

# Aripiprazole Treatment in the Adolescent Patients with Inhalants Use Disorders and Conduct Disorder: A Retrospective Case Analysis

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## Abstract

### **Aripiprazole Treatment in the Adolescent Patients with Inhalants Use Disorders and Conduct Disorder: A Retrospective Case Analysis**

Pharmacologically, aripiprazole is a partial agonist at D2 and 5-HT1A receptors and an antagonist at 5-HT2A receptors with the different effect on dopaminergic system from other antipsychotics. Partial agonists are effective for stimulants, opiate, cocaine and nicotine dependence and dopamine D2 receptors have been implicated in the abuse related effects of substances. In addition, it has shown that aripiprazole reduced substance use in schizophrenic, bipolar or schizoaffective disorder patients comorbid with substance use disorders, suggesting that aripiprazole would be useful in patients with substance use disorders and co-existing psychiatric conditions. Open-label evidence is also available for use of aripiprazole in disruptive behavior disorders in children and adolescent. Therefore, aripiprazole might be an effective strategy for adolescent patients with inhalants use disorders and conduct disorder. In the reported cases, aripiprazole treatment successfully controlled on psychiatric symptoms of adolescent patients and also reduced the frequency of substance use in these patients.

**Keywords:** aripiprazole, adolescents, inhalants, conduct disorder

## Özet

### **Uçucu Madde Kullanım Bozukluğu ve Davranım Bozukluğu Olan Ergenlerin Tedavisinde Aripiprazol Kullanımı: Bir Retrospektif Vak'a Analizi**

Aripiprazol dopaminerjik sistem üzerine diğer antipsikotik ilaçlardan farklı bir etkiye sahip olup; dopamin D2 ve serotonin 5HT2A reseptörlerine kısmi agonist, serotonin 5HT1A reseptörüne antagonist etki eden yeni nesil bir antipsikotikler ajandır. D2 ve 5HT2A reseptörlerinin bağımlılık etiolojisinde rol oynadığı bilinmektedir. Stimülanlar, opiat, kokain ve nikotin kötüye kullanımı ve bağımlılığı tedavisinde D2 parsiyel agonistlerin kullanılmasının etkili olduğu bildirilmektedir. Ek olarak kokain kullanımı olan bipolar bozukluk ve şizofreni hastalarında aripiprazol tedavisi sonrası madde kullanımının sıklığını azalttığı tespit edilmiştir. Bu nedenle aripiprazol tedavisinin madde kullanım bozukluğuna eşlik eden psikiyatrik bozuklukların tedavisinde kullanılabileceği düşünülmektedir. Aripiprazol D2 ve serotonin 5HT2A reseptörlerine etkisi nedeniyle çocuk ve ergenlerde yıkıcı davranış bozukluklarının tedavisinde ümit verici bir seçenek olabileceği bildirilmektedir. Bu yazıda uçucu madde kullanım bozukluğu ve davranım bozukluğu tanısı alan ve tedavide aripiprazol kullanan hastaların incelenmesi ve tartışılması amaçlanmıştır. Bu bildirimde uçucu madde kullanım bozukluğu olan ve tedavide aripiprazol kullanan vak'alar incelenmiştir. Tanımlanan 7 vak'ada aripiprazol tedavisi sonrası psikiyatrik belirtiler üzerinde kontrol sağlanmasının yanında madde kullanımının sıklığının azaldığı tespit edilmiştir.

**Anahtar Kelimeler:** aripiprazol, ergenler, uçucu maddeler, davranım bozukluğu

## INTRODUCTION

DSM-IV-TR (APA 2000) provides two broad categories of substance-related disorders. The first category is substance use disorders (substance abuse and substance dependence) which are characterized by maladaptive patterns of substance use. In addition to posing serious medical risks to the user, substance abuse and dependence has also been associated with a number of psychosocial problems and additional risk behaviors. (Howard and Jenson 1999, Mcgarvey et al. 1996). Most of these substance users have comorbid conduct disorder, attention-deficit/hyperactivity disorder (ADHD), major depressive disorder, dysthymic disorder, alcohol dependence and psychosis (Evren et al. 2006; Grant et al. 2004; Mackesy-Amity and Fendrich, 1999; Hernandez-Avila et al. 1998). Accurate assessment of comorbid mental disorders is essential in the development of effective interventions for adolescents with substance disorders (Shane et al. 2003).

