REVIEW ARTICLE

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Benefit-Risk Assessment of Atypical Antipsychotics in the Treatment of Schizophrenia and Comorbid Disorders in Children and Adolescents

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Contents

Abstract

Evidence on the efficacy and safety of atypical antipsychotics in children and adolescents with schizophrenia is limited. The purpose of this review is to assess the published data on the use of atypical antipsychotics in children and adolescents with schizophrenia alone and with comorbid disorders, and to establish benefit-risk guidelines for clinicians.

Risperidone, olanzapine and clozapine were found to be effective in the treatment of aggression and mania. Risperidone, and possibly also olanzapine, may be the drugs of choice in children with comorbid tic disorders. Ziprasidone has some monoamine reuptake inhibition properties and may be administered as an augmenting agent in children and adolescents with schizophrenia and comorbid anxiety and mood disorders.

Compared with the typical antipsychotics, the atypical drugs seem to be more effective, better tolerated and lead to better patient adherence. Importantly, the atypical antipsychotics have a lower propensity to induce extrapyramidal symp-

toms and a potential (shown so far only in adults) to improve cognitive function and inhibit suicidal behaviour (especially clozapine). Yet, the adverse effects associated with these agents, especially weight gain, which may also have long-term effects, can lead to non-compliance in the young population. In children and adolescents receiving clozapine, olanzapine and quetiapine (but not ziprasidone, which does not have a pro-appetite effect), particularly those with obesity or a family history of diabetes mellitus, fasting blood glucose and lipid levels must be monitored frequently. Weight gain might be better controlled when the children and their parents are properly informed about this adverse effect and diet is regulated. Another major disadvantage of the atypical antipsychotics, especially risperidone, is their association with hyperprolactinaemia, which can lead to hypogonadism-induced osteoporosis, galactorrhoea, gynaecomastia, irregular menstruation and sexual dysfunction, all seen also with typical antipsychotics. Other atypical antipsychotics, namely olanzapine and ziprasidone, have been reported to be prolactin sparing in adults, but may not be completely devoid of hyperprolactinaemic effects in children and adolescents. Thus, prolactin levels should be assessed routinely in young patients treated with atypical antipsychotics. Further, children and adolescents with hyperprolactinaemia-related effects should be switched to a prolactin-sparing agent, such as quetiapine. All atypical antipsychotics may induce sedation and they are not devoid of extrapyramidal symptoms (especially risperidone). The use of typical antipsychotics has been limited to patients who are resistant to atypical antipsychotics, intolerant to their adverse effects, or require injections or depot preparations.

Further double-blind, placebo-controlled trials and long-term safety assessments are needed before definitive conclusions can be reached about the place of atypical antipsychotics in the therapeutic armamentarium of childhood-onset schizophrenia.

Data on the efficacy and safety of typical and atypical antipsychotic drugs in children and adolescents with schizophrenia are limited.[1-5] So far, research has been modest and the clinical community lacks clear evidence-based directions for treatment.[6]

In most cases, schizophrenia appears in late adolescence and early adulthood. Nevertheless, adult efficacy studies may not necessarily be relevant to adolescents, as exemplified by the experience with tricyclic antidepressants. Furthermore, childhood-onset schizophrenia (defined as the first appearance of psychosis by the age of 12 years) is a rare and severe form of the disorder, and the question of continuity with adult-onset schizophrenia is still open. Thus, until additional, well designed pharmacodynamic and pharmacokinetic studies are conducted, extreme caution is needed when generalising clinical practices from adults with schizophrenia to patients with childhood-onset schizophrenia. While most children and adolescents may require lower and gradually increasing medication dosages[6] to reduce the risk of adverse effects and improve tolerance and compliance, the opposite may be true for some patients with acute psychosis. Because schizophrenia in children is such a devastating illness, Armenteros and Mikhail[7] have argued that placebo-controlled drug trials may be ethical in this setting. They underscored the uniqueness of this age group, the significant weight of the placebo response in acute schizophrenia and the potentially misleading findings in comparisons against an active drug. However, the rarity of the disorder would require studies on a national mul-

Table I. Pharmacodynamic profile of the various antipsychotics[3,8,9]

Relative receptor binding affinities of the various antipsychotics						
target	risperidone	olanzapine	clozapine	quetiapine	ziprasidone	haloperidol
D_1	++	++	++	+	+	++
D_2	+++	++	+	+	+++	+++
D_3	++	++	+	+	++	+++
D_4	++	++	+++	−	+++	+++
5-HT_{1A}	+	−	+	+	+++	+
5-HT_{1D}	+	+	−	−	+++	−
5-HT_{2A}	++++	+++	+++	+	++++	++
5-HT_{2C}	+++	+++	++	−	++++	+
α_1[a]	+++	++	+++	++	++	++
α_2[a]	+++	+	+++	−	+	−
M_1	−	+++	+++	++	−	−
H_1	++	+++	+++	+++	++	+
5-HT transporter	−	−	−	−	+	−
NA transporter	−	−	+	+	+	−

a Adrenoceptor.

Affinity represented as: ++++ very high (Ki <1nM); +++ high (Ki = 1–10nM); ++ moderate (Ki = 11–100nM); + low (Ki = 101–1000nM); − negligible (Ki >1000nM); **D** = dopamine; **H** = histamine; **M** = muscarinic; **NA** = noradrenaline (norepinephrine); **Ki** = inhibition constant; **5-HT** = serotonin.

tisite or multinational basis and institutional review board approval of a placebo arm would be difficult to obtain.

The purpose of this review was to assess the published data on atypical antipsychotic therapies for children and adolescents with schizophrenia alone or with comorbid disorders or conditions and to establish benefit-risk guidelines for clinicians. The pharmacodynamic profile of these agents is shown in table I.

An English language Medline search (1974–January 2004) was conducted using the terms: 'risperidone', 'olanzapine', 'clozapine', 'quetiapine', 'ziprasidone', 'aripiprazole', 'children', 'adolescents', 'schizophrenia', 'aggression', 'mania', 'bipolar', 'depression', 'schizoaffective' and 'obsessive-compulsive', alone or in various combinations. Data appearing only in abstracts from scientific meetings or in journals written in languages other than English were excluded. Data from studies on children and adolescents with bipolar disorder were included because they contain useful information on adverse drug effects in this age group owing to the similar doses used.

1. Risperidone

Risperidone is a benzisoxazole derivative with high affinity for the serotonin 5-HT_{2A} and dopamine D_2receptors and a 5-HT_{2A}/D_2affinity ratio of 8 **:** 1. Risperidone also binds with moderate to high affinity to the α_1- and α_2-adrenoceptors, D_1, D_3 and D_4 receptors and histamine H_1 receptors[10] (table I).

1.1 Clinical Efficacy in Schizophrenia

The clinical benefit of risperidone in children and adolescents with schizophrenia has been examined so far in one double-blind, three open-label trials, one chart review and several case reports.[11-26] The total number of treated patients was 86 and the most common dose schedule was 4–6 mg/day (0.05–0.08 mg/kg/day). Most of the patients were resistant to previous therapy with various antipsychotics. A significant improvement was noted in 70 patients (81%). Sikich et al.,[26] in a double-blind, randomised, 8-week trial, assessed the efficacy of risperidone (n = 19), olanzapine (n = 16) and haloperidol (n = 15) in children aged 8–19 years with psychotic disorders. All treatments reduced symptoms signifi-

cantly with p-values of 0.0018 for both risperidone and olanzapine and 0.012 for haloperidol.

