan and Rofeydeh Rehabilitation Clinics (University of Social Welfare and Rehabilitation Sciences, Tehran, Iran) from November 2012 to July 2014. The trial was performed in accordance with the declaration of Helsinki and its subsequent revisions. It was approved by the Ethics Committee of the University of Social Welfare and Rehabilitation Sciences. Written consents were obtained from patients' parents/guardians before including them in the study. Diagnosis was made based on observation of children's behaviors and psychiatric interview with parents by a child and adolescent psychiatrist. Aberrant Behavior Checklist-Community (ABC-I), Irritability subscale and Clinical Global Impression-Improvement scale (CGI-I) were used to assess severity of behavioral problems and improvement. The inclusion criteria were clinical diagnosis of autism, 3-6 years of age, and ABC-I>18. The exclusion criteria were current diagnosis of bipolar disorder, psychosis, major depression, other disorders of autism spectrum, seizures in previous year, history of severe brain trauma, severe medical diseases, history of sensitivity or intolerance or no response to Aripiprazole, having received antidepressants or antipsychotics within the previous week (Fluoxetine within the previous month), and having received psychoactive drugs and benzodiazepines within the previous72 hours. Finally, 10 patients (8 male, 2 female) with a mean age 4.2 were included in the study. Aripiprazole was administered as 1.25 mg, 2.5 mg, 5 mg, and 7.5 mg in week 1, week 2, week 3, and week 4, respectively. Afterwards, it was administered as 10 mg up until the end of the study. The trial was registered in the Iranian Registry of Clinical Trials (IRCT201209645N2).

ABC-C, irritability subscale (ABC-I) was reduced significantly at the end of week 8 ($P<0.001$). Reduction of the overall score of ABC-C was also significant ($P<0.001$). Reduction of the subscales of stereotypic behaviors and hyperactivity was also significant ($P<0.001$), although no significant reduction was observed in lethargy/social isolation and inappropriate speech subscales. All patients had a partial response to the treatment (25% reduction in ABC-I) and 60% fully recovered (50% reduction in ABC-I). 33.3% and 66.6% of the recovered patients began to recover from week 6 and 8, respectively. Assuming score 1 or 2 as the recovery level, based on the CGI-I scale, 80% of our patients are considered as

recovered. There were no significant changes of vital signs, ECG, and other laboratory, including CBC/diff, FBS, BUN, Cr, TSH, LFT and electrolytes. In addition, there was no significant change in prolactin level. Generally, Aripiprazole was well tolerated. The most common side effects included increased appetite and weight gain, sedation and agitation. The severity of side effects was either mild or moderate where none of these side effects led to discontinuation of the drug. No extrapyramidal side effect was seen. In general, the result of our research indicated the effectiveness of Aripiprazole in controlling irritability of 3-6 years old autistic children was well tolerated.

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