COLUMNS

PSYCHOPHARMACOLOGY

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

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Abstract

Objective: To review published literature regarding ziprasidone in child and adolescent psychiatry. **Methods:** A literature review was conducted using the MEDLine search term: 'ziprasidone' with limits: Human trials, English language, All Child (Age 0-18). Additional articles were identified from reference information and poster presentation data. **Results:** Two randomized controlled trials and five prospective open-label studies have been conducted with ziprasidone. Additionally, several case reports and case series are reviewed. Ziprasidone has a greater propensity for QT_c prolongation and risk for fatal arrhythmias compared to other atypical antipsychotics. Careful history taking regarding presence of congenital long QT syndrome is essential. Given limited clinical experience, electrocardiogram monitoring at baseline and following attainment of ziprasidone target dosage is warranted. No deaths from overdose have been reported in children and adolescents. Ziprasidone has a low potential for extrapyramidal side effects. Prolactin changes are small and transient. Lethargy, drowsiness, agitation and tachycardia were the most common adverse effects in randomized trials. Body weight changes with ziprasidone were comparable to placebo-treated subjects. **Conclusion:** At present, ziprasidone should be considered a second or third-line option for a limited set of conditions. A role may exist for ziprasidone in patients who have experienced significant metabolic adverse effects with other atypical antipsychotics.

Key words: ziprasidone, psychopharmacology, child, adolescent, review

Résumé

Objectif: Analyser la littérature sur l'utilisation de la ziprasidone en pédopsychiatrie. **Méthodologie:** Nous avons fait une recherche sur la ziprasidone dans MEDLine en affichant les limites suivantes: human trials, English language, all child (age 0-18). Des références et des affiches ont servi à trouver des articles supplémentaires. **Résultats:** La ziprasidone a fait l'objet de deux études aléatoires avec témoins et cinq études prospectives ouvertes. En outre, nous avons analysé plusieurs études de cas et séries de cas. Comparée à d'autres antipsychotiques atypiques, la ziprasidone présente davantage de risques d'allongement du QT_c et d'arythmie mortelle. Il est essentiel de vérifier au préalable la présence, chez les patients, d'un syndrome congénital du QT long. L'expérience clinique étant limitée, il convient de faire un électrocardiogramme en début d'étude et lorsque la dose cible est atteinte. Aucun enfant ni adolescent n'est décédé des suites d'une surdose. La ziprasidone a peu d'effets secondaires extra-pyramidaux. Les changements constatés dans la prolactine sont minimes et passagers. Les effets secondaires les plus courants signalés dans les études aléatoires sont la léthargie, la somnolence, l'agitation et la tachycardie. Les variations de poids des sujets traités sont comparables à celles des sujets témoins. **Conclusion:** La ziprasidone pourrait être une option de deuxième ou de troisième ligne dans un petit nombre de maladies. Elle pourrait remplacer les antipsychotiques atypiques chez les patients qui constatent les effets néfastes de ces produits sur leur métabolisme.

Mots clés: ziprasidone, psychopharmacologie, enfant, adolescent, vérifier

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Introduction

Ziprasidone (Zeldox®) became available in Canada in January 2008 (Pfizer Canada Inc., 2007). It is the 5th atypical antipsychotic approved by Health Canada (in addition to clozapine, risperidone, olanzapine, and quetiapine), and the 5th atypical approved by the United States (US) Food and Drug Administration (FDA) (as Geodon®) in 2001 (aripiprazole received FDA approval in 2002, but has not yet been approved for use by Health Canada). Despite widespread use of this class of medications, and official FDA-approved indications for both risperidone and aripiprazole in this age group, none of the available atypical antipsychotics have received an indication for use in patients under the age of 18 from Health Canada. Ziprasidone differs from other atypical antipsychotics available in Canada in that it is associated with less risk for

weight gain (Stigler et al., 2004) and appears to have less risk for metabolic syndrome. However, ziprasidone has been associated with an increased risk for QT_c interval prolongation and the potential for cardiac adverse events, including sudden death. Clinicians in the United States and other parts of the world have had experience with ziprasidone for the past several years, with a significant amount of literature being published regarding ziprasidone. This review will focus on the available evidence and clinical experience regarding the use of ziprasidone in child and adolescent psychiatry.

Pharmacology

In 23 youths aged 7-16, oral single-dose ziprasidone revealed linear pharmacokinetics, T_{max} (time to maximum serum concentration) range 5.0 to 5.5 hours, and $t_{1/2}$ (serum half-life) range 3.3 to 4.1 hours (Sallee et al., 2006). Ziprasidone blocks dopamine D_2 and serotonin 5-HT_{2A} receptors (antagonist) and was presumed to facilitate dopamine transmission via 5-HT_{1A} (agonist) in a study involving 24 youths aged 7-16 (Sallee et al., 2003). It has only moderate affinity for a_1-adrenoceptors and H_1 receptors and almost no affinity for the muscarinic receptor. Additionally, uniquely among the atypical antipsychotics, ziprasidone possesses both serotonin and norepinephrine reuptake inhibition properties (Seeger et al., 1995). Ziprasidone is available in 20, 40, 60 and 80 mg capsules. A formulation of ziprasidone 20 mg/mL for intramuscular injection that is used for treatment of acute agitation in schizophrenic patients is available in the US but is not available at present in Canada. Ziprasidone is recommended to be administered twice daily due to a relatively short elimination half-life. The absorption of ziprasidone is increased up to two-fold in the presence of food, and it should be taken with the morning and evening meals. In adults, approximately one-third of the absorbed ziprasidone is metabolized by cytochrome P450 (CYP) enzymes, with CYP 3A4 enzymes being the major contributor to oxidative metabolism. Approximately two-thirds of absorbed ziprasidone is cleared via reduction by aldehyde oxidase (Pfizer Canada Inc., 2007).

