

# Effectiveness and Tolerability of Aripiprazole in a Real-World Outpatient Population of Youth

Tezan Bildik<sup>1</sup>, Nazli Burcu Ozbaran<sup>1</sup>, Sezen Kose<sup>1</sup>, Saniye Korkmaz Cetin<sup>1</sup>

## ÖZET:

Günlük uygulamada ayaktan tedavi gören bir ergen hasta popülasyonunda aripiprazolün etkinlik ve tolerabilitesi

**Amaç:** Ayaktan tedavi edilen ergen hastalarda aripiprazolün endikasyon dışı kullanım özelliklerini belirlemek ve geniş bir yelpazede ruhsal belirti ve bozukluk gösteren ergenlerin tedavisinde aripiprazolün etkinliğini ve tolerabilitesini saptamaktır.

**Yöntem:** Hasta dosyaları geriye dönük kayıt taraması yöntemiyle değerlendirilmiştir. Klinik Global izlenim (KGI) ölçekleri, Kısa Semptom Envanteri (KSE) ve Extrapiramidal Belirtileri Değerlendirme Ölçeği kullanılmıştır.

**Bulgular:** Otuz bir hastanın verisine ulaşıldı. Örneklem çözümlü kız hastadan oluşmaktadır (%87.1). Ortalama yaş  $16.38 \pm 1.14$  dir ve 15-19 yaş arasındadır. Hastaların %67,8'inin en az bir komorbid bozukluğu vardır. En sık komorbid bozukluk, major depresif bozukluktur. Aripiprazolün ortalama başlangıç dozu  $4.83 \pm 3.59$  mg'dır (ranj: 2,5-20 mg/ gün) ve son vizitteki ortalama doz  $8.62 \pm 3.46$  mg'dır. (ranj: 2,5-15 mg/ gün). Ortalama aripiprazol tedavi süresi  $19.56 \pm 1.23$  aydır (ranj: 4-48 ay). Son vizit KGI şiddet puanları, başlangıç puanlarına göre anlamlı derecede daha düşüktür ( $p < 0.001$ ). Benzer şekilde, KSE depresyon ( $z = -3.232$ ;  $p = 0.001$ ), KSE anksiyete ( $z = -3.004$ ;  $p = 0.003$ ), KSE hostilité ( $z = -3.207$ ;  $p = 0.001$ ), KSE psikotizm ( $z = -1.973$ ;  $p = 0.049$ ), and KSE paranoid düşünceler ( $z = 2.733$ ;  $p = 0.006$ ) alt ölçek puanları istatistiksel açıdan anlamlı farklılık göstermiştir. KSE Global Rahatsızlık Ölçek puanları arasında da, istatistiksel açıdan anlamlı farklılık bulunmuştur (Rahatsızlık ciddiyeti indeksi:  $z = -2.987$ ;  $p = 0.003$ , Semptom rahatsızlık indeksi:  $z = -3.435$ ;  $p = 0.001$  ve Belirti toplamı:  $z = -3.023$ ;  $p = 0.003$ ). Altı hasta ilaç tedavisini kesmiştir. En sık istenmeyen etkiler yorgunluk (%50.0), uyuşukluk hali (%42.9) ve sersemliktir (%39.30). En şiddetli ekstrapiramidal belirtiler yavaşlık ve zafiyet olduğu izlenimi, günlük işleri yapmada güçlük (%11.5) ve bacakta, sırtta veya boyunda kramp ya da ağrı (%11.5)'dir. Olguların hiçbirinde bedende veya uzuvlarda anormal istem dışı hareketler saptanmamıştır.

**Sonuç:** Aripiprazol, hastalar tarafından klinik pratiğimizde oldukça iyi tolere edilmiştir ve ayaktan tedavi edilen ergenlerde güvenli ve etkili bir seçenek olarak görünmektedir. Ancak, ileriye dönük randomize kontrollü çalışmaların yapılması gereklidir.

**Anahtar sözcükler:** Aripiprazol, etkinlik, tolerabilite, istenmeyen etkiler

Klinik Psikofarmakoloji Bülteni 2012;22(3):225-34

## ABSTRACT:

Effectiveness and tolerability of aripiprazole in a real-world outpatient population of youth

**Objectives:** To identify the pattern of initiation for off-label use of aripiprazole among adolescent outpatients; determine whether or not aripiprazole is effective and tolerable for the treatment of adolescents with a wide range of psychiatric symptoms and disorders or not.

**Methods:** Medical charts were retrospectively reviewed for the effectiveness and tolerability of aripiprazole. The Clinical Global Impression Scale (CGI), the Brief Symptom Inventory (BSI), and the Extrapiramidal Symptom Rating Scale were used.

**Results:** The data were available on 31 patients. The sample consisted of mostly females (87.1%). The mean age was  $16.38 \pm 1.14$  years, and the ages range was 15-19 years. Twenty-one patients (67.8%) had at least one comorbid disorder. The most common comorbid disorder was major depressive disorder. The mean initial dosage of aripiprazole was  $4.83 \pm 3.59$  mg (2.50 mg - 20.00 mg), and the mean endpoint dosage was  $8.62 \pm 3.46$  mg (2.50 mg - 15.00 mg). The mean duration of aripiprazole medication was  $19.56 \pm 1.23$  months (range: 4-48 months). Endpoint CGI-S scores were significantly lower compared with baseline CGI-S score ( $p < 0.001$ ). Similarly, the difference between depression severity ( $z = -3.232$ ;  $p = 0.001$ ), anxiety severity ( $z = -3.004$ ;  $p = 0.003$ ), hostility severity ( $z = -3.207$ ;  $p = 0.001$ ), psychoticism severity ( $z = -1.973$ ;  $p = 0.049$ ), and paranoid ideation severity ( $z = 2.733$ ;  $p = 0.006$ ) scores were statistically significant. The difference between the baseline and endpoint BSI Global Indices of distress scores were found to be statistically significant (The Global Severity Index:  $z = -2.987$ ;  $p = 0.003$ , the Positive Symptom Distress Index:  $z = -3.435$ ;  $p = 0.001$ , and the Positive Symptom Total:  $z = -3.023$ ;  $p = 0.003$ ). Six cases (20.0%) discontinued the treatment. The most frequent adverse effects were asthenia (50.0%), somnolence (42.9%), and dizziness (39.30%). The most severe extrapyramidal symptoms were: impression of slowness or weakness, difficulty in carrying out routine tasks (11.5%), and tonic muscular contractions localized to one or several muscle groups, particularly in the throat, neck or back (11.5%). None of the cases had abnormal involuntary movements (dyskinesia) of the extremities or trunk.

