Systematic Review

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Aripiprazole for treating irritability in children & adolescents with autism: a systematic review

Ahmad Ghanizadeh[1-4], Sylvie Tordjman[5,6] & Nematollah Jaafari[7-10]

[1]Research Center for Psychiatry & Behavioral Sciences, [2]Department of Psychiatry, [3]Substance Abuse Research Center & [4]Department of Neuroscience, School of Advanced Medical Sciences & Technologies, Shiraz University of Medical Sciences, Shiraz, Iran, [5]Hospital-University Department of Child & Adolescent Psychiatry, Guillaume Régnier Hospital, Rennes 1 University, Rennes 35000, France, [6]Laboratory of Psychology of Perception, University Paris Descartes & CNRS UMR 8158, Paris 75270, France, [7]INSERM U 1084, Experimental & Clinical Neurosciences Laboratory, Team Psychobiology of Compulsive Disorders, Poitiers, F-86022, France, [8]CIC INSERM U 802, CHU de Poitiers, F-86022, France, [9]Univ Poitiers, Poitiers, F-86022, France, & [10]Unité de recherche clinique intersectorielle en psychiatrie du Centre Hospitalier Henri Laborit, 86021 Poitiers, France

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***Background & objectives*: No clear therapeutic benefits of antipsychotics have been reported for the treatment of behavioural symptoms in autism. This systematic review provides an assessment of evidence for treating irritability in autism by aripiprazole.**

***Methods*: The databases of MEDLINE/PubMed and Google Scholar were searched for relevant articles about the effect of aripiprazole in children with autism. The articles were searched according to the inclusion and exclusion criteria specifed for this review. All the double-blind, controlled, randomized, clinical trials examining the efficacy of aripiprazole for treating children and adolescents with autism were included.**

***Results*: From the 93 titles identified, 26 were irrelevant and 58 were evaluated for more details. Only five articles met the inclusive criteria. The evidence from precise randomized double blind clinical trials of aripiprazole for the treatment of autism in children and adolescents was convincing enough to recommend aripiprazole. Adverse effects were not very common and were usually mild.**

***Interpretation & conclusions*: Current evidence suggests that aripiprazole is as effective and safe as risperidone for treating irritability in autism. However, further studies with larger sample size and longer duration are required.**

Key words Aripiprazole - autism - children - clinical trial - irritability

Aripiprazole, 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy}-3,4-dihydro-2(1H)-quinolinone, is an atypical antipsychotic. It is approved for the treatment of bipolar I disorder (in children aged 10-17 yr), schizophrenia (in children aged 13-17 yr)[1] and autism in children and adolescents[2] by the Food and Drug Administration (FDA). There is strong evidence for its efficacy for treating tic disorder[3,4]. In addition, there is some weak evidence for its efficacy for treating attention deficit hyperactivity disorder (ADHD)[5]. It is a partial agonist of serotonin (5-hydroxy tryptamine, 5-HT) 5-HT1A[6] and dopamine D2 receptors[7]. It is also a 5-HT2A receptor antagonist without considerable affinity at the cholinergic muscarinic receptor[2]. Its serum half-life in adults is 72 h. Aripirprazole has only one active metabolite, dehydroaripiprazole. The half-life of this metabolite is about 94 hours in adults[8].

Autism is a complex neurodevelopmental disorder and its aetiology is not clearly known. At present, two medications including risperidone and aripiprazole are FDA approved for treatment of symptoms associated with autism[2]. A 14-week, prospective, open-label study including 25 children with irritability and pervasive developmental disorder not otherwise specified and Asperger's disorder reported that aripiprazole had no significant cardiac effects[9].

The aim of this systematic review was to evaluate the evidence from clinical trials of therapeutic intervention testing aripiprazole for autism in children and adolescents. A systematic review was conducted in May 2011 to determine the safety and efficacy of aripiprazole for patients with autism spectrum disorders (ASD)[10]. This study found two randomized controlled trials using aripiprazole for a duration of eight weeks to treat autism in children.

There was no study conducted on adult patients with autism. It was found that aripiprazole improved irritability in children with autism, but increased weight more than placebo[9]. The current systematic review was aimed to update the evidence for administering aripiprazole for treating autism.

Material & Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol was used to perform this systematic review[11].