Efficacy Data

A review of the literature was conducted using MEDLine with the search term: 'ziprasidone', and limits set to: Human trials, English Language and All Child (Age 0-18). Additional articles were identified from reference information, and supplemental poster presentation data which was provided by the manufacturer.

Table 1 summarizes the published pediatric literature on ziprasidone. The studies are ranked by Level of Evidence (Centre for Evidence Based Medicine, 2001). Only two prospective, randomized controlled trials(RCT) were found for ziprasidone in children or adolescents (Sallee et al., 2000; DelBello et al., 2008). Sallee and colleagues (Sallee et al., 2000) studied 28 subjects with Tourette's syndrome or chronic tic disorder, aged 7-16 years (mean 11.5), randomized to either ziprasidone or placebo for 8 weeks. Significant improvement was seen as measured by the Yale Global Tic Severity Scale for Global Severity (p=0.016) and Total Tic score (p=0.008), and mean dose was 28.2 ± 9.6mg. DelBello and colleagues (DelBello et al., 2008) studied 238 subjects with bipolar I disorder, aged 10-17 years, randomized to either ziprasidone or placebo for 4 weeks. Mean age for the ziprasidone group was 13.6 years and the mean for the placebo group was 13.7. Although the overall mean dose was not specified, the mean dose in subjects greater than 45kg was 119mg/day. The ziprasidone group had 62% of the subjects achieving 50% reduction of the Young Mania Rating Scale (YMRS), while the placebo group had 35% achieving this reduction. Significant differences were observed in the estimated least squares (LS) mean changes from baseline to end point in the intent-to-treat (ITT) population in both the YMRS total score (p = 0.0005) and the Clinical Global Impression-Severity (CGI-S) score (p=0.0001).

Five open-label prospective studies exist for ziprasidone in children and adolescents; for autism (Malone et al., 2007; McDougle et al., 2002), bipolar disorder (Biederman et al., 2007; Findling et al., 2008) and bipolar disorder/schizophrenia/schizoaffective disorder (Versavel et al, 2005). McDougle and colleagues (McDougle et al., 2002) studied 12 subjects with autism, aged 11.6 ± 4.4, who received open-label treatment with ziprasidone. The mean dose was 59.2 ± 34.8mg/day (range 20-120mg/day) for a mean duration of 14.2 ±

Table 1. Review of Published Pediatric Literature on Ziprasidone

Level of Evidence*	Type of Report	Lead Author	Journal	Year	# of patients (n)	% male	Patient age (mean and/or range) (years)	Indication(s)	Dose	M
1b	Prospective RCT (DB, R, PC)	Sallee FR	JAACAP	2000	28	79	mean 11.5 (range 7-16)	TS/Tic Disorders	mean 28.2 mg/day (range 5-40 mg/day)	M
1b	Prospective RCT (DB, R, PC)	Delbello MP	APA Poster Presentation	2008	238	not specified	mean: Z pts: 13.6 years; Pl pts: 13.7 years (Range 10-17 years)	Bipolar I disorder	Range 40-160 mg/day split BID (overall mean dose not specified; mean dose in pts ≥ 45 kg: 119 mg/day)	M (l
2b	Prospective Open-Label trial	McDougle CJ	JAACAP	2002	12	83	11.6+/-4.4	Autism/PDD	mean 59 mg/day (range 20-120 mg/day)	N
2b	Prospective Open-Label trial	Versavel M	Neuropsychopharmacology	2005	63	67	Bipolar Disorder: mean 13.7 (range 10-17), psychotic disorders: mean 14.6 (range 11-17)	Bipolar/Schizophrenia/ Schizoaffective Disorder	Acute phase: Low Dose: 10-40 mg BID, High Dose: 20-80 mg BID. Continuation phase: Flexible dose 10- 80 mg BID	M w
2b	Prospective Open-Label (to assess QTc effects in children/ adolescents only)	Blair J	JAACAP	2005	20	80	7-18	TS/OCD/PDD	5-40 mg (split BID)	M
2b	Prospective open-label trial	Sallee FR	JAACAP	2006	24	79	range 7-16	TS/Tic Disorders	0.2-0.3 mg/kg (single dose)	M
2b	Prospective open-label trial	Beiderman J	Bipolar Disord	2007	21	81	mean 10.3 +/- 2.6	Bipolar I/Bipolar Disorder-NOS	56.2 +/- 34.4 mg/day (range 20-120 mg/day)	M (s pe
2b	Prospective open-label trial	Malone RP	JCAP	2007	12	80	14.5+/-1.8	Autism	mean 98 mg/day (range 20-160 mg/day)	M
2b	Prospective Open-Label trial (safety and tolerability extension of 4-week RCT (see Delbello MP 2008 above)	Findling RL	APA Poster Presentation	2008	162	56	13.3 (range 10-18)	Bipolar I disorder	Range 40-160 mg/day split BID (mean dose not specified; target dose: pts <45 kg = 60-80 mg/day; pts > 45 kg = 120-160 mg/day)	M (s st

