PSYCHOPHARMACOLOGY:

Focus on Aripiprazole: A Review of its use in Child and Adolescent Psychiatry

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ABSTRACT

Objective: To review published literature regarding aripiprazole in child and adolescent psychiatry. **Method:** A literature review was conducted using the MEDLine search term: 'aripiprazole' with limits: Human trials, English language, All Child (aged 0-18 years). Additional articles were identified from reference information and poster presentation data. **Results:** Aripiprazole is an atypical antipsychotic which was recently approved for use in Canada, but has been available for several years in the United States. Pharmacologically, aripiprazole is a partial agonist at D_2 and 5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors. Randomized controlled trial data is available showing efficacy for aripiprazole in the treatment of children and adolescents with schizophrenia, bipolar disorder and behavioural problems associated with autism. Open-label evidence is also available for use of aripiprazole in other disorders such as tic disorders, aggression and disruptive behavior disorders. Unlike some other available atypical antipsychotics, there does not appear to be any effect on QTc interval on the electrocardiogram. Adverse effects including extrapyramidal symptoms (EPS), akathisia, sedation, headache, nausea were significant in clinical trials in children and adolescents. The possibility of aripiprazole causing tardive dyskinesia cannot be excluded. In this population, aripiprazole appears to have minimal impact on the metabolic profile compared to most other atypical antipsychotics, with minimal changes in weight or body mass index, no significant changes in glucose or lipid metabolism, and a decrease in serum prolactin. **Conclusion:** Aripiprazole may represent an important alternative for some children and adolescents who have experienced poor efficacy or significant metabolic adverse effects with their current antipsychotic treatment regimen.

RÉSUMÉ

Objectif: Examiner la documentation publiée sur l'aripiprazole en psychiatrie de l'enfant et de l'adolescent. **Méthode:** Un examen de la documentation a été effectué par le biais de la recherche terminologique sur MEDline pour les termes: aripiprazole et ses limites, essais sur les humains, langue anglaise, enfants (0-18 ans). Des articles supplémentaires ont été identifiés dans des documents de référence et des données de présentations de communications par affichage. **Résultats:** L'aripiprazole est un antipsychotique atypique dont l'emploi a récemment été approuvé au Canada mais qui est disponible aux États-Unis depuis plusieurs années. En matière de pharmacologie, l'aripiprazole est un agoniste partial des récepteurs D_2 et 5-HT_{1A} et un antagoniste des récepteurs 5-HT_{2A}. Les données relatives aux essais contrôlés pris au hasard sont disponibles, elles indiquent l'efficacité de l'aripiprazole pour traiter les enfants et les adolescents qui souffrent de schizophrénie, de trouble bipolaire et de problèmes de comportement associés à l'autisme. L'évidence ouverte est également disponible pour l'emploi de l'aripiprazole pour traiter d'autres problèmes tels que les tics, l'agression et les désordres disruptifs de comportement. Contrairement à certains autres antipsychotiques atypiques disponibles, il ne semble pas y avoir d'effets sur l'intervalle QTc de l'électrocardiogramme. Les effets indésirables tels que les symptômes extra-pyramidaux, l'akathisie, la sédation, le chagrin, la nausée étaient significatifs lors des essais cliniques parmi les enfants et les adolescents. La possibilité que l'aripiprazole cause une dyskinésie tardive ne peut pas être exclue. Parmi cette population, l'aripiprazole semble avoir des effets minimes sur le profil métabolique, par rapport à la plupart des autres antipsychotiques atypiques: les changements de poids ou de l'indice de masse corporelle sont minimes, les changements de métabolisme du glucose ou des lipides sont insignifiants et la sécrétion de prolactine est en baisse. **Conclusion:** L'aripiprazole représente peut-être une alternative importante pour certains enfants et adolescents qui ont eu des résultats peu efficaces ou des effets métaboliques indésirables significatifs avec le traitement antipsychotique qu'ils suivent actuellement.

Introduction

Aripiprazole (Abilify®, Bristol Myers Squibb) received a Notice of Compliance from Health Canada in July 2009, and will become available in Canada in early fall 2009. It was approved by the United States (US) Food and Drug Administration (FDA) in 2002 and is the seventh atypical approved by Health Canada (in addition to clozapine, risperidone, olanzapine, quetiapine, paliperidone and most recently ziprasidone).

There is widespread use of this class of medications in pediatric age groups, including FDA approved indications for risperidone and aripiprazole (Ortho-McNeil-Janssen Pharmaceuticals, Inc., 2007, Otsuka Pharmaceutical Co., 2008). Aripiprazole is approved specifically for treatment of Bipolar I Disorder (in children aged 10-17 years) and Schizophrenia (in children aged

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13-17 years) by the FDA. None of the atypical antipsychotics have received approval from Health Canada for use in any indication for patients under the age of 18 years, and Bristol-Myers Squibb did not apply for any pediatric indications as part of their initial submission to Health Canada for aripiprazole. Due to the availability of aripiprazole in the US and other countries for several years prior to its launch in Canada, a significant amount of literature regarding use of aripiprazole in children and adolescents has been published. This review will focus on the available evidence and clinical experience regarding the use of aripiprazole in child and adolescent psychiatry.

Pharmacology

Aripiprazole is sometimes referred to as a third-generation antipsychotic to denote a difference from other available atypical (second-generation) antipsychotics. Unlike other atypicals which have varying levels of D_2 receptor antagonism, aripiprazole is a partial agonist at dopamine D_2 and serotonin 5-HT_{1A} receptors (Otsuka Pharmaceutical Co., 2008). This means that aripiprazole is able to modulate the degree of the blockade of these receptors. If the level of blockade at these receptors is very high, when aripiprazole is present, it will produce a net lowering of the strength of the blockade. If the level of blockade at the receptors is low, when aripiprazole is present, it will produce a net increase in the level of blockade. In common with other atypicals, aripiprazole is also an antagonist at 5-HT_{2A} receptors. Aripiprazole also has strong affinity for D_3 receptors, moderate affinity for D_4, 5-HT_{2C}, 5-HT_7, alpha-1 adrenergic receptors, histamine H_1 receptors and the serotonin reuptake transporter, with no appreciable affinity at the cholinergic muscarinic receptor.

In a pharmacokinetic study of 21 children and adolescents (Findling et al., 2004), oral maintenance dose aripiprazole revealed linear (dose-proportional) pharmacokinetics, and a time to maximum serum concentration (T_{max}) of 2 hours. Aripiprazole has a long serum half-life ($T_{1/2}$) and though it was not calculated in this pediatric study due to termination of blood sample collection after 24 hours, $T_{1/2}$ has previously been reported to be 75 hours for aripiprazole in adults (Otsuka Pharmaceutical Co., 2008). There is one active metabolite, dehydroaripiprazole, which has been reported to have a $T_{1/2}$ in adults of 94 hours. Though pharmacokinetic parameters were similar in children and adolescents compared to adults, for equivalent doses, children and adolescents had mean peak steady-state concentrations (C_{max}) that were higher than observed in adults, with T_{max} occurring more rapidly compared to adults. Based on these observations, children may be more susceptible to dose-related side effects of aripiprazole treatment, and gradual upwards titration of aripiprazole to the target dose may help to minimize adverse effects in this population. Aripiprazole may be administered once daily, and its absorption does not appear to be affected by food. Aripiprazole is a major substrate of both cytochrome p450 (CYP) 2D6 and 3A4 enzymes, and may be subject to interactions with other drugs that are strong inhibitors or inducers of these enzymes. Aripiprazole does not have inhibitory or inducing effects on these or other CYP enzymes.