**Conclusion:** Aripiprazole was well tolerated and effective in our clinical practice and appears to be a safe and efficacious alternative in adolescents. However, a prospective clinical trial with a randomized controlled design is warranted.

**Key words:** Aripiprazole, effectiveness, tolerability, adverse effects

Bulletin of Clinical Psychopharmacology 2012;22(3):225-34

<sup>1</sup>M.D., Department of Child & Adolescent Psychiatry, Ege University, School of Medicine, Izmir - Turkey

Yazışma Adresi / Address reprint requests to: Dr. Tezan Bildik, Department of Child & Adolescent Psychiatry, Ege University School of Medicine, Izmir - Turkey

Telefon / Phone: ++90-232-390-1396

Elektronik posta adresi / E-mail address: tezanbildik@yahoo.com

Gönderme tarihi / Date of submission: 2 Ocak 2012 / January 2, 2012

Kabul tarihi / Date of acceptance: 3 Temmuz 2012 / July 3, 2012

## Bağınıt beyanı:

T.B., N.B.O., S.K., S.K.C.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

## Declaration of interest:

T.B., N.B.O., S.K., S.K.C.: The authors reported no conflict of interest related to this article.

## INTRODUCTION

Pharmacoepidemiological studies in developed countries report an increase in antipsychotics prescriptions, mainly because of a dramatic rise in atypical antipsychotic (ATA) prescriptions (1-3). Verdoux underlined that antipsychotics are often prescribed for non-psychotic disorders in adults as well as in children and adolescents (4). Despite the lack of formal indications, ATAs are prescribed off-label for the treatment of a variety of mental disorders that are associated with aggressive and disruptive behaviors, such as mental retardation, severe attention-deficit/hyperactivity disorder, disruptive behavior disorders, tic disorders, Tourette's disorder and obsessive-compulsive disorder (1,5,6). There is, however, a lack of empirical evidence to support an ever widening pattern of prescribing in the pediatric age group (7). Neither evidence-based treatment guidelines nor consensus guidelines on monitoring of antipsychotics exist for this age group.

Initiation or switching antipsychotics is common in daily clinical practice and there is very little empirical research on why clinicians select a particular agent in an individual case and not another available alternative (8,9). Limited research findings show that medical decisions about drug selection are multidimensional and influenced by several factors, such as previous exposure to treatment issues, formulary restrictions, prior authorization policies, commercial promotion, patients' compliance with medication, and the perceived efficacy and tolerability of different psychoactive medications by clinicians. The initial choice of psychoactive medication is especially important for the pediatric population because of limited knowledge about safety and long-term effects on the developing brain and body (10).

There is a growing interest in the use of aripiprazole in children and adolescents (11,12). Aripiprazole is a second-generation (atypical) antipsychotic. Second-generation antipsychotics have a lower propensity to cause tardive syndromes and extrapyramidal side effects (13). Aripiprazole acts as a partial agonist at the dopamine (D2) receptor. In areas of dopaminergic hyperactivity, it acts as an antagonist and in areas of dopaminergic hypoactivity, acts as an agonist (14). Clinical trials involving children and adolescents have demonstrated the efficacy of aripiprazole in bipolar disorders, schizophrenia, mood disorders associated with pervasive developmental

disorders, and in tics and Tourette Syndrome (15). Aripiprazole is widely used in conduct disorder (16) and in aggression (17), and is well tolerated. A prospective multicenter study in China reported the effectiveness and safety of aripiprazole use in tic disorders (18). Aripiprazole has been evaluated in several open-label studies and two large placebo-controlled trials in children with autistic disorder. In these studies, aripiprazole has been found to be effective in the treatment of children and adolescents with irritability associated with autism (13).

The most frequent side effects are extrapyramidal symptoms and sleepiness, and are dose-dependent (15). Findling et al. reported significant improvements in manic symptoms in their open-label study with bipolar children and most common side effects were stomach ache, increased appetite, and headache (19). Zuddas et al summarized in their review that adverse effects of aripiprazole were usually relatively minor, easily predictable and manageable, whereas long-term open-label studies have indicated that some adverse events, such as the metabolic effects, may be severe and potentially life threatening in the long-term (20). Studies with aripiprazole in autistic children suggest high effectivity rates for the reduction of irritability symptoms up to one year (21). Aripiprazole is also used as augmentation therapy in obsessive compulsive disorder and reported as effective and well tolerated (22). The results of clinical trials provide preliminary evidence that aripiprazole appears to be a useful addition to the treatment options available for patients with bipolar disorders, schizophrenia, mood disorders associated with pervasive developmental disorders, tics and Tourette's (15). The current available evidence base for the use of aripiprazole in adolescents is relatively small and it is rapidly expanding, but these studies have focused only on patients with a particular Axis I disorder or spectrum of disorders (12). In addition, it is claimed that there is an unanswered question regarding whether symptom-focused or syndromal-based treatment approaches are more appropriate in pediatric population (23).