onotherapy ?	Duration of treatment	Rating Scales used (Bold = Primary Endpoint)	Efficacy	Adverse Effects	QTc effects	Metabolic effects
onotherapy	8 weeks	**YGTSS Global Severity**, YGTSS Total Tic score, CGI-TS, CY-BOCS, Goetz videotape rating scale, AIMS	YGTSS Global severity improved Z 39% vs Pl 16% (p=0.016), YGTSS Total Tic score improved Z 35% vs. Pl 7% (p=0.008), CGI-TS improved 30% vs. Pl 16% (p=0.107 (NS)), CY-BOCS improved Z 26.5% vs. worsened Pl 5%, Goetz videotape rating scale improved Z 54% vs Pl 1% (p=0.043) though Z pts had higher baseline scores). Improvement noted to be "somewhat less than typically seen with haloperidol or pimozide."	1 case each of severe somnolence and akathisia (though did not D/C treatment), common transient mild sedation, no changes on AIMS testing noted, 1 male Z pt with mild gynecomastia	"no change in ECG parameters", though QTc interval not specifically addressed	Mean wt gain Z 0.7 +/- 1.5 mg vs. Pl 0.8 +/- 2.3 kg (NS). 5 males in Z group had prolactin elevation above upper limit of normal
onotherapy orazepam permitted)	4 weeks	CGI-S**, YMRS**	>50% decrease in YMRS score: Z 62% vs Pl 35% (observed cases). Mean change in YMRS score: Z -13.8 vs Pl -8.6. Mean change in CGI-S Z -1.43 vs. Pl -0.74	Discontinuations: Z 35% vs Pl 42%. For all adverse effect, shown value is % greater than placebo group: sedation (29%), somnolence (17%), dizziness (8%), nausea (7%), fatigue (7%), insomnia (6%), vomiting (6%), blurred vision (5%), muscle stiffness (5%). 1/149 pts had a dystonic reaction following excess dosing on day 2 of study.	mean baseline to peak increase QTc: Z 8.1 msec Pl - 2.5 msec. 1/149 Z pts had peak QTc of 478 msec.	Note: pts with BMI Z-scores greater than 2.0 or less than -1.65 were excluded. Mean weight change: Z -0.6 kg vs Pl -0.2 kg. No significant changes in fasting glucose, fasting insulin, cholesterol or triglycerides.
o for most pts	mean 14 weeks (6-30)	**CGI-I**	6/12 (50%) much improved or very much improved	No adverse cardiac events. 1 oral dyskinesia (possibly r/t stopping quetiapine), transient sedation	Only baseline EKGs done. No post-treatment EKGs	Many pts. had previous treatment with large weight gains. 5/11 lost weight, 1/11 gained weight. Mean weight change -2.65 kg
onotherapy for 3 eek acute phase only	3 week acute phase, followed by 26 week continuation trial	**BPRS,** CGI-I, **CGI-S**, **YMRS**	89% of patients entered 6 month continuation. 55% of those completed continuation phase. Y-MRS improved mean of 11.1 (low dose group) -14.9 (high dose group) in bipolar patients. BRPS improved mean of 9 (low dose group) - 14 (high dose group) in pts with psychotic disorder. Mean improvement in CGI-S ranged from 1.33 - 2.14.	Sedation (28.6%), somnolence (30.3%), nausea, headache dizziness, vomiting (incidence of all these appears dose-related). Suicidal ideation in 5 patients and self-harm (overdose) in 1 case (suicidal ideation was pre-existing in all cases).	mean baseline to peak increase of 3.6 msec (low-dose) and 10 msec (high-dose). No pts had QTc > 500 msec.	No clinically relevant changes in lipid or glucose metabolism occurred. Weight gain reported as an adverse effect in 8.9% (amount/mean population change not specified. Adjustment for growth not specified).
onotherapy	4.6 +/- 2 months	None	Not commented	No cardiac events	mean baseline to peak increase of 28 +/- 26 msec. 3/20 pts had QTc intervals >450 msec	Not commented
onotherapy	Single dose	None	N/A	2 pts with mild postural hypotension, transient sedation	mean increase of 7.3 msec . No pts with QTc>450 msec or >15% increase	transient increases in prolactin.
onotherapy timulants for ADHD ermitted)	8 weeks	**YMRS**, CDRS-R, BPRS, **CGI-I**	57% ≥ 30% decrease in YMRS, 33% ≥ 50% decrease in YMRS, 71% much improved or very much improved (CGI-I)	sedation (46%), headache (38%), GI problems (34%)	mean baseline to peak change of -3.1 msec. No pts with QTc > 460 msec	mean wt gain 0.6 kg +/- 2.5 kg. mean BMI increased by 0.2. No comment on how many pts treated with antipsychotics or mood stabilizers previously. Mean BMI z-score of cohort was elevated at baseline. Slight mean increase in prolactin, slight mean decrease in fasting glucose.
onotherapy	6 weeks	**CGI-I**, ABC, CPRS, TESS, AIMS	9/12 (75%) much improved or very much improved	1 pt with "red eyes" d/c'd study early, 2 dystonic reactions, sedation which decreased over time	mean baseline to peak increase of 14.7 +/- 6 msec. No pts with QTc >450 msec	5/11 gained weight, 6/11 lost weight (mean change not specified). Mean BMI decreased by 0.14, significant decrease in Tchol by 0.27 mmol/L, no change in LDL or HDL, prolactin increased by mean 3.4 ug/L
onotherapy timulants and Mood abilizers permitted)	Mean 105.7 days (up to 26 weeks)	AIMS, BARS, SAS, YMRS	YMRS: All pts: mean change from end of RCT to end of open-label extension -3.3 For pts receiving Pl in preceding RCT: mean change -8 For pts receiving Z in preceding RCT: mean change 0.3	40% with discontinuation, temporary discontinuation or dose reduction due to adverse effects. Sedation (26%), headache (22%), somnolence (22%), insomnia (14%), abdominal pain (9%), nausea(8%), nasal congestion (7%), dizziness (7%), vomiting (7%), fatigue (7%), stomach discomfort (6%). 5 pts with cardiovascular adverse effects, including tachycardia (2), palpitations (2), atrial fibrillation (1). Suicidal ideation in 6/162 pts, Homicidal ideation in 1/162 pts.	mean baseline to peak increase of 5.3 msec. 1/162 pts with QTc>460 msec (baseline QTc=433 msec, peak QTc=463 msec in this pt).	Mean wt gain 2.6 kg (corresponding mean height growth of 1.7 cm during study period). Mean BMI increase of 0.1. Mean waist circumference gain of 0.5 cm.