Search strategy: Systematic literature searches were conducted to retrieve all randomized clinical trials (RCTs) of aripiprazole for treating pervasive developmental disorder. The databases of MEDLINE, Google Scholar, The Cochrane Library and Web of Science were searched upto 2013. The International Clinical Trials Registry Platform was also searched to find currently ongoing trials.

The terms for conducting the search were "aripiprazole+pervasive developmental disorder", "autism+aripiprazole", and "autistic disorder+aripiprazole". Potentially relevant titles were selected and articles retrieved. A preliminary selection based on the titles was conducted. The references of the articles were also searched to find possible relevant articles. No language limitation was imposed.

Study inclusion criteria: All the randomized controlled clinical trials that investigated the effect of aripiprazole on irritability in pervasive developmental disorders were included. There were no age, publication date, and gender limitations. Any trial using a valid and reliable measurement to assess irritability was included. Intent-to-treat analysis was not an exclusion criterion.

Evaluation of validity: Methodological issues such as method of randomization, blinding of participants, and having any controlled groups were considered.

Data extraction: An extraction data sheet was designed. Study design, sampling, intervention, and adverse effects were extracted.

Results

The number of identified articles was 93 (Figure). Of these, 26 were found to be irrelevant. These studies had not examined the effect of aripiprazole on irritability in autism. The other reasons for exclusion were as follows: not a clinical trial[10,12-38], not double blind trials[37,39-42], post-hoc analyses[43-45], no control group[46], case reports[47-55], switching risperidone to aripiprazole[56,57], data re-analysis[58], assessed body mass index changes[59], prevention of irritability[60], and retrospective studies[61-65]. One study reported anti-manic effect of aripiprazole in patients with autism spectrum disorder and bipolar disorder[66]. Another reported lack of any significant effect of aripiprazole on electrocardiographic data in paediatric patients[9]. A post-hoc analysis reported quality of life of children with autism[44].

Only five articles met the inclusion criteria[67-71]. In these trials, the effect of aripiprazole on patients with autism was investigated. The details of these studies are indicated in the Table. Only one trial compared

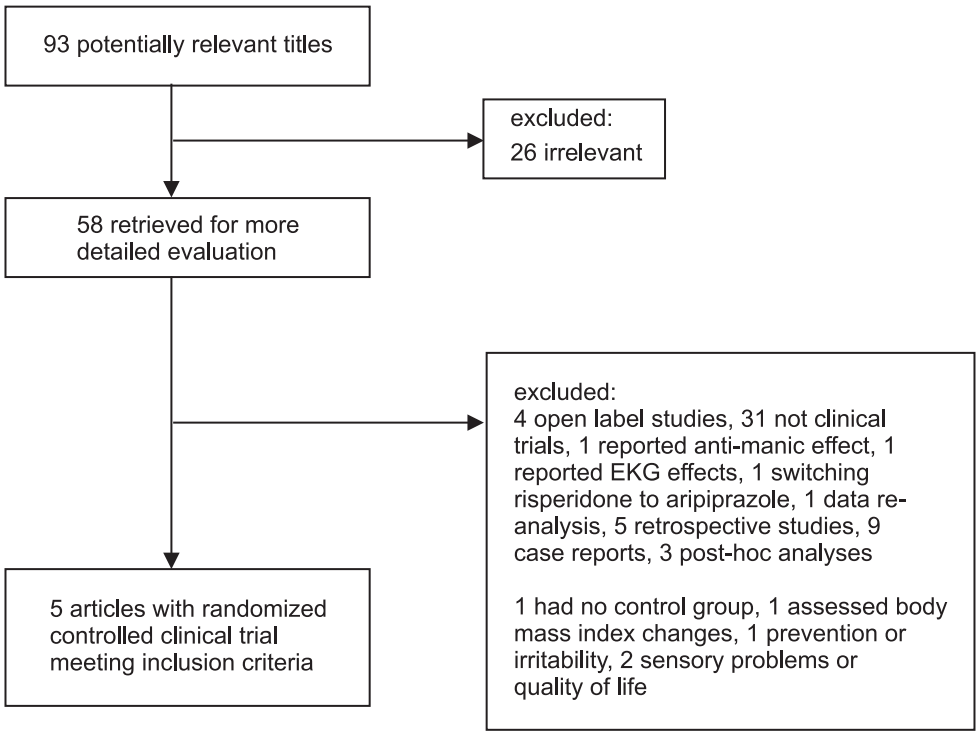

Figure. Flowchart of trial selection process.

the safety and efficacy of aripiprazole with another antipsychotic, risperidone, for treating children with autism[71].