Inhalant drugs are widely available and frequently misused, especially by adolescents (Hansen and Rose 1995). Inhalants are appealing to adolescents for a variety of reasons. They are relatively inexpensive; legal; and readily available in homes, offices, supermarkets, hardware stores, and drug stores (Kurtzman et al. 2001, Wu and Howard 2007). Inhalant drugs are most widely misused substances in Turkey (Kaya and Özcan 1999, Yazman 1995). The most commonly abused inhalants among Turkey adolescents are toluene, glue, shoe polish, lighter fluid, and gasoline (Ögel et al. 2001). Recurrent inhalant use is associated with serious health problems including cerebellar ataxia, Parkinsonism, encephalopathy, trigeminal neuropathy, hepatorenal syndrome, hepatotoxicity, and "sudden sniffing death" (Meadows and Verghese 1996, Maruf et al. 1998). Numerous studies indicate that inhalant abuse can be a predictor of polysubstance abuse, particularly the use of intravenous drugs (Boruette and Anton, 2001).

Aripiprazole is a D2 partial agonist, resulting in a high occupancy of D2 but also 5-HT2 receptors in humans (Burris et al. 2002). Open-label evidence is also available for use of aripiprazole in bipolar disorders, psychotic disorders and disruptive behavior disorders including conduct disorder and ADHD (Findling et al. 2009). Because the stimulation of the mesolimbic dopamine system plays a major part in substances' addictive effect, the dopamine receptor blocking effects of antipsychotic drugs have made them of interest as potential pharmacotherapy for abuse and dependence treatment (Wee et al. 2007, Childress and

O'Brien 2000). Open label study of aripiprazole in schizophrenic and bipolar outpatients with comorbid cocaine dependence and alcohol-dependent patients indicates that aripiprazole can reduce alcohol and cocaine use as well as cocaine and alcohol craving in this group of patients (Beresford et al. 2005, Brown et al. 2005). We hypothesized that aripiprazole as a partial agonist might be a treatment choice of inhalant use disorder as well. We herewith report a group of patients with inhalant abuse and conduct disorder who were successfully treated with aripiprazole for more than 6 months. To our knowledge, this is the first case series using aripiprazole in the treatment of inhalant abuse to be reported in the literature.

## METHOD

This study was conducted at the Department of Child and Adolescent Psychiatry, Faculty of Medicine, Karaelmas University in Zonguldak, Turkey. The files of adolescents with substance use disorders and conduct disorder who had been admitted to Child and Adolescent Psychiatry outpatient and inpatient unit between September 2007 and September 2009 were screened retrospectively. All the patients' prescription charts and medical records were reviewed in order to identify those who were diagnosed as substance use disorder and conduct disorder and treated with aripiprazole. The files of the patients are scanned and sociodemographical data, psychiatric diseases, alcohol and frequency of inhalants use were noted. Aripiprazole dosage, treatment duration and side effects was also recorded.

The criteria for inclusion were patients under 18 years of age receiving aripiprazole for conduct disorder comorbid with inhalants use disorders. In order to enroll in the study, all patients were required to have a minimum of six months of follow-up. The criteria for exclusion were lacking follow-up information, prescriptions for more than one antipsychotic on the same date, using more than one substance. Subjects dependent on any additional drug and alcohol were excluded.

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria used for substance use disorders and for the other psychiatric diagnoses. In routine clinical assessments The Turgay DSM-IV Disruptive Behaviour Disorders Scale was used for the disruptive behavior disorder diagnoses and symptomatology. A Clinical Global Impression-Improvement Score (CGI) was extracted from the report of the 1., 3., 6. months treatment visit, compared to the initial eva-

uation. Data collected from medical, laboratory and pharmacy records was noted and entered into a SSPS database. Relations between two or more variables were described by (chi)2 test, t-test.

### FINDINGS

Fourteen adolescents were reached at the end of file scanning. Two patients excluded from the study for lacking follow-up information and one patient excluded for using more than one antipsychotic on the same date. Two of them were not taken into this study since they had been using more than one substance. Another two subjects who did not come to follow up visits were also excluded. Eligible cases consist of 7 male patients between 12-17 years old (mean age of 15.53±11.27 years). Males comprised 100% of the sample. Three patients (42.8%) dropped out primary school and others were educated through the high school level (47.2%), two of these patients having one year loss in the high school. Demographic and clinical characteristics of the sample are presented in Table 1.