Efficacy Data

A review of the literature was conducted using the MEDLine search term: 'aripiprazole' with limits: Human trials, English language, All Child (aged 0-18 years). Additional articles were identified from reference information and poster presentation data. Table 1 summarizes the published pediatric literature on aripiprazole. The studies are ranked by Level of Evidence (Centre for Evidence Based Medicine, 2009).

There have been four prospective, randomized control trials (RCT) of aripiprazole in children or adolescents. In a multicenter trial (Findling et al., 2008a), 302 subjects with Schizophrenia, aged 13-17 years, were randomized to receive either aripiprazole 10 mg/day, aripiprazole 30 mg/day or placebo for six weeks. The primary outcome was the Positive and Negative Symptom Scale (PANSS) from baseline to endpoint. Secondary outcomes were measured using the Clinical Global Impression-Improvement and Severity (CGI-I, CGI-S) and the Children's Global Assessment Scale (CGAS). Aripiprazole was found to be superior to placebo in the treatment of adolescents with Schizophrenia. There was a significant reduction in the overall PANSS score in both the 10 and 30 mg/day groups compared to placebo.

The significant reductions were noticed by week one in the 30 mg/day group however by week six in this same group there was only significant reduction in the positive subscale and not in the negative subscale. In the 10 mg/day group both positive and negative subscales showed significant reductions but not until the trial endpoint at week six.

Owen (Owen et al., 2008a) enrolled 98 children and adolescents aged 6-17 years with serious behavioural problems associated with Autism in a flexible dose (aripiprazole 2-15 mg/day) 8 week trial.

The behavioural problems were identified as tantrums, aggression and self-injurious behaviour. Primary efficacy outcomes were measured by the caregiver-rated Aberrant Behaviour Checklist-Irritability (ABC-I). Secondary outcomes were measured by the CGI-I, CGI-S, the other ABC subscale scores and the Children's Yale-

Table 1 - Review of aripiprazole evidence in children and adolescents

Level of Evidence*	Report Type	Year/Lead Author/Journal	# of pts (n), % males	Pt age (mean and/or range) (years)	Indication(s)	Aripiprazole Daily Dose	Aripiprazole Monotherapy ?	Duration of treatment	Efficacy Rating Scales (Bold = 1Y Endpoint)	Efficacy Results	Adverse Effects	Metabolic effects
1b	**Prospective Randomized Controlled Trial**	2009; Corey-Lisle P; Kamen L; APA poster presentations NR2-061, NR2-063 (flexible-dose trial) 2008a; Owen R; AACAP poster presentation 3.59	n=98 (88% male)	PI: 8.8 ± 2.6 A: 9.7 ± 3.2	Autistic Disorders	Flexible Dose (range: 2-15 mg) vs placebo	Yes (implied)	8 weeks	**ABC-I**, CGSQ, PedsQL	**ABC-I: (treatment difference vs PI, - score denotes improvement) -7.9** CGSQ: (treatment difference vs PI, - score denotes improvement) -1.9 ± 0.8 PedsQL: (treatment difference vs PI, + score denotes improvement) +11.4 ± 5.6	Pooled reporting of flexible and fixed-dose trials (% above PI): Sedation (17%), fatigue (15%), EPS (11%), tremor (10%), drooling (10%), vomiting (8%), increased appetite (7%), fever (7%), somnolence (6%), decreased appetite (5%), increased salivation (5%)	Pooled reporting of flexible and fixed-dose trials: Mean weight change: PI: 0.4 kg; A: 1.6 kg Mean BMI change: PI: 0.2; A: 0.7 Mean BMI z-score change: PI: 0.01; A: 0.11 Negligible changes in glucose, lipids
1b	**Prospective Randomized Controlled Trial**	2009; Corey-Lisle P; Kamen L; APA poster presentations NR2-061, NR2-063 (fixed-dose trial) 2008b; Owen R; AACAP poster presentation 3.60	n=218 (89% male)	PI: 10.2 ± 3.1 A5: 9 ± 2.8 A10: 10 ± 3.2 A15: 9.5 ± 3.1	Autistic Disorders	5, 10 or 15 mg vs placebo (1:1:1:1 randomization)	Yes (implied)	8 weeks	**ABC-I**, CGSQ, PedsQL	**ABC-I: (treatment difference vs PI, - score denotes improvement)** **A5: -4.5; A10: -5.8; A15: -6.5** CGSQ: (treatment difference vs PI, - score denotes improvement) A5: -0.4 ± 0.8; A10: -0.2 ± 0.75; A15: -1.1 ± 0.8 PedsQL: (treatment difference vs PI, + score denotes improvement) A5: 3.4 ± 6.6; A10: -0.2 ± 6.7; A15: 8.2 ± 6.8	Pooled reporting of flexible and fixed-dose trials (% above PI): Sedation (17%), fatigue (15%), EPS (11%), tremor (10%), drooling (10%), vomiting (8%), increased appetite (7%), fever (7%), somnolence (6%), decreased appetite (5%), increased salivation (5%)	Pooled reporting of flexible and fixed-dose trials: Mean weight change: PI: 0.4 kg; A: 1.6 kg Mean BMI change: PI: 0.2; A: 0.7 Mean BMI z-score change: PI: 0.01; A: 0.11 Negligible changes in glucose, lipids
1b	**Prospective Randomized Controlled Trial**	2008; Werner C; CINP poster presentation	N=296 (54% males)	13.43 (range: 10-17)	Bipolar Disorder - type I	10 or 30 mg vs placebo (1:1:1 ratio)	Yes (implied)	4 weeks plus 26 week double-blind continuation	ARS-IV, CDRS-R, CGAS, CGI BP, GBI, **YMRS**	(shown as change from basline) ARS-IV: PI: -4.6; A10: -11.6; A30: -10.1 CGAS: PI: -7; A10: -16; A30: -17 CGI-BP: PI: -0.8; A10: -1.6; A30: -1.8 GBI (mania): PI: -4.3; A10: -9; A30: -8.9 **YMRS: PI: -8.2; A10: -14.1; A30: -14.9 (p<0.001 for A10 and A30 vs placebo)** **Responders (≥ 50% reduction in YMRS):** **PI: 27%; A10: 50%; A30: 56%**	relative to placebo: A10: somnolence (24.5%), fatigue (18.4%), EPS (12.2%), blurred vision (10%), nausea (8%), akathisia (7%), increased appetite (5%), suicidal ideation (1%) A30: EPS (28.3%), somnolence (27.3%), fatigue (12.1%), akathisia (11%), nausea (8%), blurred vision (8%), increased appetite (5%), suicidal ideation (1%)	Mean change in weight z-score: PI: 0; A10: 0.13; A30: 0.19 (z-score changes of < 0.5 considered not clinically significant) No significant changes in cholesterol, triglycerides, glucose Prolactin: PI: -0.4 mcg/mL; A10: -4 mcg/mL; A30: -2.3 mcg/mL
1b	**Prospective Randomized Controlled Trial (1b)**	2008a; Findling RL; Am J Psychiatry	n=302 (57% males)	15.5 ± 1.3 (range: 13-17)	Schizophrenia	10 or 30 mg vs placebo (1:1:1 ratio)	Yes (adjunctive benzodiazepines or benztropine permitted)	6 weeks	CGAS, CGI-I, CGI-S, **PANSS,** PQLESQ	CGAS week 6 change: PI: +9.8 ± 1.3; A10: +14.7 ± 1.5; A30: + 14.8 ± 1.3; CGI-I week 6 scores: PI: 3.1 ± 0.1; A10: 2.7 ± 0.1; A30: 2.5 ± 0.1 CGI-S week 6 changes: PI: -0.9 ± 0.1; A10: -1.2 ± 0.1; A30: -1.3 ± 0.1 **PANSS week 6 change:** **PI: -21.2 ± 1.9;** **A10: -26.7 ± 1.9; (p=0.05 vs placebo)** **A30: -28.6 ± 0.9 (p=0.007 vs placebo)** PQLESQ week 6 change: PI: 4.5 ± 0.9; A10: 5.2 ± 0.9; A30: 5.9 ± 0.9	Side effects occurring at ≥ 5% incidence (relative to placebo) A10: EPS (8%), headache (6%), somnolence (5%) A30: EPS (17%), somnolence (16%), tremor (10%), akathisia (7%)	Mean weight changes: PI: -0.8 ± 2.6 kg; A10mg: 0 ± 2.1 kg; A30mg: 0.2 ± 2.3 kg pts with weight gain ≥ 5%: PI: 2%; A10: 11%; A30: 9% No significant change in glucose, prolactin, cholesterol or triglyceride levels in either treatment group compared to placebo
2b	**Prospective Open label trial**	2009; Bastiaens L; Community Mental Health J	n=46 (78% males)	11.9 ± 2.6 (range 6-17)	Aggression (largest group: Conduct Disorder: 30%)	Assigned to A or Z in non-randomized fashion A:4.5 ± 2.3 mg Z: 42.9 ± 18 mg	No (30% on stimulants; 22% on atomoxetine)	2 months	CGI-I, GAF, HALFS, **OAS,** pYMRS	**OAS: 70% of A completers (58% by ITT) had ≥ 50% decrease in OAS** **(A mean change 6.8 ± 1.8 to 2.3 ± 2.9);** **71% of Z completers (45% by ITT) had ≥ 50% decrease in OAS** **(Z mean change 7.4 ± 2.1 to 3.1 ± 2);** CGI-I: mean rating at endpoint: A: 2 ± 1.2; Z: 2.3 ± 1.4; GAF: A: 50 ± 4.7 to 61 ± 7.7; Z: 46.4 ± 2.4 to 57.9 ± 7.6 HALFS: A: 9.7 ± 4 to 13.1 ± 4; Z: 8.1 ± 4.7 to 11.6 ± 3.6 pYMRS: A: 24.7 ± 9.3 to 9.8 ± 8.2; Z: 23.3 ± 7 to 8.7 ± 7 (all figures shown are for study completers only)	Sedation (50% of completers), dizziness, EPS, headaches, nausea (each in 10% of completers) 4/24 pts discontinued study (17%) - 2 of these 4 due to sedation	Not reported