Level of Evidence*	Type of Report	Lead Author	Journal	Year	# of patients (n)	% male	Patient age (mean and/or range) (years)	Indication(s)	Dose	Mo
4	Naturalistic retrospective evaluation	Staller JA	JCAP	2004	49	35%	8-16	Acute Agitation/Psychosis	10-20 mg by IM injection (20 mg = 87% of doses)	Mo
4	Naturalistic retrospective evaluation	Khan SS	JCAP	2006	100 (50 pts on Z, 50 pts on olanzapine)	32% in Z group, 68% in olanzapine group	14.6 +/- 2.1	Acute Agitation/Aggression	Z 20 mg by IM injection or Olanzapine 5-10 mg by IM injection	No
4	Naturalistic retrospective evaluation	Barzman DH	JCAP	2007	59	66%	5-19 (73% ≥age 12)	Acute Agitation/Aggression	10-20 mg by IM injection (20 mg = 81% of doses)	No
4	Case series	Alessi NE	JAACAP	2003	3	67	15-17	Bipolar I (acute, maintenance)	20 mg BID, titrated up to 100-120 mg BID	No
4	Case series	Barnett MS	JCAP	2004	4	75%	7-16	Bipolar Disorder	40-80 mg/day (HS or split BID to TID)	No
4	Case series	Meighen KG	JCAP	2004	2	50%	15-17	Brief Psychotic Disorder	40-80 mg/day (split BID)	Mo
4	Case series	Hazaray R	JCAP	2004	3	100%	12-13	Acute Agitation/Aggression	10 mg by IM injection	No
4	Case Report	Goforth H	Aust NZ J Psych	2003	1	100	7	Autism	10 mg HS	No
4	Case Report	Jordan MP	JAACAP	2003	1	0	17	ODD, ADHD, DBD	60 mg TID (180 mg/day)	No
4	Case Report	Ramos AE	JAACAP	2003	1	100	11	PDD-NOS, mild MR, Tic disorder, Psychosis-NOS	20 mg twice daily	Mo
4	Case Report	Leibold J	Clin Ther	2004	1	100	15	Schizoaffective disorder	80 mg ONCE DAILY	No
4	Case Report	Yumru M	Prog Neurol Biol Psych	2006	1	100	18	OCD	40 mg twice daily	No

*** Level of Evidence - as per Oxford Centre Evidence Based Medicine document May 2001**
Z= Ziprasidone Pl=Placebo pt = patient wt= weight
DB= Double-Blind, R= Randomized PC= Placebo-controlled

Abbreviations of Rating Scales used
ABC: Aberrant Behavior Checklist
AIMS: Abnormal Involuntary Movement Scale
BARS: Behavior Activity Rating Scale
BPRS: Brief Psychiatric Rating Scale
CDRS-R: Children's Depression Rating Scale - Revised
CGI-I: Clinical Global Impresssion - Improvement
CGI-S: Clinical Global Impression - Severity
CPRS: Conners Parent Rating Scale
CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale
SAS: Simpson-Angus Scale
TESS: Treatment-Emergent Symptom Scale
YGTSS = Yale Global Tic Severity Scale
YMRS: Young Mania Rating Scale

8.3 weeks (range 6-30 weeks). Six of the 12 subjects responded (50%) as measured on the Clinical Global Impression-Improvement (CGI-I) rating of 2 “much improved” or 1 “very much improved”. Malone and colleagues (Malone et al., 2007) also studied 12 subjects with autism, mean age 14.5 ± 1.8 years, who received open-label ziprasidone over a 6-week period. The mean dose was 98.3 ± 40.4mg/day (range 20-160mg/day). Nine of 12 responded (75%) as measured on the CGI-I as “much improved” or “very much improved”. Although ziprasidone is marketed as an antipsychotic agent for adults, at present reports of ziprasidone for treatment of psychotic illness in children or adolescents is limited. The 2005 study by Versavel and colleagues (Versavel et al, 2005) had a majority composition of bipolar disorder patients, but it is the only known study of ziprasidone to include children and adolescents with schizophrenia or schizoaffective disorder. Following randomized enrollment and titration to low-dose (20-80 mg/day) or high dose (40-160 mg/day) ziprasidone, mean improvement on CGI-S and either YMRS or BPRS was noted in all groups, with patients with psychotic illness receiving high-dose ziprasidone experiencing the largest mean improvement.