The main aims of this study were to (1) identify the pattern of initiation and switching for off-label use of aripiprazole among adolescent outpatients and (2) determine, whether aripiprazole is effective and tolerable for the treatment of adolescents with a wide range of psychiatric symptoms and disorders in a sample of psychiatric outpatients or not. Risperidone is the preferred

atypical antipsychotic medication on our adolescent unit; therefore, we expected that initiation of treatment with aripiprazole would be relatively rare. We hypothesized that patients who were switched to aripiprazole would show evidence of “treatment resistance,” as defined by multiple previous pharmacological treatments that had been ineffective, including augmentation or combination strategy. This definition of treatment resistance was used in several previous studies (10,24,25).

## METHODS

This study was a naturalistic, retrospective evaluation of 37 outpatients whose first prescription for aripiprazole occurred at the adolescent outpatient clinic of the Department of Child Psychiatry, School of Medicine, Ege University, Izmir, Turkey. The medical charts were retrospectively reviewed to determine the effectiveness and tolerability of aripiprazole. These chart reviews included all patients, who underwent a structured psychiatric evaluation in this adolescent unit between January, 2009 and October 2010, were started on aripiprazole, and returned for at least one follow-up visit. Axis I and Axis II diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition (DSM-IV-TR) criteria.

### Measures

**The Clinical Global Impression Scale (CGI):** The CGI consists of three modules, severity of illness (CGI-S), global improvement (CGI-I), and the efficacy index. The CGI-Severity subscale is a 7-point Likert scale ranging from profoundly ill to no clinical symptoms. The CGI-Improvement subscale is a 7-point Likert scale ranging from very much worse to no change to very much improved (26).

**The Brief Symptom Inventory (BSI):** The BSI is a self-reported screening instrument used in clinical and research settings to assess psychopathology and psychological distress (27). It is a 53-item shortened version of the SCL-90-R and evaluates psychological symptoms experienced during the previous week. The nine subscales of the BSI are: obsessive-compulsive symptoms, paranoid ideation, hostility, phobic anxiety, psychoticism, somatization, interpersonal sensitivity,

depression, and anxiety. In addition to these, BSI scores are summarized in three global indices of distress: the Global Severity Index (GSI), the Positive Symptom Distress Index (PSDI), and the Positive Symptom Total (PST). All scales range from 0 = not at all to 4 = extremely. The psychometric properties of the BSI with Turkish adolescents and youth have been extensively studied (28).

**The Extrapyrimal Symptom Rating Scale (ESRS):** It was designed to measure extrapyramidal side effects from antipsychotic medication. The ESRS is a 12-item scale that detects the presence of drug induced parkinsonism-like symptoms, akathisia, dyskinesia, and dystonia (29).

In clinical practice, the patients, who were started on medication, were scheduled for a return visit one month later, and were subsequently seen for follow-up in every one to two months. Follow-up visits included both patient and parents to review progress, adverse events, mental status, and the medication regimen. Adverse effects were elicited by a combination of open-ended and closed-ended questioning. Treatment-emergent movement disorders were assessed using the ESRS.

Patients treated with aripiprazole were routinely started with a daily dose of 2.5 mg titrated to 5 mg/day after 2 days and the dosage was increased gradually to 10 mg/day. Doses were further titrated depending on tolerability and clinical response. The decision to start with aripiprazole was made after consideration of informed consent of the parent and the patient, formulary restrictions, and previous exposure to treatment issues. Information extracted from the medical charts included demographic data, diagnoses, previous medication trials, treatment response, adverse events, and follow-up. The CGI-S and the BSI scores were extracted from the report of the last treatment visit, compared to the initial evaluation CGI-I score was assigned using pre-aripiprazole behavior and function as a baseline. The endpoint was defined as the date the last dose of aripiprazole was given.

### Data Analysis

Statistical tests were performed using the SPSS for Windows, version 16.0. Wilcoxon’s signed-rank test was used to detect the difference between baseline and endpoint outcome scores. All tests were 2-tailed and significance was defined as p less than 0.05.

## RESULTS

### Subject Characteristics

The case records of these 37 patients showed that 31 patients had their complete records at the end of the follow-up period. Four patients were not started

**Table 1: The psychiatric diagnoses of the adolescents using aripiprazole\* (N=31)**

Psychiatric Diagnoses	N	(%)
Major Depressive Disorder	14	(45.2)
Borderline Personality Disorder	11	(35.5)
ADHD	6	(19.4)
Conduct Disorder	6	(19.4)
Bipolar Disorder	5	(16.1)
Generalized Anxiety Disorder	5	(16.1)
Tic/Tourette's Disorder	4	(12.9)
Poor insight OCD	3	(9.7)
Mild Mental Retardation	2	(6.5)
Dissociative Disorder	2	(6.5)
Oppositional Defiant Disorder	1	(3.2)
MDD, with psychotic features	1	(3.2)
Conversion Disorder	1	(3.2)
Panic Disorder	1	(3.2)
Schizophrenia	1	(3.2)
Body Dysmorphic Disorder	1	(3.2)

\*Some cases had more than one diagnosis, ADHD: Attention Deficit Hyperactivity Disorder, OCD: Obsessive compulsive disorder; MDD: Major Depressive Disorder

medication due to poor medication adherence and the two patients were lost to follow-up visits. The statistical analysis was performed for the 31 patients who completed the study.