*** Level of Evidence - as per Centre for Evidence Based Medicine document (2009)**

Abbreviations

A=aripiprazole BMI=Body Mass Index CPK=Creatine Phosphokinase EPS=extrapyramidal symtpoms HbA1c=glycosylated Hemoglobin A1c ITT = intention-to-treat analysis Na=sodium NOS=not otherwise specified PI=placebo pt(s)=patient(s) WBC=White Blood Cells Z=ziprasidone

Abbreviations of Rating Scales used

ABC-I: Aberrant Behavior Checklist Irritability subscale
ARS-IV: ADHD Rating Scale-IV
BAI: Beck Anxiety Inventory
BPRS: Brief Psychiatric Rating Scale
CDRS(-R): Children's Depression Rating Scale (- Revised)
CDSS: Calgary Depression Scale for Schizophrenia
CGAS: Children's Global Assessment Scale
CGI-I: Clinical Global Impresssion - Improvement
CGI-Rage: Clinical Global Impression - Rage
CGI-Tics: Clincal Global Impression - Tics
CGI-S: Clinical Global Impression - Severity
CGSQ: Caregiver Strain Questionnaire
CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale
CY-BOCS-PDD: Children's Yale-Brown Obsessive Compulsive Scale (modified for PDD)
GAF: Global Assessment of Functioning
GBI: General Behavior Inventory
HALFS: Health and Life Functioning Scale
HCRF: Heinrichs-Carpenter Quality of Life role functioning subscale
MOVES: Motor and Vocal tic Evaluation Scale
OAS: Overt Aggression Scale
PANSS: Positive and Negative Symptom Scale
PedsQL: Pediatric Quality of Life Inventory
PQLESQ: Patient Quality of Life Enjoyment and Satisfaction Questionnaire
pYMRS: Parent's Young Mania Rating Scale
SFS: Social Functioning Scale
SNAP-IV: Swanson, Nolan & Pelham ADHD rating scale-IV
SOPS: Scale of Prodromal Symptoms
VABS: Vineland Adaptive Behavior Scales
YGTSS = Yale Global Tic Severity Scale
YMRS: Young Mania Rating Scale

