Use of Atypical Neuroleptics in Child and Adolescent Psychiatry

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Background: This article reviews the published clinical experience with atypical neuroleptics in children and adolescents.

Method: A computerized literature search was conducted (MEDLINE, 1974–1998) to retrieve all reports on the use of atypical neuroleptics in children and adolescents. A hand search was performed as well. All relevant clinical data were collated by type of drug.

Results: We found 5 blind placebo-controlled clinical trials (105 patients), 24 open-label clinical trials (387 patients), and 33 case series (115 patients) describing the use of the atypical neuroleptics clozapine, risperidone, olanzapine, sulpiride, tiapride, amisulpride, remoxipride, and clothiapine in children and adolescents. Some of these agents, especially clozapine, risperidone, and olanzapine, were found to be efficacious in the treatment of schizophrenia, bipolar disorders, and pervasive developmental disorders. The role of atypical neuroleptics as augmenters of serotonin reuptake inhibitors in obsessive-compulsive disorder is unclear. Risperidone appears to possess anti-tic properties in patients with Tourette's disorder.

Conclusion: The most convincing evidence of the efficacy of atypical neuroleptics in children and adolescents concerns clozapine in the treatment of schizophrenia. Data on other atypical neuroleptics in other disorders are still sparse, and further research is needed. Some of the atypical neuroleptics may become the first-line treatment for childhood schizophrenia and pervasive developmental disorders.

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Conventional neuroleptics have proved effective in children for the treatment of various symptoms and disorders such as schizophrenia, psychotic mood disorders, pervasive developmental disorders, Tourette's disorder, conduct disorder, attention-deficit/hyperactivity disorder (ADHD), and impulsive and aggressive behavior.[1–3] However, their value is diminished by such side effects as lethargy, weight gain, dysphoria, and cognitive blunting and the increased risk of extrapyramidal symptoms (EPS), particularly parkinsonism, akathisia, and dyskinesia.[4,5] The tardive and withdrawal dyskinesias are potentially irreversible and can occur in this population as early as 3 months after initiation of neuroleptic medications,[6] or even sooner.[4] This finding is especially important considering that a major factor in the development of tardive dyskinesia is the length of treatment,[7] and children with a chronic disorder may need neuroleptics long term. Indeed, the reported incidence of neuroleptic-induced tardive and withdrawal dyskinesia in children and adolescents on long-term treatment is 8% to 51%.[6] Thus, the use of neuroleptics in this age group must be carefully weighed, particularly in view of the fact that early onset schizophrenia is often associated with a preponderance of negative symptoms[5] that are not improved, or may even be exacerbated, by conventional neuroleptics.[8] Finally, clinical experience has shown that nonresponse to conventional neuroleptics is even higher in children than in adults, reaching 40% to 50% in some reports.[9,10]

Atypical neuroleptics may be beneficial in chronic neuroleptic-resistant schizophrenic adults.[11,12] They act on negative as well as positive symptoms and are associated with a negligible risk of EPS, with no sustained elevation in prolactin.[13,14] Studies conducted over the last decade have established clozapine as the prototype atypical neuroleptic. Clozapine's effectiveness and relative lack of parkinsonlike and dyskinetic side effects have been attributed to its sparing effect on the nigrostriatal dopamine system,[15] central anticholinergic and adrenolytic actions,[16] and combined serotonin-dopamine ($5\text{-}HT_2/D_2$) antagonism,[17] among others.

The initial clinical success with clozapine has spurred the development of other atypical neuroleptics with broad-spectrum combined serotonin and dopamine antagonism, such as risperidone, clothiapine, sertindole, olanzapine, quetiapine, and ziprasidone. Another subgroup of atypical neuroleptics is the antipsychotics considered to be se-

lective dopamine receptor blockers: sulpiride, tiapride, remoxipride (mainly D_2), and amisulpride (D_2/D_3).