1.2 Effect on Comorbid Symptoms

1.2.1 Aggression

Using a rigorous, randomised, placebo-controlled multisite design, the Research Units on Pediatric Psychopharmacology Autism Network (RUPPAN)[27] treated 101 children (mean age 8.8 ± 2.7 years) with autistic disorder with risperidone (dose range 0.5–3.5 mg/day). The drug was found to be well tolerated and effective for the management of tantrums, aggression and self-injurious behaviour. These findings were supported by a smaller, 10-week, double-blind placebo-controlled study of 20 children and adolescents (mean age 9.2 years) with conduct disorder, which suggested that low doses of risperidone (0.75–1.5 mg/day) may be superior to placebo in reducing symptoms of aggression.[28] Risperidone was also found to be effective for the treatment of severe aggression in 38 adolescents[29] and 118 children[30] with disruptive behavioural disorders and sub-average intelligence. Similar results were noted in other studies as well.[31,32] Using a chart review of children and adolescents (aged 4–17 years), one study noted a reduction in aggression with low doses of risperidone in 28 of 28 patients with bipolar disorder, 25 of 28 patients with attention deficit/hyperactivity disorder and 10 of 28 patients with oppositional defiant disorder.[33] Another retrospective study reported good results in children and adolescents with treatment-resistant behavioural disorders (13 conduct disorder, five oppositional defiant disorder, two 'behavioural disorder, not otherwise specified').[34]

1.2.2 Mania

In the same chart-review study noted in the previous section, Frazier et al.[33] reported an 82% rate of improvement in manic symptoms among 28 risperidone-treated patients with bipolar disorder (and various co-morbidities). Fras and Major[35] reported a substantial response to risperidone in two adolescents with bipolar disorder. They suggested that the anti-aggressive effect of risperidone led to the symptomatic improvement.

1.2.3 Obsessive-Compulsive Symptoms

Reports exist of a therapeutic effect of adjunctive risperidone in refractory obsessive-compulsive disorder (OCD) in adults.[36] However, risperidone may also worsen OCD in adults.[37] Risperidone has not been thoroughly studied as an adjunctive treatment in children with OCD and the results so far are controversial. Fitzgerald et al.[38] observed an improved treatment response in four children with refractory OCD with risperidone augmentation, whereas Dryden-Edwards and Reiss[23] reported a risperidone-induced exacerbation of incapacitating OCD symptoms in a 13-year-old boy with schizophrenia and OCD. Accordingly, Hanna et al.[39] reported on the exacerbation of obsessive-compulsive symptoms in a 13-year-old boy and partial remission of obsessive-compulsive symptoms in an 18-year-old adolescent, both treated with risperidone augmentation. The authors also noted the appearance of separation anxiety during risperidone treatment in three children and adolescents. This issue was briefly reviewed by Toren et al.[40]

1.3 Adverse Effects

Risperidone treatment is generally well tolerated in children and adolescents.[12,14] Common adverse effects include mild sedation and weight gain (mean increase 4.85kg[11]), followed by extrapyramidal symptoms at higher dosages (mean 5.93 mg/kg[12]).

1.3.1 Fatigability/Sedation

The RUPPAN study[27] reported that 47% of the children in their risperidone group had mild fatigue and 12% had moderate fatigue compared with 27% in the placebo group reporting either mild or moderate fatigue. In most cases, the fatigue subsided by week 6. Aman et al.[31] noted a 51% sedation rate compared with 10% in the placebo group and Malone et al.,[41] in an open-label study, documented mild and transient sedation in 15 of 22 children and adolescents (68.2%). Gothelf and co-workers,[24] in an open-label comparative trial of risperidone, olanzapine and haloperidol, found that fatigability

occurred with all three drugs, though to a lesser extent with risperidone (11.8% for risperidone vs 42.1% for olanzapine and 71.4% for haloperidol). A similar pattern was observed for sedation and increased duration of sleep. Accordingly, McDougle et al.[42] reported transient sedation in 6 of 18 risperidone-treated children and adolescents (33%) with mental retardation and pervasive developmental disorder and Armenteros et al.[11] described mild sedation in eight of ten patients, which subsided after 2 weeks. In related studies, rates of transient sedation following risperidone use in this age group were 54.5% (6 of 11),[32] 31.3% (5 of 16),[12] and 7.9% (5 of 63).[34]

1.3.2 Weight Gain

Our literature search identified four studies specifically designed to evaluate weight gain in children and adolescents treated with risperidone.[43-46] Weight gain was also assessed as part of several other drug studies.[25,27,29,30,32,33] Kelly et al.[43] retrospectively divided 60 inpatient adolescents (aged 12–18 years) with various disorders into three groups: 6-months' treatment with risperidone (n = 18); 6-months' treatment with typical antipsychotics (n = 23); and, no antipsychotic medication (n = 19). Mean weight gain was found to be significantly higher in the risperidone group (8.64kg) compared with the other two groups (3.03kg and –1.04kg, respectively), with no difference between sexes. The fact that the control group actually lost weight may indicate that the weight gain in the risperidone group was unrelated to hospitalisation *per se*. In another retrospective study, Martin et al.[44] evaluated 37 inpatients with various disorders treated with risperidone for 6 consecutive months and 33 psychiatric inpatients with no atypical antipsychotic exposure. Risperidone treatment was associated with clinically significant weight gain (mean 7.0kg) in 78% of patients, as opposed to a 24% rate of weight gain in the comparison group (mean 0.7kg). The risk of weight gain was not associated with risperidone dosage, baseline weight, or demographic characteristics. Hellings et al.[45] evaluated weight gain in a double-blind crossover study of risperidone versus placebo for the treatment of aggressive behaviour in 11 children and adolescents and eight adults with mental retardation. Weight gain during the active acute drug phase and open maintenance phase of risperidone treatment was significantly greater than during the placebo phases preceding them. Mean weight gain by age over approximately 1 year was 8.2kg (range 2.7–17.7kg) in patients aged 8–12 years (n = 5), 8.4kg (range 3.6–15.5kg) in patients aged 13–16 years, and 5.4kg (range 0–9.5 kg) in adults. Further, Ratzoni et al.[46] conducted a prospective study of 50 adolescent inpatients with schizophrenia (n = 46), schizoaffective disorder (n = 2) and conduct disorder (n = 2) who were treated with risperidone, olanzapine or haloperidol. By week 12, the risperidone group showed a significant weight gain (3.9 ± 4.8kg) compared with the haloperidol group (although not with the olanzapine group). Extreme weight gain (>7% of baseline) occurred in nine adolescents (42.9%) treated with risperidone (and 90.5% treated with olanzapine). In this study, the most prominent weight increase occurred during the first month of risperidone therapy, whereas in the study by Hellings et al.[45] weight gain was first evident within 2 months of treatment and progressed steadily thereafter at an average of 1.2 kg/month, without reaching a plateau during the 6 months of follow-up. Martin et al.[44] also reported a steady increase over the same duration. Ratzoni et al.[46] reported that the risk rises in thinner individuals, in males, in females with low concern about gaining weight and in adolescents with obese fathers.