2b	**Prospective Open label trial**	2009; Stigler K; JCAP	n=25 (76% males)	8.6 (range: 5-17)	PDD-NOS, Asperger's Disorder	7.8 mg (range: 2.5-15 mg)	Yes	14 weeks	**ABC, CGI-I,** CY-BOCS-PDD, VABS	**ABC: 29 ± 7.3 to 8.1 ± 7.5** **CGI-I: 88% rated as much improved or very much improved (CGI-I ≤ 2) and with ≥ 25% improvement on ABC** CY-BOCS-PDD: 11.9 ± 2 to 6.8 ± 4.1 VABS: improvement on socialization domain noted	tiredness (56%), cough (48%), increased appetite (44%), nausea/vomiting (40%), rhinitis (40%), constipation (36%), dry mouth (32%), dyspepsia (32%), sialorrhea (16%), tremor (12%)	Mean weight change: 2.7 kg (range: -3.3 to 8.1 kg). 76% of pts gained weight (not adjusted for growth) Mean BMI change: 20.3 ± 6.1 to 21.1 ± 5.7 Prolactin levels decreased significantly, no significant change in blood glucose or lipids noted
2b	**Prospective Open label trial**	2008; Seo W; JCAP	n=15 (93% males)	12.2 ± 3.7 (range: 7-19)	Tourette Disorder or Chronic Tic Disorder	8.17 ± 4.06 mg (range: 2.5-15 mg)	Monotherapy in 60%	12 weeks	**YGTSS**	**YGTSS: 24.53 ±11.12 to 10.87 ± 7.54** **Changes noted starting at week 3 and continuing to study endpoint**	sedation (47%), nausea (33%)	Mean BMI change: 0.08 ± 0.63
2b	**Prospective Open label trial (2b)**	2008c; Findling R; J Clin Psychopharmacol	n=21 (67% male)	12.2 ± 2.1 (Range: 10-17)	Bipolar Disorder, Tourette Syndrome, schizophrenia, ADHD, OCD, PDD	Titrated to 20, 25 or 30 mg day (1:1:1 ratio)	Yes (67% on various concomitant non-psychotropic medications)	2 weeks (at target dose)	**CGI-I, CGI-S**	**CGI-I: 85% of all pts much improved or very much improved (CGI-I ≤ 2)** **CGI-S: A20: 4 to 2.4;** **A25: 3.7 to 2.3;** **A30: 3.5 to 1.2**	headache (29%), abdominal pain (24%), dizziness (19%), vomiting (14%), fatigue (10%), stiffness (10%), dystonia (10%), sedation (10%), somnolence (10%)	Mean weight changes: A20: -0.2 ± 2.5 kg; A25: 0.9 ± 2.3 kg; A30: 0.4 ± 1.8 kg No clinically relevant changes in glucose, prolactin, cholesterol or triglycerides
2b	**Prospective Open label trial**	2008b; Findling R; JCAP	n=23 (61% males)	10.2 ± 1.4 (range: 8-12)	ADHD (Combined subtype or Inattentive subtype)	6.7 ± 2.4 mg	Yes (35% pre-treated with stimulants were stopped on enrollment)	6 weeks	**ARS-IV**, CGAS, **CGI-I**, CGI-S	**ARS-IV: 36.8 ± 11.5 to 21.5 ± 11.1** CGAS: 62.8 ± 4.6 to 71 ± 8.6 **CGI-I: 61% much improved or very much improved (CGI-I ≤ 2)** CGI-S: 4 ± 0.3 to 3.2 ± 0.7	sedation (78%), headache (47%), nausea (30%), increased appetite (26%), musculoskeletal pain (26%), EPS (22%), stomach ache (22%), hiccups (17%), flu-like symptoms (17%), vomiting (13%), sore throat (13%)	Mean weight changes: no prior stimulant Rx: + 1.7 kg prior stimulant Rx:+ 3.7 kg 9% discontinued due to weight gain Glucose: 4.5 ± 0.5 to 4.73 ± 0.46 mmol/L (NS) Prolactin: 4.45 ± 1.45 to 2.88 ± 2.61 (p<0.05)
2b	**Prospective Open label trial**	2007; Yoo H; J Clin Psychiatry	n=24 (79% male)	11.8 ± 3.8	Tic Disorders	9.8 ± 4.8 mg		8 weeks	CGI-I, CGI-S, **YGTSS**	CGI-I: 88% rated as much improved or very much improved (CGI-I ≤ 2) at endpoint CGI-S: 5.5 ± 0.5 to 3 ± 1.4 **YGTSS: 26.7 ± 5.5 to 12.6 ± 7.6**	parkinsonism (46%), hypersomnia (38%), nausea (21%), headache (17%), EPS, akathisia, decreased volition (8% each)	Not reported
2b	**Prospective Open label trial**	2007; Woods S; Br J Psychiatry	n=15 (53% male)	17.1 ± 5.5	Prodromal Schizophrenia	15.7 ± 5.9 mg	Yes (benzodiazepines and anticholinergics permitted)	8 weeks	BAI, CDSS, GAF, HCRF, SFS, **SOPS,** YMRS	(scores shown as change from baseline) BAI: -13.1 ± 11.2 CDSS: -3.8 ± 4.2 GAF: +9.2 ± 5.3 HCRF: +3.2 ± 5.1 SFS: -2 ± 21 **SOPS: -29.1 ± 12.3 (p<0.001)** YMRS: -3.9 ± 3.6	akathisia (53%), irritability (33%), increased appetite (27%), sedation (20%), insomnia, nervousness, memory impaired, sensory perception impaired, increased salivation, decreased libido, excessive sweating (13% each)	Mean weight change: +1.2 ± 2 kg (not adjusted for growth)
2b	**Prospective Open label trial**	2007; Tramontina S; CNS Spectr	n=10 (50% male)	9 ± 3.5 (range: 8-17)	Juvenille Bipolar Disorder with comorbid ADHD	11.7 ± 5.7 mg	No	6 weeks	**CGI-S, SNAP-IV, YMRS**	**CGI-S: 4 ± 1.15 to 3 ± 1.63** **SNAP-IV: 1.83 ± 0.76 to 1.47 ± 0.75** **YMRS: 35.5 ± 11.85 to 20.6 ± 11.68** 70% of pts had ≥ 30% reduction in YMRS score, including 2 pts achieving remission.	sialorrhea (70%), sedation/tiredness (70%), confusion (60%), depressive symptoms (60%), increased appetite (50%), decreased appetite (50%), sweating (50%), tremor (50%), nervousness/anxiety (50%), suicidal ideation (20%)	Actual values not reported, but "a small but significant increase in weight was observed during the trial." All patients had been off other medications for > 10 weeks prior to enrollment.
2b	**Prospective Open label trial (2b)**	2007; Biederman J; CNS Spectr	n=19 (58% males)	11.6 ± 3.6 (range: 6-17)	Bipolar Disorder (I and II)	9.4 ± 4.2 mg	Monotherapy in 89% (11% receiving stimulants)	8 weeks	BPRS, CDRS, CGI-I, **YMRS**	**YMRS: 79% had ≥ 50% reduction** **mean: 27.3 ± 4.9 to 9.4 ± 4.2;** BPRS: 38.9 ± 7.6 to 28.8 ± 9.9; CDRS: 38.6 ± 11.2 to 32.6 ± 17.4; CGI-I: 95% much improved or very much improved (CGI-I ≤ 2)	Sedation (57%), GI upset (42%), respiratory tract infection (32%), headache (32%), akathisia (15%), sleep problems (15%), depression, slurred speech, pain, anxiety, tremor, EPS (each 11%)	No significant changes in weight, prolactin or metabolic parameters at 8 weeks; mean weight change: +1.8 kg ± 0.6 kg
2b	**Prospective Open label trial**	2006; Yoo H; JCAP	n=14 (86% male)	11.93 ± 3.41 (range: 7-17)	Tourette Disorder	10.89 mg (range: 2.5-15 mg)	Yes	8 weeks	**YGTSS**	**YGTSS: 27.64 ± 5.96 to 16.57 ± 5.23**	Nausea/vomiting (14%), hypersomnia (7%), weight gain (7%)	Not systematically assessed. One pt reported weight gain of 3 kg
2b	**Prospective Open label trial**	2004; Stigler K; JCAP	n=5 (100% male)	12.2 ± 5.07 (range: 5-18)	PDD-NOS	12 ± 2.74 mg (range: 10-15 mg)	Monotherapy in 40%	mean 12 weeks (range: 8-16 weeks)	**CGI-I**	**CGI-I: 100% rated as much improved or very much improved (CGI-I ≤2)**	somnolence (40%), dizziness (20%)	Mean weight change: -3.7 kg (range: -13.6 to 0.45 kg). Some pts previously treated with other second generation antipsychotics
2b	**Prospective Open label trial**	2004; Findling R; CINP poster presentation	n=23 (% males not reported)	range: 6-17	Conduct Disorder	Based on weight (range: 1-10 mg, amended from 2-15 mg after significant adverse effects following enrollment of first 4 pts)	Yes (implied)	2 weeks	**CGI-I**	**CGI-I: 64% of children (≤ 12) and 45% of adolescents (≥ 13) rated as much improved or very much improved (CGI-I ≤ 2)**	vomiting (26%), somnolence (26%), dyspepsia (23%), lightheadedness (13%), pharyngitis (9%)	Not reported
4	Naturalistic Retrospective Evaluation	2008; Budman C; JCAP	n=37 (70% males)	13.4 ± 2.8 (range: 8-18)	Tourette Disorder (84% also met criterion for ADHD and OCD, 78% met critieria for IED)	11.7 ± 7.2 mg (range: 2.5-40 mg)	Monotherapy in 24%	6-12 weeks	**CGI-Rage, CGI-Tics**	**CGI-Rage: (in completers) 4.96 ± 1.22 to 2.53 ± 1.13;** **CGI-Tics: (in completers) 4.38 ± 0.81 to 2.69 ± 0.88**	akathisia (16%), agitation (8%), mood lability (8%), EPS (3%), extreme sedation (3%), headache, dizziness, nausea, sedation also noted (not quantified); 8/37 pts discontinued study (22%)	Weight data available in only 15 of 37 pts; 13/15 (87%) gained weight; mean change in weight gainers: 8.2 ± 5.6 kg
4	Naturalistic Retrospective Evaluation	2007; Gibson A; Int Clin Psychopharmacol	n=45 (29% males)	15.1 ± 1.5 (range: 11-18)	Any Axis I diagnosis (Most common: Bipolar Disorder (40%), PTSD (31%), substance abuse (22%), depressive disorder, ODD/conduct disorder (20% each)	16.9 ± 7.9 mg	No	31.3 ± 19.6 days	**CGI-I, CGI-S**	**CGI-I: 51% rated as much improved or very much improved (CGI-I ≤ 2)** **CGI-S: 5.04 ± 0.95 to 3.33 ± 1.24)**	gastrointestinal distress (18%), nausea/vomiting (18%), sedation (11%), akathisia (9%), headache (7%), EPS (4%)	Mean weight change (22/45 pts): 83.22 ± 22.68 kg to 82.77 ± 21.23 kg Mean BMI change (22/45 pts): 30.4 ± 5.17 to 29.98 ± 4.87
4	Naturalistic Retrospective Evaluation	2004; Barzman DH; JCAP	n=30 (60% males)	13 ± 3 (range: 5-19)	Bipolar disorder/schizoaffective disorder (bipolar type)	9 ± 4 mg (range: 5-15 mg)	Monotherapy in 30%	4.4 ± 2.7 months (range: 1-9 months)	**CGI-I**, CGI-S, CGAS	**CGI-I: 67% much improved or very much improved (CGI-I ≤ 2) at endpoint;** CGAS: significant improvement (mean: 48 ± 11 to 65 ± 11); CGI-S: significant improvement (mean 4.2 ± 0.8 to 2.8 ± 1)	Sedation (33%), akathisia (23%), GI upset (7%), blurry vision, speech disturbance, dystonia, tremor (each 3%)	Weight data available in only 14 of 30 pts; Mean weight change: -3 ± 6 kg (range: -21 to +5 kg); 12/14 pts (86%) lost weight; (7 of 12 who lost weight were previously treated with another antipsychotic)
5	Case Series	2008; Bachmann CJ; Ther Drug Monit	n=33 (55% males)	18.7 ± 1.7 (range 13.5-21.6)	Schizophrenia Spectrum Disorders	12.9 mg ± 6.4 mg (range 5-30 mg)	No	range 14-489 days (naturalistic study)	None	Not reported (pharmacokinetic study)	Not reported	Not reported