Only one systematic review was found concerning the effect of aripiprazole for treating autism in the Cochrane Library published in 2012[10]. Searching Web of Science retrieved 83 titles, but these did not add to the titles retrieved from the two databases of PubMed/MEDLINE and Google Scholar.

In progress unpublished studies: There was one unpublished study in progress about the effect of aripiprazole for treating autism (NCT02069977) and there were two other studies that had not started recruiting patients yet (NCT00468130, and NCT00208533).

Discussion

In this systematic review, five published studies on the effect of aripiprazole on autism were reviewed. The best evidence from the randomized placebo controlled clinical trials confirmed that aripiprazole more than placebo reduced irritability in autism. The efficacy and safety of aripiprazole were comparable to risperidone for treating children and adolescents with autism[71]. All these studies included children and adolescents. Therefore, it is not clear whether these results can be generalized to adult individuals with autism. This systematic review of double-blind controlled RCTs showed convincing evidence of effectiveness and, therefore, supported the recommendations for the use of aripiprazole for treating irritability associated with autism. Other reviews that included open label or retrospective trials also have shown similar results.

Regarding side effects, aripiprazole in children and adolescents seemed to be safe. Many of the adverse effects reported were of mild nature. Serious adverse effects were rare. Because, the number of RCTs is very limited, larger studies need to be conducted to show if it is totally safe. One of the limitations of this review is potential incompleteness of the reviewed evidence. Publication bias cannot be ignored. The four major databases of PubMed/MEDLINE, Google Scholar, the Cochrane Library, and Web of Science were searched. In addition, we also searched International Clinical Trials Registry Platform to find ongoing trials.

In conclusion, the current evidences support the efficacy and safety of aripiprazole for treating irritability in autism in children and adolescents.

Table. Double blind randomized controlled clinical trials of aripiprazole for children and adolescents with pervasive developmental disorders

Study	Patients condition	Design	Sample size	Intervention	Main outcome measures	Main results	Main adverse effects
Ghanizadeh *et al*[71]	Children with autism spectrum disorders	8 wk randomized double blind controlled clinical trial	59 patients	Aripiprazole versus risperidone	Irritability subscale and adverse effects	The efficacy of aripiprazole (mean dose 5.5 mg/day) and risperidone (mean dose 1.12 mg/day) were not different.	The rates of adverse effects were not significantly different between the two groups.
Ribb *et al*[69]	Data were pooled from two previous studies (69, 71)	8 wk, randomized, double blind, multicenter, parallel-group trials	313 (aripiprazole 212, placebo 101)	Aripiprazole (2-15 mg/day fixed dose and 5-15 mg/day flexibly dose)	Adverse events	Aripiprazole is safe and well tolerated in 6 to 17 years old children with irritability associated with autism	Discontinuations due to adverse events with aripiprazole versus placebo were, overall, 10.4 versus 6.9 per cent. Subjects 6-12 yr: 10.8 versus 5.1 per cent, Subjects 13-17 yr: 8.9 versus 13.6 per cent. Common adverse events with aripiprazole versus placebo included sedation (20.8 vs 4.0%), fatigue (16.5 vs 2.0%), vomiting (13.7 vs 6.9%), increased appetite (12.7 vs 6.9%), somnolence (10.4 vs 4.0%), and tremor (9.9 vs 0.0%). Most adverse events were mild or moderate. Only fatigue showed a dose-response relationship ($P<0.05$). Mean body weight change (last observation carried forward, 1.6 vs 0.4 kg) was higher with aripiprazole than placebo ($P<0.001$). The extrapyramidal symptom-related adverse event: aripiprazole versus placebo was 20.8 vs 9.9 per cent.
Benton[67] Marcus *et al*[70]	These two studies were from the same sample of patients	Double blind, randomized, placebo-controlled, parallel group design	218 children, 6 to 17 yr of age assigned to one of the treatment conditions	Aripiprazole 5, 10, or 15 mg/day placebo	Aberrant Behavior Checklist (ABC)-Irritability subscale	Aripiprazole more than placebo reduced autism symptoms at week 8 for all doses	182 out of 216 patients experienced at least one mild to moderate adverse effect. The most common adverse effects leading to withdraw were: sedation, drooling, and tremor. The most common extrapyramidal symptoms (20%) were tremor, extrapyramidal disorder, and akathisia. Discontinuation rates due to adverse events: 7.7 per centfor placebo and 9.4 per cent for aripiprazole. The two serious adverse events: presyncope (5 mg/day) and aggression (10 mg/day).