1.3.3 Hyperglycaemia

Saito and Kafantaris[47] described two patients aged 13 and 17 years who developed diabetes mellitus after combined treatment with risperidone and valproate semisodium (divalproex) [a third case of diabetes mellitus following combined quetiapine-valproate semisodium treatment was presented in the same article]. Both patients were of African-American origin, obese and had a family history of diabetes mellitus. The authors discussed the possible role of risperidone in triggering the diabetes in these cases.

1.3.4 Hyperlipidaemia

Martin and L'Ecuyer[48] assessed changes in the levels of triglycerides and cholesterol and in the weight of 22 risperidone-treated youths. There were no significant changes in serum triglyceride or cholesterol levels, although the weight gain was clinically significant. Weight gain was significantly correlated with the initial triglyceride level.

1.3.5 Extrapyramidal Symptoms

In the RUPPAN study,[27] although parents or primary care-takers reported tremor in a few of the children treated with risperidone, weekly neurological assessments showed no abnormalities. In a three-arm study, Gothelf et al.[24] found extrapyramidal symptoms in 4 of 17 risperidone-treated children and adolescents (23.5%) compared with 3 of 19 children (15.8%) in the olanzapine group and 4 of 7 (57.1%) in the haloperidol group. Mandoki[17] reported extrapyramidal symptoms in six of ten children prescribed risperidone for schizophrenia (dose range 2–6 mg/day), of whom four required anticholinergic agents to treat the extrapyramidal symptoms and Armenteros et al.,[11] in a study of ten children (dose range 4–10 mg/day) found dystonia (n = 2), parkinsonism (n = 3), and mild orofacial dyskinesia (n = 1). Grcevich et al.[12] treated 16 schizophrenic adolescents with risperidone (mean 5.93 mg/day, range 2–10 mg/day) and three developed extrapyramidal symptoms. Two were treated with anticholinergic agents and one responded to a dose reduction in risperidone. In a study of 22 autistic children and one adolescent (mean age 7.1 years), Malone et al.[41] found that 2 of the 13 children (15.4%) treated for 6 months developed mild, reversible dyskinesias when risperidone was discontinued. None developed dyskinesias during treatment. Aman et al.,[31] in a placebo-controlled study of 118 children with disruptive behaviour, found no significant between-group difference in the severity of extrapyramidal symptoms. Finally, Conner et al.[49] prospectively evaluated 95 patients over a 3-month period, including 19 children (aged <13 years) and 76 adolescents (13–21 years) with diverse diagnoses. Forty-eight percent of these patients were treated with typical antipsychotics, 45% with atypical antipsychotics (30 risperidone and 16 olanzapine) and 7% with combined typical-atypical antipsychotics. Seventeen subjects had antipsychotic-induced dyskinesia, including four (13%) who were receiving risperidone (mean dose 3.75 ± 3.1 mg/day, range 1–8 mg/day) [none were receiving olanzapine]. In addition, 5.9% of the subjects had probable tardive dyskinesia, but the study did not detail their management. The emergence of tardive dyskinesia was also described in a case report of an adolescent girl with a mood disorder treated with risperidone[50] and Rowan and Malone[51] noted a 'Tourette-like syndrome' in a child upon abrupt withdrawal of risperidone.

1.3.6 Hyperprolactinaemia

Significant elevations in serum prolactin levels have been reported after single doses of risperidone in healthy adults and during long-term therapy in schizophrenic adults.[52] Aman et al.,[31] in a placebo-controlled trial of young patients, reported a significantly higher mean serum prolactin level in the risperidone group compared with baseline (6.7 ± 3.6–29 ± 22.3 ng/mL; 11% of children) than in the placebo group (6.4 ± 5.0–8.2 ± 7.6 ng/mL; 2% of children). In a study of 11 children, Frazier et al.[33] reported elevated prolactin levels in nine patients (82%) [mean 32.8 ± 12.05 ng/mL, normal range 0–15 ng/mL]. No baseline prolactin levels were available for comparison. Amenorrhoea and galactorrhoea developed in one girl and delayed ejaculation in one boy. Risperidone-associated galactorrhoea was also reported in one teenage boy[53] and three adolescent girls.[17] Cohen and Biederman[52] described four boys (aged 6–11 years) with bipolar disorder or psychoses who had risperidone-induced elevations in serum prolactin levels (57.5–129 ng/mL), but no clinical symptoms. All were successfully treated with cabergoline, a highly selective D_2 receptor agonist. Others suggested that instead of treating the hyperprolactinaemia, the patients should be gradually switched to another atypical antipsychotic.[53] Accordingly, Masi et al.[54] reported an increase in mean serum prolactin levels from 9.77 ± 3.94 mg/mL to 25.92 ± 13.9 ng/mL, with no accompanying clinical signs, in 25 autistic

children (aged 3.9–7 years) after 10 weeks of risperidone treatment (mean dose 0.52 mg/day; dose range 0.25–0.90 mg/day).

1.3.7 Elevated Liver Enzymes

The RUPPAN study[27] noted that serum glutamic-oxaloacetic transaminase level was more than twice the normal upper limit at 8 weeks after onset of risperidone treatment in one child in the treatment group and one child in the control group (out of a total of 101 subjects); one child in the placebo group also had an elevated serum glutamic-pyruvic transaminase level. Kumra et al.[55] reported liver enzyme abnormalities and fatty liver infiltration in 2 of 13 boys with schizophrenia after 6 months of risperidone treatment (6 and 8 mg/day). They suggested an association between accelerated weight gain, long treatment duration, male gender and hepatotoxicity. Landau and Martin[56] described a 13-year-old mildly obese girl with disruptive behaviour disorder and psychotic symptoms who had elevated liver enzymes and fatty infiltration only 3 days after starting risperidone 0.5 mg/day. They assumed these findings had already been present before treatment, but no baseline liver function tests were available for comparison. No changes in liver function after risperidone treatment were reported by Szighety et al.[57] in a chart review of 38 youths (age 5–17 years) with various psychiatric disorders (mean dose 2.5 mg/day, mean treatment duration 15.2 months) or by Malone et al.[41] in 22 children.

1.3.8 Depression

Mandoki[17] reported the appearance of dysthymia in four of ten children within 3 months of starting risperidone. Two of them met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)[58] criteria for major depression and required antidepressant treatment. In another study, major depression was noted in 17 of 58 (29.3%) risperidone-treated adolescents and adults (aged 13–65 years) with Tourette's syndrome, and dysphoria in 13 patients (22.4%).[59] By contrast, in a comparison study, Gothelf et al.[24] found that only 2 of 17 risperidone-treated patients with schizophrenia (11.8%) experienced depression compared with 5 of 19 (26.3%) olanzapine-treated patients and 5 of 7 (71.4%) haloperidol-treated patients.