4	Case Series	2007; Miranda M; Rev Med Chile	n=10 (% males not specified)	(range: 10-35)	Tourette Syndrome (refractory)	mean: 10 mg (range:7.5-25 mg)	No	1 month	**YGTSS, CGI-S**	90% of patients showed significant response on YGTSS and CGI-S measurements.	Not reported	Not reported
4	Case Series	2006; Valicenti-McDermott M; JCAP	n=32 (72% male)	10.9 ± 4.3 (Range: 5-19)	Developmental Disability with various comorbid conditions (Mental Retardation, Autism Spectrum Disorders, ADHD, Mood Disorders most frequent)	10.55 ± 6.9 mg	Monotherapy in 75%	6.1 ± 4.5 months (range: 0.25-15 months)	Not well defined - **Clinical global impression of improvement in target symptoms**	**Improvement in target symptoms found in 56%**	drowsiness (19%), weight gain (13%), increased aggression (7%), stiffness, myalgias, facial dyskinesia, diarrhea (3% each)	Mean BMI change: 23.3 ± 7.2 to 24.1 ± 7 mean BMI z-score change: 1.4 to 1.62 BMI z-score increase more notable in younger children
4	Case Series	2006; Duane D; J Child Neurol	n=15 (80% males)	15 (range: 9-25)	Tourette Syndrome	range: 2.5-15 mg	Not specified	8 weeks	None specified	Excellent tic control in 14/15 (93%) with variable benefits to attention behaviorally and cognitively	nausea (27%), akathisia (27%)	weight gain ≥ 5% in 4/15 (27%); weight loss of ≥ 5% in 1/15 (7%) - this pt was previously treated with olanzapine
4	Case Series	2006; Davies L; Human Psychopharmacol Clin Exp	n=11 (64% males)	26.7 ± 15.5 (range: 7- 50)	Tourette Syndrome	14.5 ± 3.5 mg (range: 10-20 mg)	Monotherapy in 36%	1- 10 months	MOVES	5/11 very much improved, 4/11 much improved	Sedation, 2/11 pts with chest pain (aged 7 and 50 respectively - no abnormalities found on cardiovascular workup)	Not reported
4	Case Series	2005; Rugino T; J Child Neurol	n=17 (88% males)	11.4 ± 3.9 (range: 5.1-17.9)	Bipolar Disorder, Autism, Psychosis NOS	12.8 ± 4.5 mg (range: 5-20 mg)	No	106.6 ± 75.5 days (range: 14-210 days)	**CGI-I, CGI-S**	**CGI-S: 5.8 ± 0.9 at baseline** **6/17 pts considered "repsonders" (much improved or very much improved (CGI-I ≤ 2)**	Aggression (35%), nausea/vomiting (12%), staring episodes, listlessness, sedation, coarse tremor (6% each).	Mean weight gain (14/17 pts): 3.9 ± 1.6 kg Mean BMI change (14/17 pts): 1.7 ± 0.7 Weight gain appeared to be more with longer duration or higher doses. 9/14 gained more weight than expected for 90% of age/gender matched peers.
4	Case Series	2005; Murphy TK; Int J Neuropsychopharmacol	n=6 (50% male)	12.1 ± 4.05 (range: 8-19)	Tourette Syndrome, OCD	11.7 mg (range: 5-20 mg)	No	12 weeks	**CY-BOCS, YGTSS**	**CY-BOCS: 28.2 ± 4.1 to 8.2± 5.5** **YGTSS: 31.2 ± 8.3 to 13.7 ± 4.4**	somnolence, dry mouth, teeth chattering, hand tremor (1 report each)	Mean weight gain: 1.9 ± 1.1 kg (range: -5 to 3 kg) 5/6 pts gained weight during trial. Subject who lost weight was actively dieting at the time. BMI increased in 2/6 pts during trial.
4	Case Series	2004; Durkin J; JCAP	n=24 (92% males)	12 (range: 5-17)	Bipolar Disorder	13.75 mg (range: 5-20 mg)	Monotherapy in 4%	Unclear - benefits noted by day 8 of treatment in responders	Patient subjective self-rating (poor, good or excellent)	59% rated response as good or excellent	sedation (8%), irritability (8%), insomnia (4%), tremor (4%), fainting (4%), agitation (4%), aggression (4%), anxiety (4%), weakness (4%), psychomotor retardation (4%), facial movements (4%), stammering (4%)	Not reported
4	Case Report	2008; Storch E; Depression Anxiety	n=1 (male)	13	OCD	up to 5 mg	No (also receiving sertraline)	~1 year	**CY-BOCS**	CY-BOCS: 30 to 3	None	No clinically significant change in weight or laboratory values reported
4	Case Report	2008; Haffejee S; Dev Med Child Neurol	n=1 (female)	14	Alternating Hemiplegia of Childhood	1.25 mg	No	1 year	None	Significant reduction of frequency, duration, severity of episodes of hemiplegia, reduced behavioural outbursts	Not reported	Not reported
4	Case Report	2008; Dhamija R; Diabetes Care	n=1 (male)	12	Mood Disorder NOS	not specified	Yes	6 months	None	Not reported	Diabetic Ketoacidosis (weight gain, hyperglycemia, polyuria, polydipsia) - resolved with insulin therapy and rehydration	weight gain, hyperglycemia, polyuria, polydipsia
4	Case Report	2008; Groff K; JCAP	n=1 (male)	17	Psychosis NOS	15 mg	Yes	10 days	None	Reduced auditory hallucinations at 1 week	Developed catatonic symptoms (echopraxia, waxy flexibility, confusion, disorientation) without rigidity, elevated temperature or elevated CPK - Resolved after 48 hours of lorazepam treatment	Not reported
4	Case Report	2007; Bachmann CJ; J Clin Psychopharmacol	n=1 (Male)	17	Schizophrenia	10 mg	No (also receiving clozapine)	40 days	None	Not reported	CPK=4572 IU/L Normalized within 8 days with continued therapy	None reported
4	Case Report	2007; Strawn JR; JCAP	n=1 (female)	15	PDD-NOS, psychosis, catatonia	15 mg/day	No	≥ 5 days	None	Response noted 8hr following initial dose, and catatonic symptoms resolved after 5 days of aripiprazole therapy	Not reported	Not reported
4	Case Report	2007; Singh M; JAACAP	n=1 (male)	10	Bipolar Disorder	10 mg	No	3 days	None	Not reported	Neck pain, stiffness, unusual sensations in jaw. Resolved within 30 minutes following benztropine administration	Not reported
4	Case Report	2007; Palakurthi H; Clin Neuropharmacol	n=1 (male)	12	PDD-NOS	10 mg	No	2 days	None	None	Tremor, acute confusional state, muscle rigidity, fever, fluctuating consciousness, increased WBC, respiratory distress, CPK 401 U/L. Resolved after 6 days following treatment in ICU with dantrolene and bromocriptine.	Not reported
4	Case Report	2007; Logue D; Am J Psychiatry	n=1 (male)	7	ADHD (Combined subtype), Aggression	2.5 mg	Yes	4 weeks	None	Not reported	Hyperglycemia (36.25 mmol/L), ketonuria, polydipsia, polyphagia, polyuria, hyponatremia (Na=127), HbA1c=10%. Blood glucose normalized after stopping aripiprazole and 4 weeks of insulin therapy	Patient had positive family history of type 2 diabetes. Seven months after initial presentation, the patient developed insulin-dependent diabetes [sic].
4	Case Report	2007; Curtis AR; Ann Clin Psychiatry	n=1 (female)	18	OCD, psychogenic excoriation	5 mg	No (fluoxetine 80 mg)	4 weeks	None	Complete resolution of psychogenic excoriation and 30-40% subjective decrease in OCD symptoms	Not reported	Not reported
4	Case Report	2006; Hammerman S; JAACAP	n=1 (female)	14	Depression with Psychotic Features	5 mg	Yes	2 days	None	Not reported	tremors, drooling, cogwheel rigidity, unsteady gait, incontinence, agitation. CPK 23,340 IU. (afebrile, WBC 9.3). Resolved with lorazepam 2mg po q4h plus sodium bicarbonate treatment.	Not reported
4	Case Report	2006; Fountoulakis K; Ann Pharmacother	n=1 (male)	18	Tourette Disorder	10 mg	Yes	3 days	None	Improvement reported on Day 2	Dystonia, facial muscle spasm, oculogyric crisis, torticollis on day 3. Symptoms resolved after 5 mg biperiden IM injection.	Not reported