All eligible patients (7 men) in the present study fulfilled current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; criteria for inhalants abuse disorder and conduct disorder. The type of the substance used was toulén in all 7 patients, none of the patients fulfilled DSM IV criteria for inhalants dependence disorder. Among four patients occasionally having alcohol, 2 had experienced psychotic symptoms associated with inhalants use, but those symptoms were transient, and none of our patient fulfilled DSM IV criteria for schizophrenia. Three of the 7 patients (42.8%) needed hospitalizasyon during the treatment period.

For these 7 patients, the mean dose of aripiprazole was 10.8±5.6 mg (5–20). During the treatment in these 7 patients, 2 subjects had mild agitation (one at a dosage of 5 and the other at a dosage of 15 mg per day), and one had akathisia (15 mg per day), whereas 2 others had daytime sleepiness (one at a daily dosage of 5 and the other one with 10 mg). None of these side effects required a cessation of the treatment, but dose es-

calation had been postponed in these patients. Two of the patients (28.59%) on aripiprazole were taking methylfenidat for treatment of ADHD, and three of the patients (42.8%) were taking selektif serotonin reuptake inhibitor (SSRI) for depressif disorders.

After approximately six months of follow-up, all patients improved significantly more as manifested by their endpoint CGI. Fig. 2 demonstrated the mean CGI scores in cases. The mean CGI scores improved from 4.03±0.91 (1. month) to 3.61±1.13 (2. months) and 3.14±1.05 (6. months). The change of CGI-S scores between treatment months was statistically significant (p<0,05; p<0,01 respectively). Four of 7 patients (57.1%) were abstinent from inhalants in the treatment period of 3 month. After 6 months of treatment, there was a trend for a decrease in the number of use days per month in other 3 patients (3.4±2. vs 1.7±1.4; p=0.01 (significant)).

### DISCUSSION

The main findings of this cases study were that aripiprazole improved the patient's conduct disorder symptoms severity and reduced the amount of inhalant use (reducing use per day and increasing days abstinent) and during treatment and observation period. Aripiprazole appeared to be safe and well tolerated in the current study population. The side effects that were reported here were similar to those reported in a clinical trial of aripiprazole (Anton et al. 2008). Similar to our findings an open-label study of aripiprazole treatment in children and adolescents with conduct disorder reported improvements in CGI scores of patients (Findling et al. 2009).

For most antipsychotics, the therapeutic window occurs between 60 and 80% of striatal occupancy. Higher levels of receptor occupancy by these drugs lead to extra-pyramidal side-effects, while aripiprazole has a safer profile even though it occupies more than 90% of receptors (Burriss et al. 2002). This partial agonistic effect of aripiprazole led to the hypothesis that this compound may act as a dopamine stabilizer. Thus, this modulatory action of aripiprazole may explain why in

**Table 1: Demographic and clinical characteristics of the sample**

	Mean±SD
Mean age	15.53±11.27
Age of onset of substance use	11.16±9.66
Duration of substance use	2.1±1.18
Number of Hospitalization	1.11±0.88

**Table 3. The mean Clinical Global Impression-Improvement Scores**

	First month	Third month	Sixth month
Ölçek	Mean±SD	Mean±SD	Mean±SD
CGI	4.03±0.91	3.61±1.13*	3.14±1.05**

\*p<0,05; \*\*p<0,01  
Clinical Global Impression-Improvement (CGI)

the present study aripiprazole reduced the inhalant use of patients. Also as dopamine abnormalities, particularly in the frontal lobe, might underlie impulsive responses, a feature of conduct disorder, and also addiction, the potential ability of aripiprazole to stabilize dopamine, particularly in the frontal cortex, might underlie its effectiveness in those patients with less self-control (Findling 2008, Greenaway and Elbe 2009).

There has been increasing interest in the use of medications that affect the dopamine receptor in the treatment of addiction. Antipsychotics have been candidates for the treatment of addiction for their ability to block dopamine receptors and counterbalance the increase in dopaminergic activity related with drugs' effects (Smelson et al.1997). In animals, at lower doses, aripiprazole increases dopamine release in precortical areas, but at slightly higher doses, reduces dopamine release in the nucleus accumbens (Li et al. 2004). This is a unique pharmacological profile for an antipsychotic agent. Particularly, their action on serotonergic system has been regarded with interest, given the involvement of serotonin neurotransmission in addictive behaviour (Burriss et al. 2002). This unique combination lends itself for potential use in addiction. Given the effects of addictive substances, including alcohol, on ventral striatum?nucleus accumbens dopamine release and frontal cortical dopamine effects, a drug like aripiprazole could hold great promise as a potential agent to reverse or block these effects (Anton et al. 2008). In fact, there have been a few small open label studies which suggest that aripiprazole was efficacious in reducing cocaine (Beresford et al. 2005) use, attenuating the effects of amphetamine challenge (Lile et al. 2005) and reducing alcohol use (Warsi et al. 2005) in humans.