Contd...

Study	Patients condition	Design	Sample size	Intervention	Main outcome measures	Main results	Main adverse effects
Marcus *et al*[70]		Randomized placebo-controlled parallel group fixed-dose study	218 children, 6 to 17 yr of age	Aripiprazole (5, 10, or 15 mg/day) or placebo	Aberrant Behavior Checklist	Aripiprazole decreased ABC checklist score more than placebo	As mentioned above
Owen *et al*[68]		8 wk, double-blind, randomized, placebo-controlled, parallel-group disorder	98 children and adolescents (aged 6-17 yr) with autistic disorder	Flexibly dosed aripiprazole (target dosage: 5, 10, or 15 mg/day) or placebo	Aberrant Behavior Checklist	Aripiprazole decreased ABC score more than placebo	Discontinuation rates due to adverse effects: 10.6 per cent for aripiprazole and 5.9 per cent for placebo. Extrapyramidal symptoms: 14.9 per cent for aripiprazole and 8.0 per cent for placebo. Serious adverse effects: 0 Mean weight gain: 2.0 kg on aripiprazole and 0.8 kg on placebo at week 8.

References

1. Greenaway M, Elbe D. Focus on aripiprazole: a review of its use in child and adolescent psychiatry. *J Can Acad Child Adolesc Psychiatry* 2009; *18* : 250-60.
2. Matson JL, Sipes M, Fodstad JC, Fitzgerald ME. Issues in the management of challenging behaviours of adults with autism spectrum disorder. *CNS Drugs* 2011; *25* : 597-606.
3. Ghanizadeh A, Haghighi A. Aripiprazole versus risperidone for treating children and adolescents with tic disorder: a randomized double blind clinical trial. *Child Psychiatry Hum Dev* 2014; *45* : 596-603.
4. Ghanizadeh A. Systemic review of aripiprazole for the treatment of children and adolescents with tic disorders. *Neurosciences (Riyadh)* 2012; *17* : 200-4.
5. Ghanizadeh A. Systematic review of clinical trials of aripiprazole for treating attention deficit hyperactivity disorder. *Neurosciences* (*Riyadh*) 2013; *18* : 323-9.
6. Jordan S, Koprivica V, Chen R, Tottori K, Kikuchi T, Altar CA. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT1A receptor. *Eur J Pharmacol* 2002; *441* : 137-40.
7. Burris KD, Molski TF, Xu C, Ryan E, Tottori K, Kikuchi T, *et al*. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther* 2002; *302* : 381-9.
8. Uzun S, Kozumplik O, Mimica N, Folnegovic-Smalc V. Aripiprazole: an overview of a novel antipsychotic. *Psychiatr Danub* 2005; *17* : 67-75.
9. Ho JG, Caldwell RL, McDougle CJ, Orsagh-Yentis DK, Erickson CA, Posey DJ, *et al*. The effects of aripiprazole on electrocardiography in children with pervasive developmental disorders. *J Child Adolesc Psychopharmacol* 2012; *22* : 277-83.
10. Ching H, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database Syst Rev* 2012; *5* : C D009043.
11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009; *62* : e1-34.
12. Curran MP. Aripiprazole: in the treatment of irritability associated with autistic disorder in pediatric patients. *Paediatr Drugs* 2011; *13* : 197-204.
13. McPheeters ML, Warren Z, Sathe N, Bruzek JL, Krishnaswami S, Jerome RN, *et al*. A systematic review of medical treatments for children with autism spectrum disorders. *Pediatrics* 2011; *127* : e1312-21.
14. Blankenship K, Erickson CA, Stigler KA, Posey DJ, McDougle CJ. Aripiprazole for irritability associated with autistic disorder in children and adolescents aged 6-17 years. *Ped Health* 2010; *4* : 375-81.
15. Farmer CA, Aman MG. Aripiprazole for the treatment of irritability associated with autism. *Expert Opin Pharmacother* 2011; *12* : 635-40.

16. Erickson CA, Stigler KA, Posey DJ, McDougle CJ. Aripiprazole in autism spectrum disorders and fragile X syndrome. *Neurotherapeutics* 2010; *7* : 258-63.