4	Case Report	2005; Wahl R; Am J Psychiatry	n=1 (female)	17	Schizophrenia	15 mg	No (continued on risperidone long-acting injection)	12 days	None	Symptomatic prolactinemia (breast pain, swelling and galactorrhea), resolved during continued risperidone therapy following addition of aripiprazole.	None reported	serum prolactin = 119 mcg/mL during symptomatic phase. Repeat prolactin following aripiprazole addition = 18 mcg/mL
4	Case Report	2005; Negin B; JAACAP	n=1 (male)	16	Bipolar Disorder NOS, PDD-NOS	5 mg	No	Approximately 1 month. Pt also receiving lithium and oxcarbazepine	None	Not reported	2 episodes of priapism. Spontaneously resolved. Oxcarbazepine discontinued, aripiprazole and lithium discontinued and priapism did not recur.	Not reported
4	Case Report	2005; Kantafaris V; JAACAP	n=1 (male)	17	Bipolar Disorder (Type I)	12.5 mg	No	6 months (then tapered off over 2 week period)	None	Not reported	Abnormal movements of jaw, tongue and hands, facial twitches - Diagnosed as withdrawal dyskinesias. Resolved after 3 weeks, following treatment with branched chain amino acids.	Not reported
4	Case Report	2004; Myers W; JAACAP	n=1 (female)	17	Delusional Disorder, Erotomanic type	10 mg	Yes	5 months	None	Lessening of delusional beliefs beginning at week 2 and maximal at week 8.	None	Not reported

Brown Obsessive-Compulsive Scale (CY-BOCS). Results showed significant improvement starting by week one in all the scales in the flexible dosing group over placebo.

Owen (Owen et al., 2008b) also enrolled 218 subjects, aged 6-17 years with behavioural problems associated with Autism in a fixed dose (aripiprazole 5, 10 or 15 mg/day or placebo) 8 week trial. The same outcome measures were used as in the flexible dose trial and significant improvements were observed in all measures for the 15 mg/day group starting by week one and for the 5 and 10 mg/day group by week two.

A placebo-controlled multicenter trial of aripiprazole (Werner et al., 2008) was completed in 296 patients aged 10-17 years with the diagnosis of bipolar I disorder, manic or mixed episode, with or without psychosis. The subjects were randomly assigned to receive aripiprazole 10 mg, 30 mg or placebo daily. On the Young Mania Rating Scale (YMRS) 50% of the 10 mg/day group were deemed responders (i.e.: more than 50% reduction in symptoms) while in the 30 mg/day group 56% of its subjects were responders. Both groups had significant reductions compared to placebo starting at week one.