In a prospective ziprasidone study in pedi-

onotherapy ?	Duration of treatment	Rating Scales used (Bold = Primary Endpoint)	Efficacy	Adverse Effects	QTc effects	Metabolic effects
onotherapy	Single dose in 98% of cases	None	2/49 patients continued to exhibit agitation and aggression during the ensuing 4 hour period	None reported	Not commented	Not commented
o	4.6 +/- 6.6 days	None	more Z pts received emergency medication for agitation/aggression. No difference in frequency of requiring restraint, or time in restraints	Sedation (16%), itching, nausea, joint stiffness (0.5% each)	No clinically relevant changes in QTc interval (details not provided)	Not commented
o	Single dose in 70% of cases	**CGI-I**, CGI-S, BARS	CGI-I: 81% "much improved" or "very much improved", BARS (goal score = 4) reduced from mean 6.5 +/- 0.7 at baseline to 3.1 +/- 1.3 at endpoint	drowsiness (60%), dizziness, epistaxis, muscle aches, confusion, increase in seizure frequency (1.3% each)	3/59 pts had baseline ECGs. No systematic follow-up	Not commented
o	Not specified	None	better concentration and socialization, auditory hallucinations stopped in 2/3 pts	sedation, lessening over 4 week period	None reported	No weight gain (3/3: previous antipsychotic therapy with weight gain)
o	4/4 pts on maintenance therapy	None	all 4 pts responders and on maintenance therapy	sedation, akathisia	Not commented	Not commented
onotherapy Page 1 of 2	1-3 months	None	Good response and return to baseline function in one pt	None	No increase in QTc interval	1/2 weight loss (0.4 kg) 1/2 weight gain (0.6 kg)
o	Multiple PRN administrations in 2/3 pts	None	De-escalation in all 3 cases, followed by somnolence	Somnolence (100%); 1/3 pts - syncope (single episode 1.5 hours post-dose)	Not systematically evaluated (pt's ECG normal following syncopal episode)	Not commented
o	8 months	**CGI-I**	"much improved", increased attention, reduced distractibility, modest increase in language function	None	Not commented	Not commented
o	unclear (~3-10 weeks)	None	Not commented	Galactorrhea	Not commented	Prolactin level 65.66 ("Normal" 1.4-24.2 ug/L). Prolactin normalized and symptoms stopped following discontinuation
onotherapy	6 weeks	None	Parents reported "significant improvement" at 4 weeks	Oculogyric crisis. Resolved within 30 minutes of diphenhydramine 50 mg administration	Not commented	Not commented
o	2 months	None	Not commented	NMS - WBC 15, CK 40,177, Temp 39.3'C, rigid, unresponsive. Symptoms resolved day 9 (was treated with IV dantrolene) and he survived.	None reported	Not commented
o	1 day	none	Not commented	Acute dystonia (torticollis, dystonic posture). Resolved with biperiden 5 mg treatment	Not commented	Not commented

atric bipolar disorder, Biederman and colleagues (Biederman et al., 2007) studied 21 youths with bipolar disorder (manic, mixed, or bipolar NOS) in an 8-week, open-label trial. The mean age was 10.3 ± 2.6 years (range 6-17 years) and the mean dose was 57.3 ± 33.9 mg/day. Twelve out of 21 responded (57%), and response was defined as CGI-I ≤2. Findling and colleagues (Findling et al., 2008) conducted an open-label extension of the 4-week RCT noted above (DelBello et al., 2008), and studied 162 youths with bipolar disorder for 26 weeks. The mean age was 13.3 years. Although the mean dose was not specified, for subjects less than 45kg, the target dose was 60-80mg/day. For subjects greater than 45kg, the target was 120-160mg/day. In all subjects, the mean change in the YMRS from the end of the RCT to end of open-label extension was -3.3. For subjects receiving placebo in the preceding RCT, and switched to ziprasidone, the mean change in the YMRS was –8. For subjects receiving ziprasidone in the preceding RCT, and who were continued on ziprasidone, the mean change in the YMRS was 0.3, which supports continuing long-term efficacy of ziprasidone.

The rest of the pediatric literature on ziprasidone consists of case reports, case series, and retrospective chart reviews. The Level 4 evidence includes case reports on autism (Goforth & Rao, 2003; Ramos et al., 2003), disruptive behavior disorders and ADHD (Jordan, 2003), bipolar disorder (Alessi, 2003; Barnett, 2004b), schizoaffective disorder (Leibold et al., 2004), psychosis (Meighen et al., 2004), and obsessive compulsive disorder (Yumru et al., 2006). Multiple case reports regarding intramuscular ziprasidone for acute agitation and aggression in youths have also been published (Barzman et al., 2007; Hazaray et al., 2004; Khan & Mican, 2006; Staller, 2004).

Safety Data

When compared to other atypical antipsychotics, ziprasidone has a greater propensity for QT_c prolongation and risk for fatal arrhythmias, which led to the FDA warning (Pfizer, 2007). In 20 youths treated with low-dose ziprasidone with a mean age of 13.2 ± 3.0 years, there were significant changes from baseline to peak values for QT_c interval, PR interval, and heart rate (Blair et al., 2005). Blair et al. found that the mean QT_c baseline to peak increase was 28 ± 26 milliseconds. In addition, 3 of 20 youths had peak QT_c ≥440 milliseconds, and one child had a prolongation of 114 milliseconds. However, a 4-week RCT in 238 subjects (DelBello et al., 2008) and its 26-week open-label extension study in 162 subjects (Findling et al., 2008) did not replicate Blair's findings (Blair et al., 2005). Nonetheless, more safety data is needed. Indeed, it is difficult to argue against Blair and colleagues, who opined that ziprasidone be used as a second or third-line medication in youths, and to obtain baseline and ongoing electrocardiograms when prescribing to children (Blair et al., 2005).