17. McDougle CJ, Stigler KA, Erickson CA, Posey DJ. Atypical antipsychotics in children and adolescents with autistic and other pervasive developmental disorders. *J Clin Psychiatry* 2008; *69* (Suppl 4) : 15-20.

18. Wink LK, Erickson CA, McDougle CJ. Pharmacologic treatment of behavioral symptoms associated with autism and other pervasive developmental disorders. *Curr Treat Options Neurol* 2010; *12* : 529-38.

19. Stachnik J, Gabay M. Emerging role of aripiprazole for treatment of irritability associated with autistic disorder in children and adolescents. *Adolesc Health Med Ther* 2010; *1* : 105-14.

20. Yui K. Useful pharmacologic treatment in impaired social interaction in autism spectrum disorders. *Seishin Shinkeigaku Zasshi* 2012; *114* : 934-40.

21. Nightingale S. Autism spectrum disorders. *Nature Rev Drug Discov* 2012; *11* : 745-6.

22. Maher AR, Theodore G. Summary of the comparative effectiveness review on off-label use of atypical antipsychotics. Journal of managed care pharmacy. *J Manag Care Pharma* 2012; *18* (5 Suppl B) : S1-20.

23. Elbe D, Lalani Z. Review of the pharmacotherapy of irritability of autism. *J Can Acad Child Adolesc Psychiatry* 2012; *21* : 130-46.

24. Cohen D, Raffin M, Canitano R, Bodeau N, Bonnot O, Perisse D, *et al*. Risperidone or aripiprazole in children and adolescents with autism and/or intellectual disability: A Bayesian meta-analysis of efficacy and secondary effects. *Res Autism Spectr Disord* 2013; *7* : 167-75.

25. Williamson ED, Martin A. Psychotropic medications in autism: Practical considerations for parents. *J Autism Dev Disord* 2012; *42* : 1249-55.

26. Mohiuddin S, Ghaziuddin M. Psychopharmacology of autism spectrum disorders: a selective review. *Autism* 2013; *17* : 645-54.

27. Mahajan R, Bernal MP, Panzer R, Whitaker A, Roberts W, Handen B, *et al*. Clinical practice pathways for evaluation and medication choice for attention-deficit/hyperactivity disorder symptoms in autism spectrum disorders. *Pediatrics* 2012; *130* (Suppl 2) : S125-S38.

28. Kirino E. Efficacy and safety of aripiprazole in child and adolescent patients. *Eur Child Adolesc Psychiatry* 2012; *21* : 361-8.

29. Siegel M, Beaulieu AA. Psychotropic medications in children with autism spectrum disorders: a systematic review and synthesis for evidence-based practice. *J Autism Dev Disord* 2012; *42* : 1592-605.

30. Benvenuto A, Battan B, Porfirio MC, Curatolo P. Pharmacotherapy of autism spectrum disorders. *Brain Dev* 2013; *35* : 119-27.

31. Politte LC, McDougle CJ. Atypical antipsychotics in the treatment of children and adolescents with pervasive developmental disorders. *Psychopharmacology* (*Berl*) 2014; *231* : 1023-36.

32. Warren Z, Veenstra-VanderWeele J, Stone W, Bruzek JL, Nahmias AS, Foss-Feig JH, *et al*. Therapies for children with autism spectrum disorders. *Comparative effectiveness review*. No. 26 AHRQ Publication no. 11-EHC029-EF Rockville MD: Agency for Healthcare Research and Quality (US); April 2011.

33. Politte LC, Henry CA, McDougle CJ. Psychopharmacological interventions in autism spectrum disorder. *Harv Rev Psychiatry* 2014; *22* : 76-92.

34. Baribeau DA, Anagnostou E. An update on medication management of behavioral disorders in autism. *Curr Psychiatry Rep* 2014; *16* : 437.

35. Deb S, Farmah BK, Arshad E, Deb T, Roy M, Unwin GL. The effectiveness of aripiprazole in the management of problem behaviour in people with intellectual disabilities, developmental disabilities and/or autistic spectrum disorder--a systematic review. *Res Disabil* 2014; *35* : 711-25.

36. Beherec L, Quilici G, Rosier A, Gerardin P, Campion D, Guillin O. Pharmacological treatments in patients with pervasive developmental disorders: a review. *Encephale* 2014; *40* : 188-96.