Nine open-label prospective studies were found for aripiprazole in children and adolescents as well as several case reports, case series and retrospective chart reviews. The major diagnostic categories studied were Tourette Disorder, Aggression with varying underlying diagnosis, Bipolar Disorder and ADHD.

There were eight articles on the use of aripiprazole in tic disorders. Three were open label studies that looked at the use of aripiprazole in Tourette Disorder (Seo, Sung, Sea & Bai, 2008, Yoo, Kim & Kim, 2006 and Miranda & Castiglioli, 2007). Outcomes in all three studies were measured by the Yale Global Tic Severity Scale (YGTSS) at baseline and endpoint. In all three studies, significant reductions in the YGTSS were noted in participants aged 7-19 years with doses ranging between 2.5-20 mg/day. In two of the three studies CGI-I and CGI-S scales also showed significant reductions at endpoint. In addition to these open label studies there was a pilot study (Yoo et al., 2006), three case series (Murphy et al., 2005, Duane, 2006, Davies, Stern, Agrawal & Robertson, 2006) and one retrospective study (Budman et al., 2008) all finding clinical improvement with reasonable tolerability with use of aripiprazole in the treatment of tic disorders.

There were five articles on the use of aripiprazole in irritability and aggression. Two of the five studies were open-label trials looking at use of aripiprazole for irritability and aggression in either the PDD population or in patients with aggression regardless of underlying diagnosis. Stigler (Stigler et al., 2009) found significant improvement in 22 of 25 patients with PDD over a 14 week trial with a dose range of 2.5-15 mg in patients aged 5-17 years. Outcomes were based on the CGI-I scale and the ABC-I. Bastiaens (Bastiaens, 2008) found clinical improvement on the Overt Aggression Scale (OAS) in 20 subjects, aged 6-17 years with severe aggression regardless of diagnosis in after two months of treatment with aripiprazole with a mean dose of 4.5 +/- 2.3 mg/day. In this same trial 14 subjects completed a trial of ziprasidone 42.9 +/-18 mg/day with no significant differences noted between groups at baseline or after two months of treatment. There are also two retrospective reviews (Rugino & Janvier, 2005 and Valicenti-McDermott & Demb, 2006) and one case series (Stigler, Posey & McDougle, 2004) which looked at target symptoms of irritability and aggression in individuals with Pervasive Developmental Disorders (PDD), Development Disabilities (DD) or Bipolar Disorder diagnosis. Aripiprazole was found to be effective and tolerated, however an Autism Diagnosis comorbid with mental retardation (MR) predicted a worse outcome.

There were four articles in addition to the above mentioned RCTs on the use of aripiprazole in Bipolar Disorder or Bipolar Disorder Comorbid with Attention-Deficit/Hyperactivity Disorder (ADHD). Two of the four articles were open label studies. Biederman (Biederman et al., 2007) found a significant improvement of 30% reduction on the YMRS in 15 of 19 participants, aged 6-17 years on aripiprazole 9.4 mg/day monotherapy for 8 weeks. There was also a significant reduction in the Brief Psychiatric Rating Scale (BPRS) scores with the exception of the negative symptom profile and no improvement in symptoms of depression as measured by the Children's Depression Rating Scale (CDRS). Tramontina (Tramontina, Zeni, Pheula, de Souza & Rohde, 2007) treated ten children and adolescents aged 8-17 years with juvenile bipolar disorder comorbid with ADHD for 6 weeks. YMRS was used to assess severity of mania and the Swanson, Nolan and Pelham Scale–Version IV (SNAP-IV) was used to monitor ADHD. CGI-S was also utilized. Significant improvement was noted on all measures, including the SNAP-IV and most notably a 30% improvement on the YMRS in 70% of the subjects. Two retrospective case series (Barzman et al., 2004, Durkin, 2004) in Bipolar patients with or without comorbid ADHD supports the view that aripiprazole may be effective and well tolerated in this population.

One open label study (Findling et al., 2008b) enrolled youths aged 8-12 years with a diagnosis of ADHD into a 6 week trial. Outcome measures included the ADHD Rating Scale-IV (ARS-IV), CGI-I, CGAS, Conners' Continuous Performance Test II, Woodcock-Johnson subscales and the Stroop Color and Word Test. Fourteen youth were given

a mean aripiprazole dose of 6.7 mg/day which led to overall significant improvement from baseline on ARS-IV (both inattentive and hyperactive symptoms) and functional outcome (CGI-I). There were no improvements or deterioration noted on cognitive measures.

Woods (Woods et al., 2007) enrolled 15 participants with a mean age of 17.1 years meeting criteria for prodromal psychosis as identified by the Criteria of Prodromal Syndromes (COPS) in conjunction with the Structured Interview for Prodromal Syndromes (SIPS). Scale of Prodromal Symptoms (SOPS) was used to measure outcome and found significant reduction from baseline at eight weeks. Aripiprazole dose range was 5-30 mg/day in addition to the pre-enrollment prescribed antidepressant, mood stabilizer or stimulant. Thirteen subjects completed treatment with no subjects converting to psychosis over an 8 week period.

Safety Data

Atypical antipsychotics as a group are generally associated with a lower risk of extrapyramidal symptoms (EPS) as identified by tremor, dystonia, akathisia, cogwheel rigidity than typical antipsychotics but generally have significant weight gain, hyperglycemia and dyslipidemia as their adverse effects. Risperidone is associated with hyperprolactinemia and ziprasidone is associated with QTc interval prolongation on the electrocardiogram (EKG). The main side effects reported in the previously mentioned articles were sedation/somnolence in as high as 50-78% of subjects in some studies. This resolved somewhat with lower doses, slower dosage titration and time. The development of EPS and akathisia was notable in most studies (incidence range: 8-28%) although usually in the mild – moderate range of severity. One individual receiving fixed-dose aripiprazole 25 mg/day dropped out of a study due to dystonia (Findling et al., 2008c) and in one study, medications were used to treat akathisia. Though potentially problematic, and in the absence of comparative studies with other antipsychotics, these reactions do not appear to occur as frequently or with the same degree of severity as with high-potency first generation antipsychotic agents. There is uncertainty at this time regarding the potential for development of Tardive Dyskinesia (TD) with use of aripiprazole in the child and adolescent population. The adult literature shows both development of TD as well as resolution of TD with aripiprazole treatment. There are 4 case reports of potential Neuroleptic Malignant Syndrome (NMS) with aripiprazole. One patient was treated with dantrolene (Palakurthi, Parvin & Kaplan, 2007), two patients were treated with lorazepam (Hammerman, Lam & Caroff, 2006, Groff & Coffey, 2008) and one continued with aripiprazole therapy with resolution of symptoms (Strawn & Delgado, 2007).

Nausea, vomiting and gastrointestinal upset upset as well as headache symptoms were found to be common ($\geq$10%) which almost always resolved with time and could be avoided through slower titration (Findling et al., 2004, Findling, 2008d.)