Cases of galactorrhea and elevated prolactin levels associated with ziprasidone in adolescent females have been reported (Jordan, 2003; Saldana & Delgado, 2007). For most trials reviewed in this article, no assessment of prolactin levels was performed. Of the trials that assessed prolactin levels, changes were transient and small in magnitude. Adult data with ziprasidone indicates changes in prolactin are usually transient, small in magnitude, and usually are observed mainly with higher doses of ziprasidone. (Pfizer Canada Inc., 2007). Despite having serotonin reuptake inhibition properties and the ability to transiently elevate prolactin, published reports in children and adolescents did not comment specifically on the issue of sexual dysfunction. Sexual side effects are listed as infrequent or rare in the manufacturer's product monograph. Neuroleptic malignant syndrome has been described in an adolescent taking ziprasidone (Leibold et al., 2004). One case reported on possible ziprasidone-induced mania in a 17 year-old female (Larson & Hauser, 2003), but another discussant opined that this may be due to the activating nature of ziprasidone, as many of his own patients are stimulated (Barnett, 2004a). Ziprasidone appears to have a low potential for extrapyramidal side effects, but one case report describes an 11 year-old male who exhibited an oculogyric crisis while taking ziprasidone (Ramos et al., 2003).

Not all of the safety data in children have been negative. In an 8-week placebo-controlled study in 28 children with Tourette's disorder aged 7-17, the mean change in weight from baseline to endpoint in the ziprasidone group (+0.7kg) was similar to the placebo group (+0.8kg) (Sallee et al., 2000). In an open-label trial with 12 children, mean age 11.6 (range 8-20 years), and mean duration of 14.2 weeks, the mean change in weight for the group was –2.6kg (McDougle et al., 2002). It appears that ziprasidone is associated with less weight gain when compared to other atypical antipsychotics (Stigler et al., 2004), possibly due to its lower affinity for the H_1 receptor. However, one case report was associated with an increase in weight (Jaworowski et al., 2004). Ziprasidone overdose has been described in nine youths, age ranging from 17 months to 17 years, and amount ingested ranging from 40mg to 2400mg. Lethargy, drowsiness, agitation, and tachycardia were the most common adverse effects, with no deaths from ziprasidone overdose (Antia et al., 2005).

Discussion and Recommendations

Given the dearth of randomized controlled trials with ziprasidone, its use in children and adolescents should only be considered a second or third-line option at best, for limited indications. We opine that there is not enough efficacy and safety data to warrant first-line treatment in youths at this time. With the recent approval of ziprasidone in Canada, clinicians and hospitals have been posing the question - should we use ziprasidone routinely in pediatric populations? From the evidence, use of ziprasidone could be justified in Tourette's disorder, tic disorders, autism, or bipolar disorder when they have failed at least one other "standard" therapy. Ziprasidone may also have a role if weight gain and/or significant metabolic adverse effects are present when prescribing an antipsychotic to a young person for psychosis or bipolar disorder.

Caution is of paramount importance when

prescribing ziprasidone to children, especially with regards to QT_c prolongation and risk for fatal arrhythmias, such as torsade de pointes (TdP). As noted above, one pediatric study observed a more pronounced increase in mean QTc interval compared to the increase observed in adult trials (Blair et al., 2005).

Concerns over QTc interval prolongation were the basis for the delay in ziprasidone reaching the Canadian market (Health Canada, 2008). The New Drug Submission for ziprasidone was originally filed with Health Canada in 1997, but a Notice of Non-compliance was issued in 2000 and 2004 due to safety concerns about the impact of QTc interval prolongation on cardiac adverse events. Following provision of dedicated studies regarding cardiac effects of QTc interval, a review by an external panel of experts, and inclusion in the product monograph of statements regarding FDA 5-year post-marketing adverse data showing small elevations in spontaneous reporting rates of cardiovascular adverse events compared to two other atypical antipsychotics, a Notice of Compliance was granted in August 2007.

Careful history taking is required to establish whether there is a family history of syncope or sudden unexplained death, as these may indicate the presence of congenital long QT syndrome. Ziprasidone is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction and uncompensated heart failure, and with any other drug with a contraindication or warning regarding demonstrated QT interval prolongation as one of its pharmacodynamic effects. The Zeldox® product monograph does not specifically mandate electrocardiogram (ECG) testing at baseline prior to initiating ziprasidone. Given the limited clinical experience with ziprasidone in children and adolescents, and that QTc interval effects may be more pronounced in this age group, ECG monitoring is warranted at baseline and following attainment of the target ziprasidone dosage.

Monitoring of QTc interval via ECG may have some pitfalls – there is a significant amount of intra-individual variability, and risk for cardiac arrhythmias does not appear to be linearly related to the extent of QTc prolongation. In addition, automated ECG reports most often use Bazett's formula for QT interval correction for heart rate, which tends to overcorrect the QTc interval at higher heart rates, and undercorrect QTc interval at lower heart rates. Use of the Fridericia formula, a regression based approach or an individualized correction may provide a more accurate determination of QTc interval (Piotrovsky, 2008).

In individual patients an absolute QTc interval of >500 msec or an increase of 60 msec from baseline is regarded as indicating an increased risk of TdP. However, TdP can occur with lower QTc values or changes (Haddad et al., 2002). Prescribers need to be alert to symptoms that could indicate cardiac arrhythmias in any patient prescribed antipsychotic medication. These include dizziness, palpitations and syncope. Such symptoms should prompt examination and an ECG. If a patient develops TdP, the responsible drug should be stopped and appropriate treatment for the arrhythmia initiated. Additional risk factors for TdP and/or sudden death include, but are not limited to, presence of an electrolyte imbalance, exceeding the recommended drug dosage, female sex, physical restraint, psychological stress and substance misuse (e.g. chronic alcohol and cocaine use).