The sample consisted of mostly females (87.1%). The mean age was 16.38±1.14 years, and the age range was 15-19 years. Patients included in our sample had a wide variety of mental disorders. The first three diagnoses included: Major Depressive Disorder (45.2%), Borderline Personality Disorders (35.5%), and Attention Deficit Hyperactivity Disorder (19.4%) (Table 1). In our study, except for 10 (32.2%) patients who had no comorbid disorders, 21 (67.8%) patients had at least one comorbid disorder. The most common comorbid disorder was major depressive disorder. Conduct disorder was the second most common comorbid diagnosis.

The case records showed that all patients had tried several psychoactive medications before the first aripiprazole prescription. These are listed in Table 2. The reason for changing the medication to aripiprazole was mostly (58.1%, n=18) unresponsiveness to the previous drugs. The other reason was the occurrence of adverse effects from the previous drugs (such as

**Table 2: Psychoactive medication used just before the first prescription of aripiprazole**

Therapeutic group (No. of users)	Medication	N	(%)
First-generation antipsychotics (n=4)	Haloperidol	2	6.5
	Zuclopenthixol	2	6.5
Non-phenothiazine antipsychotics (n=2)	Sulpride	2	6.5
Second-generation antipsychotics (n=20)	Risperidone	17	54.8
	Quetiapine	8	25.8
	Olanzapine	1	3.2
	Amisulpride	1	3.2
SSRIs (n=20)	Fluoxetine	11	35.5
	Citalopram	10	32.3
	Sertraline	9	29.0
	Paroxetine	3	9.2
	Escitalopram	2	6.5
	Venlafaxine	2	6.5
	Fluvoxamine	1	3.2
Tricyclic antidepressants (n=2)	Imipramine	1	3.2
	Clomipramine	1	3.2
Stimulants (n=3)	Methylphenidate	3	9.7
Mood stabilizers (n=2)	Valproic acid	1	3.2
	Lithium	1	3.2
Benzodiazepines (n=1)	Alprazolam	1	3.2

SSRIs: Selective Serotonin Reuptake Inhibitors

**Table 3: Initially prescribed aripiprazole-based regimens (N=31)**

	N	%
Aripiprazole monotherapy	6	19.4
Aripiprazole – SSRIs polypharmacy	24	77.4
Sertraline	8	25.8
Citalopram	7	22.6
Fluoxetine	6	19.4
Fluvoxamine	1	3.2
Escitalopram	1	3.2
Venlafaxine	1	3.2
Aripiprazole - Valproic acid polypharmacy	1	3.2

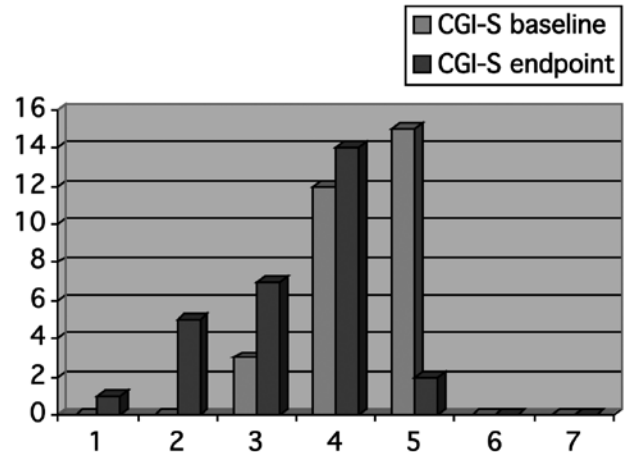
SSRIs: Selective Serotonin Reuptake Inhibitors

prolactin elevation, weight gain, seizures, and extrapyramidal side effects). In three patients with obesity, the therapeutic choice was determined because of aripiprazole low propensity to cause weight gain, dyslipidemia, glucose dysregulation, and metabolic syndrome.

Because of comorbidity, many patients (80.6%) were treated with a variety of medications in conjunction with aripiprazole, and these medications are listed in Table 3. Family history of psychiatric disorder was positive in 44.82% of cases (mothers of 27.58% of cases, fathers of 17.24% of cases). None of the siblings had a history of psychiatric disorder. Family history of psychiatric disorder was missing in two cases.

## Efficacy Results

The mean interview number was  $6.19 \pm 5.23$  (between 1 and 21). The mean initial dosage of aripiprazole was  $4.83 \pm 3.59$  mg (between 2.50 mg and 20.00 mg), and the mean endpoint dosage was  $8.62 \pm 3.46$  mg (between 2.50 mg and 15.00 mg). The mean duration of aripiprazole medication was  $19.56 \pm 1.23$  months (between 4 months and 48 months).

**Figure 1: Mean HAMD-17 scores for the 80% rTMS, 110% rTMS, and sham groups at timepoints throughout the study**

**The Clinical Global Impression Scale (CGI) scores:** Endpoint CGI-S scores were significantly lower ( $3.37 \pm 0.97$ ) compared with baseline CGI-S score ( $4.40 \pm 0.67$ ) (Wilcoxon's signed-ranks test:  $z=0.000$ ;  $p<0.001$ ) (Table 4). Baseline and endpoint clinical global impression scale-severity (CGI-S) scores for all patients are presented in Figure 1. While the difference between the baseline and endpoint improvement scores (CGI-I) was significant ( $z=-3.586$ ;  $p<0.001$ ), the difference between baseline and endpoint adverse effect severity scores was not statistically significant ( $z=-1.414$ ;  $p=0.157$ ) (Table 4).