Treatment with aripiprazole in all 4 RCTs (Findling et al., 2008a, Owen et al., 2008a, Owen et al., 2008b, Werner et al., 2008) did not result in significant increases in weight or Body Mass Index (BMI) even following a 26-week continuation phase in one RCT (Werner et al., 2008). In one open-label study, weight gain appeared to be associated with higher aripiprazole dosage and longer duration of treatment (Stigler et al., 2009). In a contrasting study, some patients lost significant amounts of weight when switched to aripiprazole from an alternate atypical antipsychotic. (Stigler et al., 2004) In the few studies (Biederman et al., 2007, Findling et al., 2008a, 2008b, Owen et al., 2008a, 2008b, Stigler et al., 2009, Werner et al., 2008) that specifically looked at metabolic parameters (cholesterol, fasting glucose, triglycerides), there were no significant changes identified. There is one case report (Logue, Gonzalez, Heligman, McLaughlin & Belcher, 2007) of severe hyperglycemia and one case report (Dhamija & Verma, 2008) of diabetic ketoacidosis in young children receiving aripiprazole.

Aripiprazole has no warnings pertaining to cardiac functioning (Bristol-Myers Squibb Canada, 2009) and may even decrease QTc interval (Goodnick, Jerry & Parra, 2002). Studies that evaluated prolactin levels (Findling et al., 2008b, Stigler et al., 2009, Werner et al., 2008) found that aripiprazole may reduce prolactin rather than causing hyperprolactinemia. One case report (Wahl & Ostroff, 2005) found addition of aripiprazole effective in reducing symptomatic hyperprolactinemia in a patient on an alternate antipsychotic medication.

Melhem (Melhem, Katz, Jameson, Shellenbarger & Akhtar, 2009) summarized 10 cases of overdose in which children presented with profound somnolence, ataxia, nausea and vomiting as well as EPS with varying doses. Overdose in adolescents with acute on chronic dosing was tolerated well with minor lethargy only. Children under the age of 5 years were particularly susceptible to prolonged neurological manifestations from relatively small ingestions. EKG findings from these cases support that aripiprazole has no impact on cardiac conduction.

Discussion and Recommendations

As is typical when reviewing pharmacotherapy evidence for this age group, there are very few RCTs with aripiprazole and given this consideration it should be considered as a second-line treatment option for limited indi-

cations. This medication is relatively new even in the adult population, and without the experience of time and the relative lack of excellent efficacy and safety data there is not enough evidence to support its use as a first-line medication in the child and adolescent population. The place in therapy of aripiprazole for this age group should be re-evaluated as new clinical trial data becomes available.

As always, in any child or adolescent in distress regardless of diagnosis, all other factors need to be part of the decision making regarding prescription of antipsychotics. Particularly in the prepubertal child and the individual with Autism with or without MR a thorough review of medical conditions, family dynamics and the community networks need to be undertaken. These factors should also be considered even when faced with a clear diagnosis of a mood and/or psychotic disorder.

With aripiprazole becoming available, the question is whether it should be used routinely in the pediatric population. From the available evidence, use of aripiprazole could be justified in Bipolar Disorder (manic or mixed episodes) and Schizophrenia, both of which are FDA approved indications in the child and adolescent population. We are not aware of any head-to-head studies directly comparing aripiprazole to other antipsychotic agents in this age group, and therefore cannot comment on comparative efficacy of aripiprazole to other antipsychotic agents. Aripiprazole appears to have efficacy in the treatment of Tourette disorder and tic disorders and further evidence via RCT would be most welcome. There is also some evidence showing efficacy for aggression and irritability regardless of underlying diagnosis. It is difficult to interpret these trials as the underlying diagnosis ranged from conduct disorder to Autism with or without MR. The difficulty is determining whether the decrease in aggression and irritability is due to treatment of the underlying disorder or due to sedation which could conceivably cause a paradoxical reaction in the population with comorbid Autism and MR.

There appear to be some potential advantages with use of aripiprazole. One is that EKG monitoring is not required as it has not been shown to have an impact on cardiac conduction even in overdose. A second advantage is the long half-life which facilitates once daily dosing. A significant incidence of sedation and somnolence secondary to aripiprazole therapy was noted in most trials. Although none of the trials specifically assessed changes in sleep parameters or use of concurrent hypnotic medications, it may be logical to administer this medication at bedtime to take advantage of its sedating effects. Another possible advantage is that aripiprazole can be used when individuals are particularly susceptible to hyperprolactinemia induced by other agents. Finally, the impact of aripiprazole treatment on metabolic parameters such as weight, fasting glucose and lipids does appear to be less than some of the other available atypical agents when used in children and adolescents.

With regard to aripiprazole dosing in children and adolescents, higher doses (30 mg/day) compared to lower doses (10 mg/day) had a greater side effect burden without clearly superior efficacy in the Schizophrenia and Bipolar RCTs (Findling et al., 2008a, Werner et al., 2008). Given that side effects appear to be reduced through slower upwards dosage titration, our recommendation is to follow the US Prescribing Information (Otsuka Pharmaceutical Co., 2008) for aripiprazole in children and adolescents. Their recommendation is a starting daily dose of 2 mg titrated to 5 mg/day after 2 days and then to the target dose of 10 mg/day after 2 additional days. Clinical evaluation will guide the clinician regarding increasing the dose past 10 mg/day. If this is done, further dose increases should occur in 5 mg increments.

With regards to dosing aripiprazole in Tourette and tic disorders and/or ADHD, there are no clear guidelines. Aripiprazole doses for treatment of these indications ranged from 6.7 to 14.5 mg/day in the available reports (Budman et al., 2008, Davies et al., 2006, Findling et al, 2008b, Miranda & Castiglioni, 2008, Murphy et al., 2005, Seo et al., 2008, Yoo et al., 2006, Yoo et al., 2007). A dose of 10 mg/day appears to be a reasonable target dose for these conditions for most children and adolescents. Given that younger children are more susceptible to the side effects of aripiprazole (EPS, nausea and vomiting and sedation/somnolence) they should be started at lower initial doses with a lower target dose. The same can be said for use of aripiprazole for treatment of irritability and aggression particularly in the population with PDD and/or MR.

Aripiprazole will be available in Canada in 2, 5, 10, 15, 20 and 30 mg tablets. Unfortunately, it will not be made available in formulations that may help promote medication administration in children who have difficulty swallowing oral tablets, such as an oral liquid or oral disintegrating tablets (ODT), both of which are available in the US. A short-acting formulation for intramuscular injection is also marketed in the US, but will not be available in Canada.

Since a number of patients taking aripiprazole developed EPS including dystonia, akathisia, tremor and cogwheel rigidity, it is our recommendation that patients be informed of the possibility of, and assessed routinely for these adverse effects. Dosage reduction of aripiprazole or introduction of either an anticholinergic agent or benzodiazepine may be required especially if clinical response

warrants ongoing use of aripiprazole. There is uncertainty regarding the relationship between aripiprazole and tardive dyskinesia so it is warranted and prudent to perform Abnormal Involuntary Movements Scale (AIMS) testing at baseline and periodically.

Despite evidence that aripiprazole is weight neutral and has minimal and insignificant impact on metabolic parameters in short term studies, our recommendation is to follow the 2004 Guidelines of the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes (Barrett et al., 2004) for baseline and follow-up monitoring of metabolic parameters.

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The authors have no financial relationships to disclose.

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