Dosing of ziprasidone in the pediatric population is unclear based on the lack of randomized trials. No results were obtained from a search for an oral liquid formulation for ziprasidone in a popular online resource (International Journal of Pharmaceutical Compounding, 2008). Since this medication is available in capsules, typically requires twice daily dosing due to a short half-life, and the smallest available capsule size is 20 mg, a starting regimen of 20 mg orally twice daily with food seems appropriate for most patients. An adjustment of the daily dosage upwards by 20-40 mg increments at no more often than 2 day intervals, and as per patient tolerability is recommended. The maximum recommended adult dose of ziprasidone is 80 mg orally twice daily. A maximum pediatric dosage of ziprasidone has not been established (Pfizer Canada Inc., 2007). Suggested target ziprasidone doses by use and weight are listed in Table 2.

Table 2. Suggested Ziprasidone Target Dose in Children and Adolescents

By Use:

Tourette's Syndrome/Autism/Pervasive Developmental Disorders: 40 mg/day

Obsessive Compulsive Disorder: 40-80 mg/day (per body weight – see below)

Bipolar Disorder/Psychotic Disorders: 40-160 mg/day (per body weight – see below)

By Weight: (for uses with target doses above 40 mg/day)

Weight under 45 kg: 60-80 mg/day

Weight above 45 kg: 120-160 mg/day

In addition to careful evaluation of cardiovascular risks, baseline testing should be performed as listed in Table 3. Ongoing monitoring is recommended as per the 2004 Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes guidelines (Barrett et al., 2004).

Table 3. Recommended Baseline Monitoring Parameters for Ziprasidone Therapy in Children and Adolescents

Serum Potassium and Magnesium

Fasting Lipid Profile

Fasting blood glucose and Hemoglobin A1c

Height, Weight and Body Mass Index, Waist Circumference

Blood Pressure

Abnormal Involuntary Movements (AIMs) testing

Electrocardiogram (ECG) (obtain at baseline and at target ziprasidone dosage)

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References

Alessi, N. E. (2003). Ziprasidone in autism. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*(6), 622-623.

Antia, S. X., Sholevar, E. H. & Baron, D. A. (2005). Overdoses and ingestions of second-generation antipsychotics in children and adolescents. *Journal of Child and Adolescent Psychopharmacology, 15*(6), 970-985. doi:10.1089/cap.2005.15.970.

Barnett, M. S. (2004a). Ziprasidone and mania. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*(4), 380.

Barnett, M. S. (2004b). Ziprasidone monotherapy in pediatric bipolar disorder. *Journal of Child and Adolescent Psychopharmacology, 14*(3), 471-477. doi:10.1089/cap.2004.14.471.

Barrett, E., Blonde, L., Clement, S., Davis, J., Devlin, J., Kane, J. et al. (2004). Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*, 27, 596-601.

Barzman, D. H., DelBello, M. P., Forrester, J. J., Keck, P. E., Jr. & Strakowski, S. M. (2007). A retrospective chart review of intramuscular ziprasidone for agitation in children and adolescents on psychiatric units: Prospective studies are needed. *Journal of Child and Adolescent Psychopharmacology, 17*(4), 503-509. doi:10.1089/cap.2007.0124.

Biederman, J., Mick, E., Spencer, T., Dougherty, M., Aleardi, M. & Wozniak, J. (2007). A prospective open-label treatment trial of ziprasidone monotherapy in children and adolescents with bipolar disorder. *Bipolar Disorders, 9*(8), 888-894. doi:10.1111/j.1399-5618.2007.00450.x.

Blair, J., Scahill, L., State, M. & Martin, A. (2005). Electrocardiographic changes in children and adolescents treated with ziprasidone: A prospective study. *Journal of the American Academy of Child and Adolescent Psychiatry, 44*(1), 73-79.

Centre for Evidence Based Medicine. (2001). *Levels of evidence.* Retrieved July 16, 2008, from http://www.cebm.net/index.aspx?o=1025.

Delbello, M. P., Findling, R. L., Wang, P. P., Gundapaneni, B. & Versavel, M. (2008). Efficacy and Safety of Ziprasidone in Pediatric Bipolar Disorder. Poster presented at the Annual Meeting of the American Psychiatric Association, Washington, DC.

Findling, R. L., Delbello, M. P., Wang, P. P., Bachinsky, M., Gundapaneni, B. & Versavel, M. (2008). Long-term safety and tolerability of ziprasidone in children and adolescents with bipolar disorder. Poster presented at the Annual Meeting of the American Psychiatric Association, Washington, DC.

Goforth, H. W. & Rao, M. S. (2003). Improvement in behaviour and attention in an autistic patient treated with ziprasidone. *The Australian and New Zealand Journal of Psychiatry, 37*(6), 775-776.

Haddad, P. M., Anderson, I. M. (2002). Antipsychotic-Related QTc Prolongation, Torsade de Pointes and Sudden Death. *Drugs*, 62(11), 1649-1671.

Hazaray, E., Ehret, J., Posey, D. J., Petti, T. A. & McDougle, C. J. (2004). Intramuscular ziprasidone for acute agitation in adolescents. *Journal of Child and Adolescent Psychopharmacology, 14*(3), 464-470. doi:10.1089/cap.2004.14.464

Health Canada. *Summary Basis of Decision (SBD) – Zeldox® (ziprasidone hydrochloride monohydrate).* Ottawa, ON: Health Products and Food Branch, 2008. [cited 2008 Jul 31]. Available from http://205.193.93.51/NocWeb/viewnoce.jsp?noc=jrpf.

International Journal of Pharmaceutical Compounding (2008). *Formulations Related Articles.* [cited 2008 Aug 7]. Available from http://www.ijpc.com/editorial/SearchByTopic.cfm?CatID=9.