1.3.9 Orthostatic Hypotension

Orthostatic hypotension is a very common adverse effect of risperidone treatment in adults.[60] However, no significant changes in blood pressure or heart rate measurements have been reported in risperidone-treated children and adolescents.[29,30]

1.3.10 Other Adverse Effects

A small number of case reports describe the appearance of risperidone-induced neuroleptic malignant syndrome in children and adolescents.[61,62] Enuresis was reported in 2 of 16 children and adolescents with schizophrenia treated with risperidone 2–10 mg/day in the trial of Grcevich et al.[12] and in five children (age 10–14 years) treated with risperidone combined with selective serotonin reuptake inhibitors in the study of Took and Buck.[63] The enuresis was treated with behavioural intervention.[12] Edelman[22] described risperidone-induced neutropenia in a 15-year-old boy with a history of neutropenia secondary to various typical antipsychotics. Posey et al.[64] treated two very young autistic children (29 months, 23 months) with risperidone, one of whom developed dose-related persistent tachycardia and corrected QT (QTc) interval prolongation. Drooling has also been observed in some children and adolescents treated with risperidone[27,29,33] and may be related to a difficulty in swallowing as part of iatrogenic extrapyramidal symptoms.

2. Olanzapine

Olanzapine is a thienobenzodiazepine derivative with moderate to high affinity for the 5-HT_{2A}, 5-HT_{2C}, muscarinic, H_1, α_1-, D_1, D_2 and D_4 receptors[10] (table I).

2.1 Clinical Efficacy in Schizophrenia

Our literature search identified one double-blind study, eight open-label studies, one retrospective study and a few case reports that deal with olanzapine treatment of schizophrenia in children and adolescents, for a total of 112 patients.[2,26,65-73]

Four studies specified an age of onset (<12 years).[66,68,71,72] Most of the patients were resistant to previous therapies with typical antipsychotics and some also to risperidone or clozapine. Eighty patients showed improvement with olanzapine 5–20 mg/day (0.15–0.41 mg/kg/day).

2.2 Effect on Comorbid Symptoms

2.2.1 Acute Mania

Frazier et al.[74] conducted an 8-week open-label study of olanzapine 2.5–20 mg/day monotherapy in 23 children and adolescents (aged 5–14 years) with a diagnosis of bipolar disorder (manic, mixed or hypomanic). A significant improvement in manic symptoms was noted. Soutullo et al.[75] studied seven adolescents with manic or mixed bipolar disorder who received olanzapine as an adjunct to their current manic therapy (lithium, valproic acid, and carbamazepine; six patients) or alone (one patient). All seven improved. Similar findings were reported by Chang and Ketter[76] and by Khouzam and El-Gabalawi.[77]

2.2.2 Aggression

Two open-label trials in children, adolescents and adults reported that olanzapine (mean final dose 7.8 mg/day) was associated with a reduction in self-injurious behaviour and aggression.[78,79] An improvement in aggression was also noted in three of five hospitalised children (aged 6–11 years) treated with olanzapine for various disorders (bipolar disorder, schizophrenia, attention deficit/hyperactivity disorder).[65] Sheikh and Ahmed[80] found olanzapine 7.5–10 mg/day to be effective in the treatment of aggression and acute agitation in a 10-year-old girl with attention deficit/hyperactivity disorder and oppositional defiant disorder.

2.2.3 Anorexia Nervosa

Mehler et al.[81] reported a beneficial effect of olanzapine in the treatment of five adolescent girls (aged 12–17 years) with chronic anorexia nervosa. Although the pattern of weekly weight gain did not change, anorexic symptoms were reduced together with the patients' 'paranoid ideation' of body image.

2.2.4 Obsessive-Compulsive Disorder

There are reports describing the effectiveness of olanzapine in the treatment of OCD in adults.[82] However, in younger patients, OCD may also be triggered by olanzapine treatment if given over the long term. De Haan et al.[83] evaluated 113 young patients (mean age 22.4 years) with schizophrenia treated with olanzapine or risperidone and noted significantly more severe OCD in the olanzapine group.

2.3 Adverse Effects

Kumra et al.[66] found 8 weeks of olanzapine 12.5–20 mg/day to be moderately well tolerated by eight children and adolescents (aged 6–18 years) with schizophrenia. Sedation is one of the most common and significant adverse effects of olanzapine treatment in this age group.[68] Other adverse effects include increased appetite (average weight gain 3.4 ± 4.1kg[66]), gastrointestinal symptoms, headache, insomnia, difficulty concentrating, liver function abnormalities, sustained tachycardia and agitation. These findings are generally consistent with reports in adults, although akathisia might be more common in adolescents.[65]

2.3.1 Sedation

Sedation was reported in six of the eight patients in the study by Kumra et al.[66] and in five of seven patients (aged 12–17 years) with bipolar disorder treated by Soutullo et al.[75] In the latter study, the sedation resolved within 2 days in one patient despite continued treatment at the same dose and was mild in another patient. Of the five children (aged 6–11 years) treated by Krishnamoorthy and King[65] with olanzapine 2.5–10 mg/day, three (60%) developed transient sedation and one patient experienced morning sedation for 2 days following each dose increase. Sholevar et al.[68] evaluated 15 hospitalised children and adolescents (aged 6–13 years) with schizophrenia who received olanzapine 2.5–5 mg/day. Eleven (73%) experienced transient sedation in the first 48 hours which lasted 1–4 days. Accordingly, sedation was noted in 9 of 16 patients in an open-label study by Findling et al.[69] and in two of three

patients (aged 14–17 years; dose 10 mg/day) described by Haapasalo-Pesu and Saarijarvi.[70]

2.3.2 Weight Gain

Our literature search identified three studies specifically designed to evaluate weight gain in children and adolescents treated with olanzapine.[46,66,84] In addition, Theisen et al.[85] assessed weight gain during antipsychotic treatment in general (mainly typical antipsychotics, clozapine and olanzapine) and others assessed olanzapine-induced weight gain in young patients as part of other factors.[65,66,78,80,86,87] In the first specific study, Gothelf et al.[84] prospectively evaluated 20 adolescents with schizophrenia, ten receiving olanzapine and ten haloperidol. Body mass index (BMI) significantly increased after only 4 weeks in the olanzapine group and was attributed to an increase in caloric intake without an accompanying change in dietary composition. Olanzapine had no significant effect on resting energy expenditure. Ratzoni et al.[46] prospectively evaluated weight gain in 50 inpatient adolescents with schizophrenia (n = 46), schizoaffective disorder (n = 2) and conduct disorder (n = 2) treated with olanzapine (mean age 17.0 years), risperidone or haloperidol. By week 12, there was a significant increase in weight in the olanzapine group (7.2 ± 6.3 kg). Olanzapine led to significantly more gain in weight and in BMI than haloperidol and a greater gain in BMI than risperidone. The most prominent increases occurred during the first month of treatment. An extreme weight gain (>7% of baseline weight) was noted in 19 of the 21 (90.5%) patients treated with olanzapine, compared with 9 of 21 (42.9%) in the risperidone group and only 1 of 8 (12.5%) patients in the haloperidol group. Kumra et al.,[66] in their open-label study, reported an average weight gain of 3.4 ± 4.1kg in eight children and adolescents with schizophrenia treated for 8 weeks with olanzapine 12.5–20 mg/day, compared with a 5.0 ± 6.0kg gain in 15 age-matched patients treated for 6 weeks with clozapine 100–600 mg/day (this difference was not statistically significant). In another prospective, open-label trial, Findling et al.[69] treated 16 adolescents with schizophrenia and noted a weight gain of 1.1–13.4kg over 8 weeks (mean 1.0 ± 0.5 kg/week). Haapasalo-Pesu and Saarijarvi[70] described a remarkable weight gain in three adolescents treated with olanzapine 10 mg/day: the 14-year-old boy gained 20kg in 4 months; the 17-year-old boy gained 25kg in 5 months; and the 14-year-old girl gained 15kg in 4 months. Two studies noted that weight loss could be induced in adult patients taking olanzapine by the addition of reboxetine[88] or metformin.[89]