It may be expected that the encouraging results with the new atypical neuroleptics in adults will be repeated in younger age groups. In the last few years, reports on the use of new atypical neuroleptics in children and adolescents for a variety of psychiatric disorders have been accumulating. The purpose of this review is to present the most recent information concerning the use of atypical neuroleptics in the pediatric population.

METHOD

An English-language MEDLINE search (1974–1998) of the terms *clozapine*, *risperidone*, *olanzapine*, *sulpiride*, *tiapride*, *amisulpride*, *remoxipride*, *clothiapine*, *children*, and *adolescents* was conducted to retrieve all reports on the use of atypical neuroleptics in children and adolescents. In addition, a hand search was carried out of all issues of the *Journal of Child and Adolescent Psychopharmacology* (Excerpta Medica), and published bibliographies were cross-referenced. We included only studies in which the number of participating children and adolescents was specified separately from adults.

RESULTS

A summary by drug of the clinical reports on the use of atypical neuroleptics in children and adolescents is presented in Table 1. These include 5 double-blind placebo-controlled clinical trials (total 105 patients), 1 with clozapine, 2 with amisulpride, and 2 with tiapride; 24 open-label clinical trials (total 387 patients) with clozapine (10 studies), risperidone (7 studies), olanzapine (1 study), sulpiride (4 studies), tiapride (1 study), and remoxipride (1 study); 1 retrospective study (8 patients) with olanzapine; and 33 case series (115 patients) on the use of clozapine (14 studies), risperidone (13 studies), sulpiride (3 studies), tiapride (1 study), clothiapine (1 study), and olanzapine (1 study). The published experience with each drug is described.

Clozapine

The bulk of clinical trials with atypical neuroleptics in children and adolescents involve clozapine: 1 double-blind clozapine-haloperidol comparison study evaluating 21 subjects (10 given clozapine and 11 given haloperidol), 10 open-label studies evaluating 217 patients, and 14 case series of 31 patients. Patient age ranged from 6 to 22 years. The most frequent indication for atypical neuroleptic use was treatment-resistant schizophrenia (Table 1), followed by mood disorder (N = 9),[21,39,40,43] pervasive development disorders (N = 4),[21,36,40] acute psychosis (in a 16-year-old with prolactinoma),[33] and tardive dyskinesia (N = 4).[35,42] Mean follow-up ranged from 6 weeks to 30 months. Clozapine dose varied from 50 mg/day to 900 mg/day, with means ranging from 240 to 370 mg/day (0.34–7.53 mg/kg/day).[18] Using a mean ± SD daily dose of 5.99 ± 2.6 mg/kg in 11 children, Piscitelli et al.[27] found a mean plasma clozapine level of 378.3 ng/mL (range, 6.2–44.3 ng/mL). Plasma concentrations appeared to be consistently and linearly related to clinical improvement in psychotic symptoms. No relationship was noted, however, between clozapine dose and clinical effects.

The results suggest that clozapine is generally effective in children and adolescents with schizophrenia. Kumra et al.[18] compared the efficacy of clozapine and haloperidol in a 6-week double-blind study of 21 patients (mean age = 14.0 ± 2.3 years) with childhood-onset schizophrenia who had been unresponsive to typical neuroleptics. The patients were randomly assigned to receive clozapine (mean final dose = 176 ± 149 mg/day) or haloperidol (168 mg/day). Clozapine proved to be superior to haloperidol on all measures of psychosis (p = .04–.002); both positive and negative symptoms of schizophrenia were alleviated. Thirteen patients continued taking clozapine for an additional 30 ± 15 months in an open trial. Of the total 21 patients (in the blind or blind plus open trial), 2 (9.5%) were rated very much improved, 11 (52.4%) much improved, 7 (33%) minimally improved, and 1 (4.8%) worse.