**The Brief Symptom Inventory (BSI) scores:** The baseline and endpoint subscale scores were compared. The difference between depression severity ( $z=-3.232$ ;  $p=0.001$ ), anxiety severity ( $z=-3.004$ ;  $p=0.003$ ), hostility severity ( $z=-3.207$ ;  $p=0.001$ ), psychoticism severity ( $z=-1.973$ ;  $p=0.049$ ), and paranoid ideation severity ( $z=2.733$ ;  $p=0.006$ ) scores were statistically significant (Table 5). The difference between the baseline and endpoint BSI

**Table 4: Baseline and endpoint CGI Scale scores for the adolescents using aripiprazole (n=29)\***

The Clinical Global Impression Scale	Baseline score mean $\pm$ sd	Endpoint score mean $\pm$ sd	p**
CGI-Severity	4.40 $\pm$ 0.67	3.37 $\pm$ 0.97	<0.001 z:0.000
CGI-Improvement	3.93 $\pm$ 0.73	2.86 $\pm$ 0.91	<0.001 z:-3.586
Adverse effect severity	1.86 $\pm$ 0.73	1.68 $\pm$ 0.60	0.157 z:-1.414

\* The information for the CGI scores of two cases are missing, \*\*Wilcoxon's signed-ranks test, significance  $p<0.05$

**Table 5: The baseline and endpoint scores of the BSI subscale scores for adolescents using aripiprazole (n=20)\***

Subscales	Baseline scores mean±s.d	Endpoint scores mean±s.d	p
Depression	13.57±6.82	7.45±6.23	0.001
Anxiety	12.50±5.90	7.66±5.35	0.003
Somatization	8.52±7.00	7.87±6.64	0.156
Hostility	12.42±5.36	8.20±5.71	0.001
Obsessive-compulsive symptoms	10.53±6.04	8.79±5.69	0.088
Interpersonal sensitivity	7.73±4.60	6.58±4.51	0.064
Psychoticism	8.34±5.02	5.50±4.84	0.049
Phobic anxiety	5.57±4.33	4.25±4.45	0.084
Paranoid ideation	9.15±5.15	6.54±3.93	0.006

\*The information from the BSI of 11 cases is missing; sd, standard deviation

**Table 6: The baseline and endpoint BSI Global Indices of distress scores for adolescents using aripiprazole (n=20)\***

Global Indices	Baseline scores mean±s.d	Endpoint scores mean±s.d	p
Global Severity Index	1.79±0.85	1.26±0.75	0.003
Positive Symptom Distress Index	10.85±4.92	6.87±3.89	0.001
Positive Symptom Total	8.56±1.15	9.40±1.23	0.003

\*The information from the BSI of 11 cases is missing; sd, standard deviation

**Table 7: Reported adverse effects due to aripiprazole treatment (n=28)\***

Adverse effects	N	%
none	-	-
headache	8	28.60
tachycardia	6	21.40
somnolence	12	42.90
dry mouth	9	32.10
asthenia	14	50.00
anxiety/fidgetiness	9	32.10
dizziness	11	39.30
nausea-vomiting	8	28.60
dyspepsia	3	10.70
hypersalivation	3	10.70
akathisia	-	-
orthostatic hypotension	-	-
higher diastolic blood pressure	1	3.60
tremor	5	17.90
blurred vision	8	28.60
insomnia	1	3.60
depression	1	3.60
constipation	2	7.10

\*The information about side effects due to aripiprazole for 3 cases is missing

Global Indices of distress scores was found to be statistically significant (The Global Severity Index:  $z=-2.987$ ;  $p=0.003$ , the Positive Symptom Distress Index:  $z=-3.435$ ;  $p=0.001$ , and the Positive Symptom Total:  $z=-3.023$ ;  $p=0.003$ ) (Table 6).

## Tolerability Results

Adverse events: Twenty-four cases (80.0%) are still continuing aripiprazole treatment. Six cases (20.0%) discontinued the treatment. The reasons of discontinuing the treatment were: due to the adverse effects (doctor's decision) ( $n=1$ , 16.7%), adverse effect (patient's decision) ( $n=1$ , 16.7%), non-adherence to drug by the patient ( $n=4$ , 66.7%), and the doctor decided to change the drug ( $n=1$ , 16.7%). One case had two reasons to discontinue the drug. All cases reported several adverse effects due to aripiprazole. The most frequent adverse effects were asthenia (50.0%), somnolence (42.9%), and dizziness (39.30%) (Table 7).

Only three patients (11.5%) had severe difficulty in carrying out routine tasks due to slowness or weakness. The three out of twenty-six patients (11.5%) tonic muscular contractions localized to one or several muscle groups, particularly in the throat, neck or back. None of the cases had abnormal involuntary movements (dyskinesia) of the extremities or trunk. Only one patient had abnormal involuntary movements (dyskinesia) of the tongue, jaw, lips, or face (Table 8).

**Table 8: The results of the Extrapyramidal Symptom Rating Scale (n=26)\***

ITEMS	None		Slight		Moderate		Severe	
	n	%	n	%	n	%	n	%
Impression of slowness or weakness, difficulty in carrying out routine tasks	18	(69.2)	2	(7.7)	3	(11.5)	3	(11.5)
Difficulty walking or with balance	20	(76.9)	2	(7.7)	2	(7.7)	2	(7.7)
Difficulty speaking or chewing	23	(88.5)	-	-	2	(7.7)	1	(3.8)
Stiffness, stiff posture	22	(84.6)	1	(3.8)	3	(11.5)	-	-
Tonic muscular contractions localized to one or several muscle groups, particularly in the throat, neck or back	18	(69.2)	4	(15.4)	1	(3.8)	3	(11.5)
Restless, nervous, unable to keep still	23	(88.5)	3	(11.5)	-	-	-	-
Tremors, shaking	19	(73.1)	4	(15.4)	3	(11.5)	-	-
Oculogyric crisis, abnormal sustained posture (dystonic reactions)	24	(92.3)	1	(3.8)	1	(3.8)	-	-
Sialorrhoea	23	(88.5)	2	(7.7)	1	(3.8)	-	-
Abnormal involuntary movements (dyskinesia) of extremities or trunk	26	(100.0)	-	-	-	-	-	-
Abnormal involuntary movements (dyskinesia) of tongue, jaw, lips, or face	25	(96.2)	-	-	1	(3.8)	-	-
Postural dizziness, particularly in the mornings	19	(73.1)	6	(23.1)	1	(3.8)	-	-