2.3.3 Hyperglycaemia

There have been several reports of olanzapine-induced hyperglycaemia and diabetic ketoacidosis in adults.[90] In younger patients, Domon and Webber[86] described the development of both hyperglycaemia and hypertriglyceridaemia in a 15-year-old boy receiving olanzapine 20 mg/day (plus valproic acid) which resolved with discontinuation of olanzapine alone, without dietary changes or use of insulin or oral hypoglycaemic agents. The patient was already obese at baseline and his weight increased by 11kg in 4 months of treatment. He also had a family history of type II diabetes. Selva and Scott[87] described a 16-year-old girl who gained 15kg during olanzapine 10–15 mg/day, followed by the development of diabetic ketoacidosis complicated by acute tubular necrosis. The ketoacidosis resolved after discontinuation of olanzapine and the addition of insulin treatment for 17 days. The patient had a strong family history of type II diabetes mellitus.

2.3.4 Hyperlipidaemia

Hypertriglyceridaemia does not appear to be a common adverse event associated with olanzapine treatment.[86] Nguyen and Murphy[91] described a case of hypertriglyceridaemia and hypercholesterolaemia associated with weight gain (10kg over several months) in a 10-year-old boy taking olanzapine 5 mg/day. The triglycerides and cholesterol blood levels returned to normal after discontinuation of the drug.

2.3.5 Extrapyramidal Symptoms

Adults treated with olanzapine have a minimal risk of parkinsonism and akathisia, and dystonia is rare.[92] Our literature search revealed only a few

reports of extrapyramidal symptoms in olanzapine-treated children and adolescents. Akathisia occurred in two of the five children (40%) treated (mean dose 7.5 mg/day) by Krishnamoorthy and King[65] and in two of the 23 children with bipolar disorder included in the open-label study (2.5–20 mg/day) of Frazier et al.[74] Kumra et al.[66] reported minimal abnormal movement and extrapyramidal symptoms and no change in total score on the Abnormal Involuntary Movement Scale or the Simpson-Angus Scale in eight children and adolescents treated with olanzapine 12.5–20 mg/day. Conner et al.[49] evaluated 95 children and adolescents treated with various antipsychotic agents. Of the 16 given olanzapine, none had extrapyramidal symptoms. The incidence of olanzapine-induced tardive dyskinesia is also minimal in adults[93] and in some cases olanzapine was even used to treat tardive dyskinesia in this age group.[94] In one study, transient tardive dyskinesia was noted in two of eight children receiving olanzapine. The dyskinesia resolved spontaneously and may have been related to withdrawal from a previous medication.[95]

Woods et al.[96] reviewed the spontaneous adverse events database of the US FDA and found that in olanzapine-treated patients, the risk of extrapyramidal symptoms was similar across all stages of development and the risk of tardive dyskinesia was similar in adolescents and adults.

2.3.6 Hyperprolactinaemia

Hyperprolactinaemia is a rare adverse effect of olanzapine in adults. Crawford et al.[97] reported no differences in prolactin levels between adults treated for 6 weeks with olanzapine or placebo. However, in a study of 23 children and adolescents (aged 5–14 years) with bipolar disorder treated with olanzapine 2.5–20 mg/day, Frazier et al.[74] noted a statistically significant mean change from baseline to endpoint in prolactin levels (0.4 ± 0.5 mmol/L, p = 0.002); endpoint values were higher than normal in 28.6% of patients and one child had a level more than twice the normal concentration (2.18 mmol/L). All patients were asymptomatic. Likewise, Alfaro et al.[98] found significantly elevated prolactin levels (27.6 ± 14.2 ng/mL) in nine children and adolescents after 6 weeks of olanzapine treatment (mean 17.5 ± 2.8 mg/day) compared with baseline (10.4 ± 4.4 ng/mL). Correlations between plasma olanzapine concentrations and serum prolactin levels were significant (r = 0.80, p = 0.002). One girl with a prolactin level of 70 ng/mL exhibited galactorrhoea.

2.3.7 Other Adverse Effects

Aurby et al.[99] reported that, like risperidone, olanzapine can cause mania and hypomania in adults. London[100] described a 16-year-old boy with pervasive developmental disorder who presented with an acute manic state 2–3 weeks after initiation of olanzapine 7.5 mg/day. The manic symptoms gradually subsided after the drug was discontinued.[74] Several case reports describe neuroleptic malignant syndrome in olanzapine-treated adults,[101] although there is only one such case in an 18-year-old boy with schizophrenia who was treated with risperidone for 8 days followed by olanzapine for 5 days.[102] In addition, asymptomatic transient olanzapine-induced liver enzyme elevations have been reported in both adults[103]and children and adolescents (aged 6–18 years) with schizophrenia.[66]

3. Clozapine

Clozapine is a dibenzodiazepine derivative with a moderate to high affinity for the 5-HT_{2A}, α_1-, muscarinic, H_1 and D_4 receptors and a mild to moderate affinity for the D_1, D_2 and D_3 receptors, as well as low affinity for the noradrenaline (norepinephrine) transporter[10] (table I).

3.1 Clinical Efficacy in Schizophrenia

There are no published efficacy studies of clozapine in children and adolescents after 1997. In the only double-blind study,[104] 21 children and adolescents (mean age 14.0 ± 2.3 years) with childhood-onset schizophrenia (beginning before age 12 years) resistant to typical antipsychotics were randomly assigned to receive clozapine (mean final dose 176 ± 149 mg/day) or haloperidol (16 ± 8 mg/day) for 6 weeks. Clozapine yielded greater benefit for both positive and negative symptoms on all

measures of psychosis. Schultz et al.[105] suggested that lower plasma adrenaline (epinephrine) levels prior to initiation of clozapine therapy may predict a better clinical response.

In addition, our literature search identified 11 open-label clozapine-efficacy studies and 11 case series, for a total of 270 children and adolescents with schizophrenia. An improvement was noted in approximately 85%.[105-127] Five studies[115-117,119,127] evaluating 89 participants reported a mean age of onset in the range of 9.4–14.9 years.

3.2 Effect on Comorbid Symptoms

3.2.1 Aggression

Chalasani et al.[128] reviewed the charts of six children and adolescents (mean age 15 ± 1 years) with schizophrenia and severe aggressive behaviour resistant to various typical and atypical antipsychotics who were treated with clozapine 50–150 mg/day. A clinically significant improvement in aggressive behaviours was noted. Chen et al.[129] described one 17-year-old boy with autism who was successfully treated with clozapine 275 mg/day for increased aggressive behaviour.