37. Stigler KA. Psychopharmacologic management of serious behavioral disturbance in ASD. *Child Adolesc Psychiatr Clin N Am* 2014; *23* : 73-82.

38. Sochocky N, Milin R. Second generation antipsychotics in Asperger's disorder and high functioning autism: a systematic review of the literature and effectiveness of meta-analysis. *Curr Clin Pharmacol* 2013; *8* : 370-9.

39. Marcus RN, Owen R, Manos G, Mankoski R, Kamen L, McQuade RD, *et al*. Aripiprazole in the treatment of irritability in pediatric patients (aged 6-17 years) with autistic disorder: results from a 52-week, open-label study. *J Child Adolesc Psychopharmacol* 2011; *21* : 229-36.

40. Erickson CA, Stigler KA, Wink LK, Mullett JE, Kohn A, Posey DJ, *et al*. A prospective open-label study of aripiprazole in fragile X syndrome. *Psychopharmacology* (*Berl*) 2011; *216* : 85-90.

41. Stigler KA, Diener JT, Kohn AE, Li L, Erickson CA, Posey DJ, *et al*. Aripiprazole in pervasive developmental disorder not otherwise specified and Asperger's disorder: a 14-week, prospective, open-label study. *J Child Adolesc Psychopharmacol* 2009; *19* : 265-74.

42. Landsberg W, Loze J-Y, Lau G, Manos G, McQuade R, Kamen R, *et al*. Safety and tolerability of aripiprazole in the treatment of irritability associated with autistic disorder in pediatric patients: results from a 52-week open-label study. *Eur Psychiatry* 2011; *26* (Suppl 1) Abstr P01-317.

43. Aman MG, Kasper W, Manos G, Mathew S, Marcus R, Owen R, *et al*. Line-item analysis of the Aberrant Behavior Checklist: results from two studies of aripiprazole in the treatment of irritability associated with autistic disorder. *J Child Adolesc Psychopharmacol* 2010; *20* : 415-22.

44. Varni JW, Handen BL, Corey-Lisle PK, Guo Z, Manos G, Ammerman DK, *et al*. Effect of aripiprazole 2 to 15 mg/d on health-related quality of life in the treatment of irritability associated with autistic disorder in children: a post hoc analysis of two controlled trials. *Clin Ther* 2012; *34* : 980-92.

45. Mankoski R, Stockton G, Manos G, Marler S, McQuade R, Forbes RA, *et al*. Aripiprazole treatment of irritability associated with autistic disorder and the relationship between prior antipsychotic exposure, adverse events, and weight change. *J Child Adolesc Psychopharmacol* 2013; *23* : 572-6.

46. Xie Q, Tang J, Xu Y, Zeng HL. Clinical observation of aripiprazole in the treatment of autism. *Zhongguo Dang Dai Er Ke Za Zhi* 2013; *15* : 294-7.

47. Huang SC, Tsai SJ, Yang HJ. Aripiprazole improves social interaction in Taiwanese children with pervasive developmental disorder. *Chang Gung Med J* 2010; *33* : 211-5.

48. Stigler KA, Posey DJ, McDougle CJ. Aripiprazole for maladaptive behavior in pervasive developmental disorders. *J Child Adolesc Psychopharmacol* 2004; *14* : 455-63.

49. Staller JA. Aripiprazole in an adult with Asperger disorder. *Ann Pharmacother* 2003; *37* : 1628-31.

50. Pardini M, Guida S, Gialloreti LE. Aripiprazole treatment for coprophagia in autistic disorder. *J Neuropsychiatry Clin Neurosci* 2010; *22* : 451-s.e33-451.e33.

51. Bozkurt H, Abali O. Aripiprazole-induced enuresis in a child with autistic disorder. *Arch Neuropsychiatry* 2011; *48* : 164-6.

52. Dratcu L, McKay G, Singaravelu V, Krishnamurthy V. Aripiprazole treatment of Asperger's syndrome in the acute psychiatric setting: case report. *Neuropsychiatr Dis Treat* 2007; *3* : 173-6.

53. Le JF, Lohr WD. Aggression and self-injury in a patient with severe autism. *Pediatr Ann* 2012; *41* : 1-3.

54. Jordan I, Robertson D, Catani M, Craig M, Murphy D. Aripiprazole in the treatment of challenging behaviour in adults with autism spectrum disorder. *Psychopharmacology (Berl)* 2012; *223* : 357-60.