\*The information for 5 cases is missing

## DISCUSSION

The results of this retrospective chart review have suggested that aripiprazole treatment is associated with a reduction in psychiatric symptom severity in adolescent outpatients. Seventy-five percent of the patients showed at least some improvement in symptoms. The aripiprazole treatment was generally well tolerated, adds a treatment option for this patient population, and that does not appear to contribute to extrapyramidal symptoms. Our results have confirmed the good tolerability profile of aripiprazole when used in combination with other psychotropics in a heterogeneous group of resistant patients. Therefore, our results have demonstrated that aripiprazole add-on therapy with SSRIs facilitated clinical remission and that this combination was well tolerated.

The strengths of our study include its naturalistic, real-world, relatively long follow-up period; observational data collection without any planned treatment intervention; a much broader spectrum of patient symptoms, and the data that are typically absent in claims databases, for example underreporting of co-morbidities. Although randomized, controlled trials (RCTs) are the gold standard for establishing the efficacy of a drug, they cannot offer complete answers to the question of how well an agent works or does not work under real-life conditions (23). The results of naturalistic observational studies may complement the findings of RCTs and facilitate their interpretation for actual clinical practice in real-world settings (30).

Inconsistent with previous studies (2,31,32), antipsychotic treatment was significantly more common in mental health visits by female patients than by male patients in our study. This gender difference might be partially explained by the antipsychotic treatment of depressive disorders, borderline personality disorder, and anxiety disorders, all of which are more common in females than males (33,34). It is possible that gender differences in the risk of suicidal behavior or self-injury have contributed to the female predominance in antipsychotic treatment among outpatients. Another factor that might contribute to gender differences could be the greater use of mental health services by females in adolescence (35).

In our study, it was found that the co-occurrence of two or more psychiatric diagnoses was high and that a high proportion of patients were on concomitant drugs. The most common co-occurring diagnoses were major depressive disorder and conduct disorder. This may be partially explained by the fact that we do not have an acute in-patient service for adolescents and we are the main child psychiatry provider for the population of children aged 14-18 years. A fairly high proportion of patients require intensive, multidisciplinary treatment which is usually indicative of more severe forms of psychiatric disorder.

In a large sample of psychiatric outpatients, Staller et al. reported that most adolescents who received an antipsychotic medication did not have a diagnosis of a psychotic disorder (36). Despite the lack of controlled

studies, there are many studies describing different combinations of aripiprazole with other psychoactive medications, besides its combination with other antipsychotics. Aripiprazole has been used in combination with antidepressants for the treatment of partially responsive or non-responsive patients with major depressive disorder (37-41). In our sample, aripiprazole has been predominantly combined with sertraline and citalopram, as well as with fluoxetine, fluvoxamine, escitalopram, and venlafaxine. This type of combination with aripiprazole has proven tolerable and effective in our sample. Also, aripiprazole has been successfully combined with antidepressants as an adjunctive agent in the treatment of resistant general anxiety disorder (GAD) (42). Aripiprazole augmentation has also been described as effective in the five patients with GAD in our sample. Consistent with previous studies, aripiprazole has also been used in combination for the treatment of other disorders like bipolar disorder (43), and bipolar disorder comorbid attention-deficit/hyperactivity disorder in our sample (44).

Our findings suggested that aripiprazole treatment was generally well tolerated; there was a relatively low rate of discontinuation due to adverse reactions and there were no known suicides or deaths. In general, pediatric patients have a higher risk than adults for experiencing adverse reactions such as EPS, akathisia, prolactin elevation, weight gain, sedation, and metabolic side effects of atypical antipsychotics (45,46). However, the safety profile of aripiprazole in pediatric schizophrenic and bipolar populations has demonstrated that overall adverse reactions are mild to moderate in severity, with a low rate of discontinuation due to adverse events (47). In our study, the most frequently reported treatment-emergent adverse events were asthenia, somnolence and dizziness.

Commonly observed adverse reactions in the present study were generally consistent with those reported in previous studies (17,43,44,48-51). Lastly, there are several reports of akathisia associated with the use of aripiprazole (12,49). Similar to the study by Nyilas et al., there were no patients suffering from akathisia in our study (52).

This retrospective chart review also had several limitations. First of all, this study had a retrospective naturalistic design with no randomization and no control group. Additionally, retrospective naturalistic studies provide strong evidence in support of significant clinical improvement, and the lack of a randomization with a control group introduces the potential for bias. Another limitation of the study was the problem of missing data. The psychopathology and psychological distress analyses did not include all patients in our study because the information from the BSI for 11 cases was missing. Also, it is possible that all adverse events were not adequately documented in the medical records. Another limitation of the study was that our study sample consisted mostly of females, which may limit the generalizability of the results to other populations.

In conclusion, aripiprazole was generally well tolerated and effective, with a low rate of discontinuation due to adverse events and a high completion rate in adolescents with a wide range of psychiatric symptoms. Our results provide support for aripiprazole use in adolescents with a wide range of psychiatric disorders in a sample of outpatients at a starting dose of 2.5 mg/day, and they provide evidence of efficacy and tolerability within dose ranges of aripiprazole of 10 to 20 mg/day. However, prospective clinical trials with a long-term randomized placebo-controlled design are needed to confirm the efficacy and safety of aripiprazole treatment in children and adolescents.