3.2.2 Bipolar Disorder

Some case reports describe a possible anti-manic effect of clozapine in children and adolescents. Clozapine induced a good response when administered together with clomipramine and lithium (five cases)[130] or lithium alone (300 mg/day clozapine + 1350 mg/day lithium; n = 1)[131] in teenage boys with bipolar disorder and long-term refractoriness to conventional treatments. The latter patient showed an apparent improvement in both mood and psychotic symptoms and there was no recurrence of the manic or psychotic symptoms throughout the 9-month follow-up period. Similar results were noted when clozapine was administered alone to five treatment-resistant patients (aged 8–15 years) at a mean dose of 128 mg/day (3.2 mg/kg/day, range 75–225 mg/day). Turpeinen[126] treated a child with severe depression with clozapine. The depressive symptoms responded well, but treatment had to be discontinued because of adverse effects.

3.2.3 Obsessive-Compulsive Symptoms

The emergence of obsessive-compulsive symptoms during clozapine treatment has been reported in adults.[108,132] Mozes et al.[111] described a 10-year-old schizophrenic child with an appearance of occasional bouts of stereotype movements (presumably obsessive-compulsive symptoms), which started after a few weeks of taking clozapine and improved spontaneously thereafter.

3.3 Adverse Effects

Clozapine has significant adverse effects that often limit its use and require intensive monitoring. In children and adolescents, these include neutropenia (neutrophil count <1500/mm^3), leukopenia, tachycardia, seizures, drowsiness/sedation, weight gain, hypersalivation, elevated liver enzyme levels, transient eosinophilia and stupor.

3.3.1 Sedation

Sedation is significantly more common with clozapine than with haloperidol,[104] occurring at a rate of 90% in the studies of Kumra et al.[104] and Turetz et al.[127] It was also frequently noted in several other trials and case reports.[111,124]

3.3.2 Weight Gain

Theisen et al.,[85] in a study of weight gain in 151 inpatient adolescents and young adults (mean age 19.5 years), of whom 109 presented with schizophrenia spectrum disorders, noted a prevalence rate of 64% for obesity in the patients treated with clozapine (n = 69), 56% in the patients treated with olanzapine or risperidone (n = 20), and 30% in the patients treated with typical antipsychotics (n = 20). Chalasani et al.[128] reported a significant increase in bodyweight (0.46–11.8kg) in six children and adolescents (mean age 15 ± 1 years) with schizophrenia and aggressive behaviour treated with clozapine 50–150 mg/day for an average of 52 days. In another study of 12 clozapine-treated adolescents (mean dose 366.7 mg/day), mean weight gain was 6.5kg after 6 weeks.[116] Similar findings were noted by Kowatch et al.[124] In the double-blind clozapine-haloperidol study of Kumra et al.,[104] mean weight gain after 6 weeks was 0.9 ± 6.47kg in the clozapine

group (n = 10) and 0.94 ± 2.89kg in the haloperidol group (n = 11); this difference was not statistically significant.

3.3.3 Cardiovascular Effects

In studies of clozapine-treated children and adolescents, tachycardia was noted by Kumra et al.[104] in seven of ten patients; by Blanz and Schmidt[110] in 37 of 57 patients; and by Frazier et al.[115] in 3 of 11 patients. One non-blind study of 36 adolescents reported tachycardia in two patients and ECG alterations in one patient.[117] Others reported clozapine-induced orthostatic hypotension in 20 of 57 patients[110] and in 2 of 11 adolescents with schizophrenia.[115] A similar finding was described in a single case report of a 13-year-old boy.[130]

3.3.4 Agranulocytosis

Kumra et al.[104] noted the occurrence of neutropenia in five patients receiving clozapine treatment; in three of them, the neutrophil count normalised spontaneously, but the other two patients had to discontinue treatment at week 4. Remschmidt et al.[117] also reported neutropenia (2900 and 2500 neutrophils/mm^3) in 2 of their 36 clozapine-treated adolescents (mean dose 330 mg/day), which was managed by drug withdrawal. Granulocytopenia was reported by Turpeinen[126] in 5 of 36 children and adolescents within the first 3 months of low-dose (75–300 mg/day) clozapine treatment. Finally, Reitzle et al.[133] described a 12-year-old boy with schizophrenia who developed agranulocytosis following 15 weeks of clozapine treatment. Blood count improved with administration of granulocyte colony-stimulating factor. Clozapine-associated leukopenia necessitates close white blood count monitoring.[134] It may occur in similar rates in adults and children and adolescents, but further large-scale studies are needed to verify this.

3.3.5 Seizures/EEG Alterations

Findling et al.[134] suggested that children and adolescents may be at higher risk than adults of seizures/EEG abnormalities during clozapine treatment. EEG monitoring should be performed prior to treatment initiation, after the optimal dose is reached and in the event of an acute behavioural change during treatment. Two of the ten clozapine-treated subjects participating in the double-blind clozapine-haloperidol trial of Kumra et al.[104] showed seizure activity without pre-existing epilepsy. In the first, myoclonus and a tonic-clonic seizure occurred at a dose of 400 mg/day. A dose reduction and the addition of anticonvulsant agents prevented further seizures, but the EEG continued to show epileptiform spikes. Therefore, clozapine treatment was discontinued. The other patient had tonic-clonic seizures at a dose of 275 mg/day and discontinued treatment.[104] Turpeinen[126] reported seizures in 1 of their 36 young patients.

3.3.6 Drooling

Drooling was noted in seven of the ten children and adolescents in the clozapine group in the study of Kumra et al.[104] (and in 2 of the 11 patients in the haloperidol group), in addition to 8 of the 11 schizophrenic adolescents (73%) studied by Frazier et al.[115] and 9 of the 11 schizophrenic patients (82%) treated by Turetz et al.[127] Lower rates were reported by Blanz and Schmidt[110] (20 of 57; 35%) and Levkovitch et al.[118] (1 of 13; 7.7%). One clozapine-treated adolescent with various disorders[126] had nocturnal hypersalivation. The mechanism underlying clozapine-induced hypersalivation is unclear, but it may be related to the drug's agonistic effect at the relevant cholinergic receptors.[135]

3.3.7 Extrapyramidal Symptoms

One of the advantages of clozapine treatment is the rarity of secondary extrapyramidal symptoms and tardive dyskinesia.[136] Extrapyramidal symptoms occurred in 5 of the 36 schizophrenic children and adolescents treated by Remschmidt et al.,[117] and in 9 of the 57 treated by Blanz and Schmidt.[110] Kumra et al.[95] noted tardive dyskinesia in 1 of 12 children and adolescents treated with clozapine for 2 years. This patient was also receiving concomitant fluoxetine and had already shown evidence of mild tardive dyskinesia during an earlier admission. Clozapine may even have some anti-tardive dyskinesia properties.[123,127,137]