Jaworowski, S., Hauser, S., Mergui, J. & Hirsch, H. (2004). Ziprasidone and weight gain. *Clinical Neuropharmacology, 27*(2), 99-100.

Jordan, M. P. (2003). Ziprasidone-associated galactorrhea in a female teenager. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*(1), 4-5.

Khan, S. S. & Mican, L. M. (2006). A naturalistic evaluation of intramuscular ziprasidone versus intramuscular olanzapine for the management of acute agitation and aggression in children and adolescents. *Journal of Child and Adolescent Psychopharmacology, 16*(6), 671-677. doi:10.1089/cap.2006.16.671.

Kutcher, S., Brooks, S. J., Gardner, D. M., Honer, B., Kopala, L., Labelle, A. et al (2005). Expert Canadian consensus suggestions on the rational, clinical use

of ziprasidone in the treatment of schizophrenia and related psychotic disorders. *Neuropsychiatric Disease and Treatment. 1 (2)*, 89-108.

Larson, M. F. & Hauser, A. (2003). Possible ziprasidone-induced mania. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*(9), 1012; discussion 1012-3.

Leibold, J., Patel, V. & Hasan, R. A. (2004). Neuroleptic malignant syndrome associated with ziprasidone in an adolescent. *Clinical Therapeutics, 26*(7), 1105-1108.

Malone, R. P., Delaney, M. A., Hyman, S. B. & Cater, J. R. (2007). Ziprasidone in adolescents with autism: An open-label pilot study. *Journal of Child and Adolescent Psychopharmacology, 17*(6), 779-790. doi:10.1089/cap.2006.0126.

McDougle, C. J., Kem, D. L. & Posey, D. J. (2002). Case series: Use of ziprasidone for maladaptive symptoms in youths with autism. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*(8), 921-927.

Meighen, K. G., Shelton, H. M. & McDougle, C. J. (2004). Ziprasidone treatment of two adolescents with psychosis. *Journal of Child and Adolescent Psychopharmacology, 14*(1), 137-142. doi:10.1089/104454604773840580.

Pfizer. (2007). *Geodon® prescribing information.* Retrieved July 14, 2008, from http://www.pfizer.com/pfizer/download/uspi_geodon.pdf.

Pfizer Canada Inc. (2007). Zeldox® product monograph. Kirkland, QC: Pfizer Canada Inc. 2007. [cited 2008 Aug 7] Available from http://www.pfizer.ca/ourproducts/prescriptionpharmaceuticals/default.asp?s=1&id=42&doc=enmonograph.

Pfizer Canada Inc. (2008). *New schizophrenia treatment now available in Canada.* Retrieved July 8, 2008, from http://www.pfizer.ca/english/newsroom/press%20releases/default.asp?s=1&releaseID=258.

Piotrovsky V. Pharmacokinetic-Pharmacodynamic Modeling in the Data Analysis and Interpretation of Drug-induced QT/QTc Prolongation. *AAPS Journal*. 2005; 7(3): E609-E624. doi: 10.1208/aapsj070363.

Ramos, A. E., Shytle, R. D., Silver, A. A. & Sanberg, P. R. (2003). Ziprasidone-induced oculogyric crisis. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*(9), 1013-1014.

Saldana, S. N. & Delgado, S. V. (2007). Ziprasidone-associated galactorrhea in an adolescent female. *Journal of Child and Adolescent Psychopharmacology, 17*(2), 259-260. doi:10.1089/cap.2006.0053.

Sallee, F. R., Gilbert, D. L., Vinks, A. A., Miceli, J. J., Robarge, L. & Wilner, K. (2003). Pharmacodynamics of ziprasidone in children and adolescents: Impact on dopamine transmission. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*(8), 902-907. doi:10.1097/01.CHI.0000046897.27264.46.

Sallee, F. R., Kurlan, R., Goetz, C. G., Singer, H., Scahill, L., Law, G., et al. (2000). Ziprasidone treatment of children and adolescents with Tourette's syndrome: A pilot study. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(3), 292-299.

Sallee, F. R., Miceli, J. J., Tensfeldt, T., Robarge, L., Wilner, K. & Patel, N. C. (2006). Single-dose pharmacokinetics and safety of ziprasidone in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(6), 720-728. doi:10.1097/01.chi.0000215347.93902.3e.

Seeger, T. F., Seymour, P. A., Schmidt, A. W., Zorn, S. H., Schulz, D. W., Lebel, L. A., et al. (1995). Ziprasidone (CP-88,059): A new antipsychotic with combined dopamine and serotonin receptor antagonist activity. *The Journal of Pharmacology and Experimental Therapeutics, 275*(1), 101-113.

Staller, J. A. (2004). Intramuscular ziprasidone in youth: A retrospective chart review. *Journal of Child and Adolescent Psychopharmacology, 14*(4), 590-592. doi:10.1089/cap.2004.14.590.

Stigler, K. A., Potenza, M. N., Posey, D. J. & McDougle, C. J. (2004). Weight gain associated with atypical antipsychotic use in children and adolescents: Prevalence, clinical relevance, and management. *Paediatric Drugs, 6*(1), 33-44.

Versavel, M., Delbello, M. P., Ice, K., Kowatch, R., Keller, D. & Miceli, J. (2005). Ziprasidone Dosing Study in Pediatric Patients with Bipolar Disorder, Schizophrenia, or Schizoaffective Disorder. *Neuropsychopharmacology,* 30 (suppl 1): S122-3. [abstract].

Yumru, M., Savas, H. A., Selek, S. & Savas, E. (2006). Acute dystonia after initial doses of ziprasidone: A case report. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 30*(4), 745-747. doi:10.1016/j.pnpbp.2006.01.024.