## References:

- Doey T, Handelman K, Seabrook J, Steele, M. Survey of atypical antipsychotic prescribing by Canadian child psychiatrists and developmental pediatricians for patients aged under 18 years. *Can J Psychiatry* 2007; 52(6): 363-8.
- Olfson M, Blanco C, Liu L, Moreno C, Laje G. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Arch Gen Psychiatry* 2006; 63(6): 679-85.
- Zito JM, Safer DJ, de Jong-van den Berg LTW, Janhsen K, Fgert JM, Gardner JF, et al. A three-country comparison of psychotropic medication prevalence in youth. *Child Adolesc Psychiatry Ment Health* 2008; 2(1): 26.
- Verdoux H, Tournier M, Bégau B. Antipsychotic prescribing trends: a review of pharmaco-epidemiological studies. *Acta Psychiatr Scand* 2010; 121(1): 4-10.
- Findling RL, Steiner H, Weller EB. Use of antipsychotics in children and adolescents. *J Clin Psychiatry* 2005; 66 (Suppl 7):S29-S40.
- Riordan HJ, Antonini P, Murphy MF. Atypical antipsychotics and metabolic syndrome in patients with schizophrenia: risk factors, monitoring, and healthcare implications. *Am Health Drug Benefits* 2011; 4(5): 292-302.

7. James AC. Prescribing antipsychotics for children and adolescents. *Adv Psychiatr Treat* 2010; 16(1): 63-75.
8. Linden M, Pyrkosch L, Dittmann RW, Czekalla J. Why do physicians switch from one antipsychotic agent to another? The "physician drug stereotype." *J Clin Psychopharmacol* 2006; 26(3): 225-31.
9. Voruganti L, Cortese L, Oweyemi L, Kotteda, Z Cernovsky, S Zirul et al. Switching from conventional to novel antipsychotic drugs: results of a prospective naturalistic study. *Schizophr Res* 2002; 57(2-3): 201-8.
10. Penfold RB, Kelleher KJ, Wang W, Strange B, Pajer K. Pediatric uptake of a newly available antipsychotic medication. *Pediatrics* 2010; 125(3): 475-82.
11. Bildik T, Ozbaran B, Kucukkose M, Akyol Ardic U. Aripiprazole use in children and adolescents: a case series. *Klinik Psikofarmakoloji Bülteni - Bulletin of Clinical Psychopharmacology* 2010; 20(1): 84-93. (Turkish)
12. Gibson A, Crismon ML, Mican LM, Fischer C. Effectiveness and tolerability of aripiprazole in child and adolescent inpatients: a retrospective evaluation. *Int Clin Psychopharmacol* 2007;22(2):101-5.
13. 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; 29(4): 375-81.
14. Crismon ML, DeLeon A, Miller AL. Aripiprazole: does partial dopaminergic agonism translate into clinical benefits? *Ann Pharmacother* 2003; 37(5): 738-40.
15. Chevreuil C, Polard E, Lemonnier E, Guillemot P, Bentué-Ferrer D. Aripiprazole use in children and adolescent psychiatric patients. *Therapie* 2011; 66(2): 123-30.
16. Findling RL, Kauffman R, Sallee FR, Salazar DE, Sahasrabudhe V, Kollia G et al. An open-label study of aripiprazole: pharmacokinetics, tolerability, and effectiveness in children and adolescents with conduct disorder. *J Child Adolesc Psychopharmacol* 2009; 19(4): 431-9.
17. Kuperman S, Calarge C, Kolar A, Holman T, Barnett M, Perry P. An open-label trial of aripiprazole in the treatment of aggression in male adolescents diagnosed with conduct disorder. *Ann Clin Psychiatry* 2011; 23(4): 270-6.
18. Liu ZS, Chen YH, Zhong YQ, Zou LP, Wang H, Sun D, et al. A multicenter controlled study on aripiprazole treatment for children with Tourette syndrome in China. *Zhonghua Er Ke Za Zhi* 2011; 49(8): 572-6.
19. Findling RL, McNamara NK, Youngstrom EA, Stansbrey RJ, Frazier TW, Lingler J, et al. An open-label study of aripiprazole in children with a bipolar disorder. *J Child Adolesc Psychopharmacol* 2011; 21(4): 345-51.
20. Zuddas A, Zanni R, Usala T. Second generation antipsychotics (SGAs) for non-psychotic disorders in children and adolescents: a review of the randomized controlled studies. *Eur Neuropsychopharmacol* 2011; 21(8): 600-20.
21. 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(3): 229-36.
22. Masi G, Pfanner C, Millepiedi S, Berloffia S. Aripiprazole augmentation in 39 adolescents with medication-resistant obsessive-compulsive disorder. *J Clin Psychopharmacol* 2010; 30(6): 688-93.
23. Patel NC, ML, Hoagwood K, Jensen PS. Unanswered questions regarding a typical antipsychotic use in aggressive children and adolescents. *J Child Adolesc Psychopharmacol* 2005; 15(2): 270-84.
24. Cobo Gómez JV, Fuste G, Coronas R, Benito N, Barbero JD, Domenech C, et al. Combination of aripiprazole and other psychopharmacological treatments in resistant and multi-resistant patients. *Curr Drug Saf* 2008; 3(3): 210-5.
25. Souery D, Papakostas GI, Trivedi MH. Treatment-resistant depression. *J Clin Psychiatry* 2006; 67 (Suppl 6):S16-S22.
26. Guy W. Clinical Global Impression. In ECDEU Assessment Manual for Psychopharmacology. Revised (DHEW Publ No ADM 76-338). Rockville, MD: U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976. p. 218-22.
27. Derogatis LR. Brief Symptom Inventory (BSI): Administration, scoring, and procedures manual. 4<sup>th</sup> ed. Minneapolis, MN: National Computer Systems; 1993.
28. Sahin NH, Durak A. Brief Symptom Inventory (BSI): A study of the Brief Symptom Inventory in Turkish Youth. *Türk Psikoloji Dergisi - Journal of Turkish Psychology* 1994; 9(31): 44-56. (Turkish)
29. Chouinard G, Ross-Chouinard A, Annable L, Jones BD. Extrapyramidal rating scale. *Can J Neurol Sci* 1980; 7(3): 233-44.
30. Möller HJ. Do effectiveness ("real world") studies on antipsychotics tell us the real truth? *Eur Arch Psychiatry Clin Neurosci* 2008; 258(5): 257-70.
31. Cooper WO, Hickson GB, Fuchs C, Arbogast PG, Ray WA. New users of antipsychotic medications among children enrolled in TennCare. *Arch Pediatr Adolesc Med* 2004; 158(8): 753-9.
32. Curtis LH, Masselink LE, Ostbye T, Hutchison S, Dans PE, Wright A, et al. Prevalence of atypical antipsychotic drug use among commercially insured youths in the United States. *Arch Pediatr Adolesc Med* 2005; 159(4): 362-6.
33. Bradley R, Conklin CZ, Westen D. The borderline personality diagnosis in adolescents: gender differences and subtypes. *J Child Psychol Psychiatry* 2005; 46(9): 1006-19.
34. Coopeland JR, Beekman AT, Dewey ME, Hooijer C, Jordan A, Lawlor BA, et al. Depression in Europe: geographical distribution among older people. *Br J Psychiatry* 1999; 174(4): 312-21.
35. Tyler JD, Gren R, Newberry D. Adolescent preferences for help with mental health problems. *Journal of Rural Community Psychology* 2004; E7(1).
36. Staller JA, Wade MJ, Baker M. Current prescribing patterns in outpatient child and adolescent psychiatric practice in central New York. *J Child Adolesc Psychopharmacol* 2005; 15(1): 57-61.
37. Carter WG 3<sup>rd</sup>, Schillcutt SD. Aripiprazole augmentation of venlafaxine in the treatment of psychogenic excoriation. *J Clin Psychiatry* 2006; 67(8): 1311.