Furthermore inhalants use can lead to symptoms mimicking psychosis with hallucinations, paranoia etc and the use of anti psychotics relieve these symptoms

(Kurtzman et al. 2001). Some of the antipsychotic more commonly studied for this purpose are for example haloperidol, olanzapine, quetiapine, clozapine and risperidone (Hart 2005). Aripiprazole also might be effective in special populations of substance use disorder patients. For example, in schizophrenic patients, aripiprazole decreased the number of cocaine-positive urines, and in another study in patients with bipolar or schizoaffective disorder, aripiprazole reduced cocaine craving, suggesting that aripiprazole would be useful in cocaine-dependent individuals with co-existing psychiatric conditions (Beresford et al. 2005; Brown et al. 2005). Thus, the efficacy of aripiprazole to manage inhalants abuse and dependence remains to be determined.

One limit of this study is the absence of urinary sampling, estimation of inhalant use being made only on declarative data. However, in these patients with heavy medical, psychiatric, and social consequences of inhalant abuse, clinicians noticed an improvement in functioning.

### CONCLUSION

In conclusion, we report the case series of aripiprazole in treatment of inhalant abuse disorders comorbid with conduct disorder. In the present cases, the patient's conduct disorder symptoms severity and frequency of inhalant use were significantly reduced with aripiprazole treatment. Taken together, our data suggest that aripiprazole may find utility in the treatment of inhalant use disorders in adolescent who has comorbid conduct disorder. This study should enhance research on the partial agonist hypothesis to treat inhalants abuse and dependence. Further controlled studies are required to confirm its efficacy in patients of this type.