3.3.8 Other Adverse Effects

Frazier et al.[115] found transient eosinophilia (lasting 4 weeks) in 1 of the 11 clozapine-treated (mean dose 370 mg/day) schizophrenic patients (aged 12–18 years) and enuresis in six patients. In another report, a 17-year-old patient treated with clozapine for refractory psychotic symptoms developed acute pancreatitis.[138] The patient also had eosinophilia at the time of an earlier (first) episode of pancreatitis, suggesting a possible allergic aetiology. Other findings in this age group include elevated liver enzyme levels,[104,117] hyperglycaemia in 11 clozapine-treated (100–1000 mg/day) adolescents (aged 13–18 years)[139] and neuroleptic malignant syndrome without rigidity in one 17-year-old boy (dose 200 mg/day), which resulted in residual brain injury.[140] A retrospective study of the incidence of diabetes, hyperlipidaemia and hypertension among 3013 schizophrenic adults receiving clozapine (n = 552) and various other typical antipsychotics (n = 2461) yielded no significant difference. However, when the young group (aged 20–34 years) was analysed separately, clozapine was associated with a significantly higher incidence rate of diabetes mellitus and hyperlipidaemia.[141] Another study reported hypertriglyceridaemia in adults receiving clozapine treatment.[142] Alfaro et al.[98] evaluated prolactin levels in 30 clozapine-treated children and adolescents with schizophrenia or 'psychotic disorder, not otherwise specified' with onset of psychosis before age 13 years and found no significant difference in mean level from baseline (9.6 ± 4.8 ng/mL) to the end of 6 weeks of treatment (11.6 ± 4.8 ng/mL).

4. Quetiapine

Quetiapine is a dibenzothiazepine compound with moderate to low affinity for D_1, D_2, 5-HT_{2A} and 5-HT_{1A} receptors, and low affinity for the noradrenaline transporter (table I).

4.1 Clinical Efficacy

A few open-label studies[143,144] and some case reports[145-147] describe the use of quetiapine in the treatment of schizophrenia or other psychotic disorders in children and adolescents. Of the 22 patients described overall, 21 showed improvement. The largest study was that of Shaw et al.[144] in 15 adolescents (aged 13–17 years, mean 15.1) with psychotic disorders (of whom, five had schizophrenia and four had schizoaffective disorder) treated with quetiapine 300–800 mg/day (mean 467 mg/day, 6.5 mg/kg/day). All improved.

4.2 Effect on Comorbid Symptoms

4.2.1 Aggression

Bardenstein et al.[148] evaluated 12 adolescents with conduct disorder treated with quetiapine 25–50 mg/day and noted an improvement in aggression and social functioning in all subjects.

4.2.2 Mania

DelBello et al.[149] conducted a double blind placebo-controlled trial of adjunctive quetiapine (mean dose 432 mg/day) in 30 adolescents with bipolar disorder, 47% of whom had psychotic symptoms. Quetiapine-treated adolescents showed a greater reduction in manic symptoms than those treated with valproate alone. A few case reports also describe the efficacy of quetiapine for manic symptoms in children and adolescents with bipolar disorder.[144,150]

4.3 Adverse Effects

Some patients complained of sedation and headache, in addition to weight gain (mean 3.4kg[144]), extrapyramidal symptoms and agitation. There was also a tendency towards decreased levels of levothyroxine sodium without increased levels of thyrotropin alfa.[144]

4.3.1 Sedation

Sedation was noted by Shaw et al.[144] in 4 of 15 psychotic adolescents treated with quetiapine and by Martin and co-workers[151] in three of six children with autistic disorder, leading to drug discontinuation in these patients.

4.3.2 Weight Gain

McConville et al.[143] reported weight gain (mean gain 1.5kg) in six of ten quetiapine-treated adolescents. Domon and Cargile[152] described a 17-year-

old boy with quetiapine-associated hyperglycaemia and hypertriglyceridaemia, and Saito and Kafantaris[47] described an obese, African-American, 16-year-old girl with a positive family history who developed diabetes mellitus after combined treatment with quetiapine and valproate semisodium.

4.3.3 Extrapyramidal Symptoms

Martin et al.[151] reported akathisia in one of their patients. By contrast, McConville et al.[143] found that extrapyramidal symptoms actually improved during treatment with quetiapine (400mg twice daily for 3 weeks) in ten of ten adolescents.

4.3.4 Cardiovascular Effects

Nine of the ten patients evaluated by McConville et al.[143] developed mild or moderate postural tachycardia due to quetiapine use. However, none had QT prolongation. In addition, Martin et al.[151] reported an epileptic episode in a 9-year-old boy with autistic disorder treated with quetiapine 350 mg/day.

4.3.5 Other Adverse Effects

No changes in prolactin levels were noted in one 8-week open-label trial in 15 children and adolescents with psychotic symptoms.[144]

5. Ziprasidone

Ziprasidone has a high 5-HT_{2A}/D_2 affinity ratio of 11 : 1.[153] *In vitro* studies have also indicated a high affinity of ziprasidone for 5-HT_{1A} (agonistic affinity) and 5-HT_{2C} receptors, and moderate affinity for α_1-adrenoceptors and H_1 receptors. Affinity for the muscarinic receptors is negligible but moderate for serotonin and noradrenaline transporters[5] (table I). The clinical relevance of the moderate inhibitory effect of ziprasidone on serotonin and norepinephrine reuptake for the treatment of depressive and anxiety symptoms in children and adolescents merits further investigation.[154,155]

5.1 Clinical Efficacy in Schizophrenia and Comorbid Symptoms

Patel et al.[156] conducted a retrospective analysis of 13 children and adolescents (aged 13–18 years) treated with ziprasidone (mean dose 52.3 ± 25.2 mg/day). Diagnoses included schizophrenia in four, major depressive disorder with psychotic symptoms in four, bipolar disorder in three, and 'psychotic disorder, not otherwise specified' in two. Improvement was noted in ten patients. In another open-label study 12 patients (mean age, 11.62 ± 4.38 years; range 8–20 years) with autism-spectrum disorders received ziprasidone (mean daily dose, 59.23 ± 34.76mg; range 20–120mg) for at least 6 weeks (mean duration 14.15 ± 8.29 weeks, range 6–30 weeks),[157] with improvements in symptoms of aggression, agitation, and irritability. Two of these patients had a comorbid bipolar I disorder, and they did less well. Our literature search did not identify other studies assessing ziprasidone treatment of schizophrenia in children and adolescents.

5.2 Adverse Effects

Sallee et al.[158] randomised 28 patients (aged 7–17 years) with Tourette's syndrome to receive ziprasidone (mean dose 28.2 ± 9.6 mg/day; 0.64 ± 0.24 mg/kg/day) or placebo for 56 days. The most common adverse effect was mild transient sedation. One patient had severe somnolence, which necessitated a dose reduction. Another patient developed akathisia, which resolved with dose reduction. No other clinically significant extrapyramidal symptoms were noted. There was no between-group difference in mean change in bodyweight. Five boys in the ziprasidone group experienced mild transient hyperprolactinaemia, which normalised by the end of the study. One boy had mild gynaecomastia. Ziprasidone has been noted to cause QTc prolongation in adults and is contraindicated in patients receiving other agents that increase the QT interval. Sallee et al.[158] did not find any clinically significant changes in ECG parameters in the ziprasidone group, but Patel et al.[156] noted a 19 msec increase in one of their four patients (out of a total of 13) who underwent follow-up ECGs during ziprasidone treatment. Labellarte et al.[159] noted that the FDA called for pre-treatment screening, careful selection of psychotropic and/or somatic medication combinations and recognition of QTc prolongation in electrocardiographic tracings during treatment with ziprasidone.