55. Celik G, Tahiroglu AY, Firat S, Avci A. Aripiprazole improved obsessive compulsive symptoms in Asperger's disorder. *Clin Psychopharmacol Neurosci* 2011; *9* : 134-6.

56. Ishitobi M, Hiratani M, Kosaka H, Takahashi T, Mizuno T, Asano M, *et al*. Switching to aripiprazole in subjects with Pervasive Developmental Disorders showing tolerability issues with risperidone. *Prog Neuro-Psychopharmacol Biol Psychiatry* 2012; *37* : 128-31.

57. Ishitobi M, Kosaka H, Takahashi T, Yatuga C, Asano M, Tanaka Y, *et al*. Effectiveness and tolerability of switching to aripiprazole from risperidone in subjects with autism spectrum disorders: a prospective open-label study. *Clin Neuropharmacol* 2013; *36* : 151-6.

58. Scahill L, Hallett V, Aman MG, McDougle CJ, Eugene Arnold L, McCracken JT, *et al*. Social Disability in Autism spectrum disorder: results from Research Units on Pediatric Psychopharmacology (RUPP) Autism Network Trials. *J Autism Dev Disord* 2013; *43* : 739-46.

59. Wink LK, Early M, Schaefer T, Pottenger A, Horn P, McDougle CJ, *et al*. Body mass index change in autism spectrum disorders: comparison of treatment with risperidone and aripiprazole. *J Child Adolesc Psychopharmacol* 2014; *24* : 78-82.

60. Findling RL, Mankoski R, Timko K, Lears K, McCartney T, McQuade RD, *et al*. A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *J Clin Psychiatry* 2014; *75* : 22-30.

61. Masi G, Cosenza A, Millepiedi S, Muratori F, Pari C, Salvadori F. Aripiprazole monotherapy in children and young adolescents with pervasive developmental disorders: a retrospective study. *CNS Drugs* 2009; *23* : 511-21.

62. Valicenti-McDermott MR, Demb H. Clinical effects and adverse reactions of off-label use of aripiprazole in children and adolescents with developmental disabilities. *J Child Adolesc Psychopharmacol* 2006; *16* : 549-60.

63. Hellings JA, Boehm D, Yeh HW, Butler MG, Schroede SR. Long-term aripiprazole in youth with developmental disabilities including autism. *J Ment Health Res Intellect Disabil* 2011; *4* : 40-52.

64. Fung LK, Chahal L, Libove RA, Bivas R, Hardan AY. A retrospective review of the effectiveness of aripiprazole in the treatment of sensory abnormalities in autism. *J Child Adolesc Psychopharmacol* 2012; *22* : 245-8.

65. Adler BA, Wink LK, Early M, Shaffer R, Minshawi N, McDougle CJ, *et al*. Drug-refractory aggression, self-injurious behavior, and severe tantrums in autism spectrum disorders: a chart review study. *Autism* 2015; *19* : 102-6.

66. Joshi G, Biederman J, Wozniak J, Doyle R, Hammerness P, Galdo M, *et al*. Response to second generation antipsychotics in youth with comorbid bipolar disorder and autism spectrum disorder. *CNS Neurosci Ther* 2012; *18* : 28-33.

67. Benton TD. Aripiprazole to treat irritability associated with autism: a placebo-controlled, fixed-dose trial. *Curr Psychiatry Rep* 2011; *13* : 77-9.

68. Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, *et al*. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics* 2009; *124* : 1533-40.

69. Robb AS, Andersson C, Bellocchio EE, Manos G, Rojas-Fernandez C, Mathew S, *et al*. Safety and tolerability of aripiprazole in the treatment of irritability associated with autistic disorder in pediatric subjects (6-17 years old):results from a pooled analysis of 2 studies. *Prim Care Companion CNS Disord* 2011; 13.pii:Pcc.10m01008.

70. Marcus RN, Owen R, Kamen L, Manos G, McQuade RD, Carson WH, *et al*. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry* 2009; *48* : 1110-9.

71. Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry Hum Dev* 2014; *45* : 185-92.

Reprint requests: Dr Ahmad Ghanizadeh, Research Center for Psychiatry & Behavioral Sciences, Department of Psychiatry
Shiraz University of Medical Sciences, Hafez Hospital, Shiraz, Iran
e-mail: ghanizad@sina.tums.ac.ir