## REFERENCES

- American Psychiatric Association, (1994) Diagnostic and Statistical Manual of Psychiatric Disorders. Washington, DC.
- Anderson CE, Loomis GA (2003) Recognition and Prevention of Inhalant Abuse. *Am Fam Physician*; 68: 869-874.
- Anton RF, Kranzler H, Breder C, Marcus RN, Carson WH, Han J (2008) A randomized, multicenter, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole for the treatment of alcohol dependence. *J Clin Psychopharmacol*; 28:5-12.
- Beresford TP, Clapp L, Martin B, Wiberg JL, Alfors J, Beresford HF (2005) Aripiprazole in schizophrenia with cocaine dependence: A pilot study. *J Clin Psychopharmacol*; 25: 363-366.
- Boruette T, Anton R. Clinical Review of inhalants (2001) *Am J Addict*; 10: 79-94.
- Brown ES, Jeffress J, Liggin JD, Garza M, Beard L (2005) Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. *J Clin Psychiatry*; 66: 756-760.
- Burris KD, Molski TF, Xu C, Ryan E, Tottori K, Kikuchi T, Yocca FD, Molinoff PB (2002) Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther*; 302: 381-389.
- Childress AR, O'Brien CP (2000) Dopamine receptor partial agonists could address the duality of cocaine craving. *Trends Pharmacol Sci*; 21: 6-9.
- Ercan ES, Amado S, Somer O, Cikoglu S (2001) Dikkat eksikliği hiperaktivite bozukluğu ve yıkıcı davranım bozuklukları için bir test bataryası geliştirme çabası. *Çocuk ve Gençlik Ruh Sağlığı Dergisi*; 8: 132-144.
- Evren C, Barut T, Saatcioglu O, Cakmak D (2006) Axis I psychiatric comorbidity among adult inhalant dependents seeking treatment. *J Psychoact Drugs*; 38: 57-64.
- Findling RL (2008) Atypical antipsychotic treatment of disruptive behavior disorders in children and adolescents. *J Clin Psychiatry*; 69 Suppl 4: 9-14.
- Findling RL, Kauffman R, Sallee FR, Salazar DE, Sahasrabudhe V, Kollia G, Kornhauser DM, Vachharajani NN, Assuncao-Talbot S, Mallikaarjun S, Iwamoto T, McQuade RD, Boulton DW, Blumer J (2009) An open-label study of aripiprazole: pharmacokinetics, tolerability, and effectiveness in children and adolescents with conduct disorder. *J Child Adolesc Psychopharmacol*; 19: 431-439.
- Grant BF, Stinson, FS, Dawson DA, Chou SP, Dufour MC, Compton W (2004) Prevalence of co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*; 61: 807-816.
- Greenaway M, Elbe D (2009) Focus on Aripiprazole: A Review of its use in Child and Adolescent Psychiatry. *J Can Acad Child Adolesc Psychiatry*; 18: 250-60.
- Hart CL (2005) Increasing treatment options for cannabis dependence: A review of potential pharmacotherapies. *Drug Alcohol Depend*; 80: 147-159.
- Hansen WB, Rose LA (1995) Recreational use of inhalant rugs by adolescents: a challenge for family physicians. *Fam Med*; 27: 383-387.
- Hernandez-Avila CA, Ortega-Soto HA, Jasso A, Hasfura-Buenaga CA, Kranzler HR (1998) Treatment of inhalant-induced psychotic disorder with carbamazepine versus haloperidol. *Psychiatr Serv*; 49: 812-815.
- Howard MO, Jenson JM (1999) Inhalant use among antisocial youth: prevalence and correlates. *Addict Behav*; 24: 59-74.
- Kaya B, Özcan ME (1999) Uçucu Bağımlılığı ve Kötüye Kullanımı: Epidemiyoloji, Risk Grupları ve Önleme Programlarının Gerçekliliği. *Klinik psikiyatri*; 2: 189-196.
- Kurtzman TL, Kimberlyn BA, Otsuka MD, Wahl RA (2001) Inhalant abuse by adolescents. *Journal Adolesc Health*; 28: 170-180.
- Li Z, Ichikawa J, Dai J, Meltzer HY (2004) Aripiprazole, a novel antipsychotic drug, preferentially increases dopamine release in the prefrontal cortex and hippocampus in rat brain. *Eur J Pharmacol*; 493: 75-83.
- Lile JA, Stoops WW, Vansickel AR, Glaser PE, Hays LR, Rush CR (2005) Aripiprazole attenuates the discriminative-stimulus effects of d-amphetamine in humans. *Neuropsychopharmacol*; 30: 2103-2114.
- Mackesy-Amity ME, Fendrich M (1999) Inhalant use and delinquent behavior among adolescents: a comparison of inhalant users and other drug users. *Addiction*; 94: 555-564.
- Maruff P, Burns CB, Tyler P, Currie BJ, Currie J (1998) Neurological and cognitive abnormalities associated with chronic petrol sniffing. *Brain*; 121: 1903-1917.
- Mcgarvey EL, Canterbury RJ, Waite D (1996) Delinquency and family problems in incarcerated adolescents with and without a history of inhalant use. *Addict Behav*; 21: 537-542.
- Meadows R, Verghese A (1996) Medical complications of glue sniffing. *South Med J*; 89: 455-462.
- Ogel K, Tamar D, Evren E, Cakmak D (2000) Uçucu madde kullanımının yaygınlığı: Çok merkezli bir araştırmanın verilerinin değerlendirilmesi. *Anadolu Psikiyatri Dergisi*; 1: 220-224.
- Ogel K, Tamar D, Evren E, Cakmak D (2001) Lise gençleri arasında sigara, alkol ve madde kullanım yaygınlığı. *Türk Psikiyatri Derg*; 12: 47-52.
- Shane P, Jasiukaitis P & Green RS (2003). Treatment outcomes among adolescents with substance abuse problems: The relationship between comorbidities and post-treatment substance involvement. *Eval Program Plann*; 26: 393-402.
- Smelson D, Roy A, Roy M (1997) Risperidone diminishes cue-elicited craving in withdrawn cocaine dependent patients. *Can J Psychiatry*; 42: 984.
- Warsi M, Sattar SP, Bhatia SC, Petty F (2005) Aripiprazole reduces alcohol use. *Can J Psychiatry*; 50: 244.
- Wee S, Wang Z, Woolverton Z, Pulvirenti L, Koob GF (2007) Effect of aripiprazole, a partial dopamine D2 receptor agonist, on increased rate of methamphetamine self-administration in rats with prolonged session duration. *Neuropsychopharmacol*; 32: 2238-2247.
- Wu L, Howard MO (2007) Psychiatric disorders in inhalant users: results from The National Epidemiologic Survey on Alcohol and Related Conditions. *Drug Alcohol Dep*; 88: 146-155.
- Yaşan A, Gürgen F (2004) Güneydoğu Anadolu bölgesinde ergenlerde uçucu madde kullanım özellikleri. *Bağımlılık Dergisi*; 5: 77-83.