38. Papakostas GI, Petersen TJ, Kinrys G, Burns AM, Worthington JJ, Alpert JE, et al. Aripiprazole augmentation of selective serotonin reuptake inhibitors for treatment-resistant major depressive disorder. *J Clin Psychiatry* 2005; 66(10): 1326-30.
39. Simon JS, Nemeroff CB. Aripiprazole augmentation of antidepressant for the treatment of partially responding and non-responding patients with major depressive disorder. *J Clin Psychiatry* 2005; 66(10): 1216-20.
40. Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2007; 68(6): 843-53.
41. Goforth HW, Carroll BT. Aripiprazole augmentation of tranylcypromine in treatment-resistant major depression. *J Clin Psychopharmacol* 2007; 27(2): 216-7.
42. Menza MA, Dobkin RD, Marin H. An open-label trial of aripiprazole augmentation for treatment-resistant generalized anxiety disorder. *J Clin Psychopharmacol* 2007; 27(2): 207-10.
43. Biederman J, McDonnell MA, Wozniak J, Spencer T, Aleardi M, Falzone R, et al. Aripiprazole in the treatment of pediatric bipolar disorder: a systematic chart review *CNS Spectr* 2005; 10(2): 141-8.
44. Tramontina S, Zeni CP, Ketzer CR, Pheula GF, Narvaez J, Rohde LA. Aripiprazole in children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder: a pilot randomized clinical trial. *J Clin Psychiatry* 2009; 70(5): 756-64.
45. Correll CU, Penzner JB, Parikh UH, Mughal T, Javed T, Carbon M, et al. Recognizing and monitoring adverse events of second-generation antipsychotics in children and adolescents. *Child Adolesc Psychiatry Clin N Am* 2006; 15(1):177-206.
46. Taylor D, Paton C, Kapur S. The South London and Maudsley NHS Foundation Trust & Oxleas NHS Foundation Trust Prescribing Guidelines. 10<sup>th</sup> ed. London: Informa Healthcare; 2009. p. 252.
47. Nyilas M, Forbes R, Jin N, Aurang C, Johnson B, Owen R, et al. Long term tolerability and safety of aripiprazole in the treatment of pediatric patients with schizophrenia or bipolar I disorder. *Schizophr Res* 2008; 102(Suppl. 2): S243.
48. Findling RL, Robb A, Nyilas M, Forbes RA, Jin N, Ivanova S, et al. Multiple-Center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. *Am J Psychiatry* 2008; 165(11): 1432-41.
49. Barzman DH, DelBello MP, Kowatch RA, Gernert B, Fleck DE, Pathak S. The effectiveness and tolerability of aripiprazole for pediatric bipolar disorders: a retrospective chart review. *J Child Adolesc Psychopharmacol* 2004; 14(4): 593-600.
50. 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(11): 1110-9.
51. Lyon GJ, Samar S, Jummani R, Hirsch S, Spigel A, Goldman R, et al. Aripiprazole in children and adolescents with Tourette's disorder: an open-label safety and tolerability study *J Child Adolesc Psychopharmacol* 2009; 19(6): 623-33.
52. Findling RL, Blumer JL, Kauffman R, Batterson JR, Gilbert DL, Bramer S, et al. Aripiprazole in pediatric conduct disorder: a pilot study. *Eur Neuropsychopharmacol* 2003; 13(Suppl 4): S335.