The most common adverse effects in the latter study were akathisia and agitation, followed by gastrointestinal upset, sedation and dizziness. In the open-label study of 12 children and adults with autism conducted by McDougle et al.,[157] ziprasidone was generally well tolerated, with four patients having no adverse effects and the other eight showing mostly sedation. No cardiovascular adverse effects were observed. The mean change in bodyweight for the group was –2.9 ± 6.26kg (range –17.5 to +3kg; five patients lost weight). Jordan[160] described a 17-year-old girl with ziprasidone-associated galactorrhoea (serum prolactin level 65.66 ng/mL; laboratory reference value 1.39–24.20 ng/mL).

6. Aripiprazole

Aripiprazole, the first of a new class of atypical antipsychotics, is a high-affinity partial agonist for D_2 and 5-HT_{1A} receptors, has low affinity for histaminergic, cholinergic, muscarinic and α_1 receptors and is an antagonist for 5-HT_{2A} and 5-HT_{2C} receptors.[161] A case report[162] of a 34-year-old man with Asperger disorder suggests a beneficial effect of aripiprazole 10 mg/day on the core and comorbid symptoms of the disorder. Further, Lindsey et al.[163] reported on a 16-year-old girl with mental retardation and schizophrenia who developed severe extrapyramidal symptoms on aripiprazole treatment (10 mg/day).

7. Conclusions

The last 30 years have witnessed very little research on the efficacy and safety of antipsychotic drugs in children and adolescents with schizophrenia, despite the devastating nature of this illness in the young. No placebo-controlled trials with the well established atypical antipsychotics have been conducted in children and adolescents. One placebo-controlled study examined the efficacy of the atypical antipsychotic amisulpride, which is available only in France.[164] It is of note that even with typical antipsychotics, only two placebo-controlled trials have been conducted.[165,166] In addition, there are two double-blind parallel-group studies, one comparing clozapine and haloperidol[104] and the other comparing risperidone, olanzapine and haloperidol.[26] Open-label studies are also scarce.

Comparisons among the studies are difficult, because some limited their patient selection to individuals with childhood-onset schizophrenia (onset before age 12 years), whereas others may have included patients in whom the first episode of schizophrenia occurred in late adolescence. Furthermore, while investigators concentrated mainly on inpatients, many users of antipsychotic drugs are outpatients. Recently, several studies specifically designed to evaluate adverse effects of antipsychotic drugs in children and adolescents, especially weight gain[43-46,69] and extrapyramidal symptoms,[49] have been published, but long-term safety assessments are still needed. The medical consequences of comorbid weight gain in childhood are manifold and it may also lead to serious conditions in adulthood, such as cardiovascular illness, hypertension, diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia and fatty liver (table II). Furthermore, obesity in adolescents has adverse psychosocial consequences and may interfere with treatment compliance.

Despite the limited efficacy data on atypical antipsychotics, their use for the treatment of children and adolescents with schizophrenia has increased in recent years. Compared with typical antipsychotics, the atypical drugs are more effective in some dimensions of schizophrenia, better tolerated and lead to better patient adherence. For these reasons, the use of typical antipsychotics should be limited to patients who are resistant to atypical antipsychotics, intolerant to their adverse effects, or require injections or depot preparations. Importantly, the atypical antipsychotics have a lower propensity to induce extrapyramidal symptoms and a potential (shown so far only in adults) to improve cognitive function and inhibit aggressive and suicidal behaviour (especially clozapine[167]). Risperidone may alleviate (but also aggravate) obsessive-compulsive symptoms when added to selective serotonin reuptake inhibitors in children with OCD alone or combined with schizophrenia. In addition, both risperidone and olanzap-

Table II. Occurrence of adverse effects of antipsychotic treatments in children and adolescents

Drug	EPS	Hyperprolactinaemia	Weight gain	Sedation	Others
Haloperidol	+++	++	±	+	TD, NMS
Risperidone	+	+++	++	+	Depression
Olanzapine	±	±	+++	++	Hyperlipidaemia, hyperglycaemia
Clozapine	−	−	+++	+++	Agranulocytosis, seizures, hyperlipidaemia, hyperglycaemia
Quetiapine	−	−	+	+++	
Ziprasidone	±	±	−	++	QTc prolongation

EPS = extrapyramidal symptoms; **NMS** = neuroleptic malignant syndrome; **QTc** = corrected QT interval; **TD** = tardive dyskinesia; **−** = absent; ± = most probably rare; **+** = infrequent; **++** = low frequency; **+++** = high frequency.

ine possess some mood-stabilising effect,[74,154] at least in adults, and may be combined with established mood stabilisers in bipolar and schizoaffective patients. Risperidone[168] and possibly olanzapine[169] may be the drugs of choice in patients with comorbid tic disorders. Ziprasidone has some monoamine reuptake inhibition properties and may be administered as an augmenting agent in children and adolescents with schizophrenia and comorbid anxiety and mood disorders.[19] Clozapine, despite its marked efficacy, should not be used as a first-line medication because of the risk of agranulocytosis (about 1%), though it seems to be the drug of choice in patients with resistant schizophrenia.[111,127]

A major disadvantage of the atypical antipsychotics, especially risperidone, is their association with hyperprolactinaemia, which can lead to hypogonadism-induced osteoporosis,[170] galactorrhoea, gynaecomastia, irregular menstruation and sexual dysfunction, all adverse effects also seen with typical antipsychotics. Other atypical antipsychotics, namely olanzapine and ziprasidone, have recently been reported to be prolactin-sparing in adults, but they may not be completely devoid of hyperprolactinaemic effects in children and adolescents.[74,98,158,160] Thus, prolactin levels should be assessed routinely in young patients on maintenance therapy with these agents. Clinicians should try to avoid the addition of prolactin-suppressing agents, which can aggravate the psychosis. Children and adolescents who show hyperprolactinaemia-related effects should be switched to a known prolactin-sparing agent, such as quetiapine. Clozapine, olanzapine and, to some extent also risperidone, are associated with increased appetite and marked weight gain[25,46,71,72] and, together with quetiapine, with significant sedation. Ziprasidone apparently has no pro-appetite effect, but there is insufficient data about this adverse effect in young patients. Other concerns of atypical antipsychotic use include hyperlipidaemia, hyperglycaemia, prolonged QTc interval, and as noted previously, agranulocytosis (clozapine).

Thus, from a clinical point of view, there is no 'ideal' antipsychotic. Because of the lack of long-term studies and relatively small study samples, there is insufficient evidence on which to base practice guidelines and parameters. Clinicians must consider the different benefit-risk profiles (including costs) when prescribing treatment. At this stage, bodyweight should be monitored in all treated patients. Baseline ECG is recommended before starting patients on ziprasidone. Lipid and glucose monitoring is needed in patients receiving clozapine or olanzapine, prolactin measurements in patients receiving risperidone, eye examinations for quetiapine and white blood cell counts for clozapine. Follow-up monitoring of extrapyramidal symptoms and tardive dyskinesia is required. These measures will be necessary until additional large-scale, long-term, placebo-controlled comparative studies become available which allow for definitive conclusions on the efficacy, effectiveness, tolerability and safety profiles of the various atypical antipsychotics in the

treatment of psychotic disorders in the paediatric population.

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