Remschmidt et al.[24] conducted a study of 36 schizophrenic adolescents treated with clozapine in open clinical trials for a mean of 154 days (mean daily dose = 330 mg; range, 50–800 mg daily) following treatment failure with at least 2 conventional neuroleptics. Seventy-five percent (27 of 36) showed notable symptomatic improvement, including 4 with essentially complete remission. The majority were able to participate in a comprehensive rehabilitation program after treatment. Positive symptoms were more responsive than negative ones, although there was also a modest improvement in negative symptoms. Three patients (8%) did not respond to clozapine, and 6 (17%) discontinued treatment owing to adverse effects.

All case studies reported improvement in positive symptoms, and some in negative symptoms as well. Burke et al.[41] noted an improvement in cognitive function with clozapine treatment in a 14-year-old mildly retarded adolescent with schizophrenia; other reports also describe clozapine-induced improvement in scholastic achievements.[35]

Adverse effects. Clozapine is generally safe and well tolerated. Table 2 presents the adverse effects described in 1 double-blind controlled study[18] and 4 open-label trials[21,22,24,25] (total, 127 children and adolescents). The frequency of adverse events varied, but the types of side effects were similar to those reported in adults taking clozapine,[83] i.e., electroencephalogram (EEG) alterations, fatigue, increase in liver enzymes, postural hypotension, tachycardia, fever, and hypersalivation. Two of the studies reported a 14% to 16% risk of acute EPS in pediatric patients.[21,24]

Table 1. Reports on the Use of Atypical Neuroleptics in Child and Adolescent Psychiatry

Drug Trial	No. of Subjects	Diagnosis and Comorbidity*	Mean Age, y (range)	Treatment Duration	Mean Dose, mg/d (range)[a]	Outcome Measures†	Results	Reference
Clozapine								
Controlled trial	10	Schizophrenia	14.4 ± 2.9	6 wk + 30 ± 15 mo	176 ± 149	BPRS, CGI, BHS, SAPS, SANS, SAS, AIMS	Positive + negative symptoms improved, clozapine > haloperidol (p = .04–.002)	Kumra et al, 1996[18]
Open trials	21	Schizophrenia	18.1 (57% < 18)	133 d	352 (150–800)	NA	80% improved	Siefen & Remschmidt, 1986[19]
	57	Schizophrenia (N = 53), mood disorders (N = 2), PDD (N = 2)	16.8 (10–21)	311 d (1–75 mo)	285 (75–800)	NA	88% improved, 7% no change, 5% worse	Schmidt et al, 1989[20] Blanz & Schmidt, 1993[21]
	11	Schizophrenia	(12–18)	6 wk	370 (125–900)	BPRS, CGAS, BHS, SAPS, SANS, AIMS	> 50% improved	Frazier et al, 1994[22] Gordon et al, 1994[23]
	36	Schizophrenia	(14–22)	154 d	330 (50–800)	SANS, SAPS	75% improved, 8% no change, 17% worse	Remschmidt et al, 1994[24]
	13	Schizophrenia	16.6 (14–17)	NA	240	BPRS	77% improved	Levkovitch et al, 1994[25]
	6	Psychosis with TD or PTSD	NA	NA	300	NA	6/6 improved	Mandoki, 1994[26]
	11[b]	Schizophrenia	14.1 (6–18)	6 wk	350	BPRS, BHS	Improved[c]	Piscitelli et al, 1994[27]
	31	Schizophrenia	NA	NA	NA	NA	Improved	Abczynska et al, 1995[28]
	20	Schizophrenia	(14–22)	30 wk	307 (75–600)	BPRS, SAPS, SANS	Improved[d]	Schulz et al, 1996[29]
	11	Schizophrenia	11.3 (9–13)	16 wk	230 (200–300)	PANSS, BPRS, CGI	4/11 improved	Turetz et al, 1997[30]
Case reports	3	Schizophrenia	(17–18)	(6–12 mo)	300 (100–400)	NA	3/3 improved	Birmaher et al, 1992[31]
	1	Schizophrenia	17	9 mo	(400–600)	NA	Improved	Boxer & Davidson, 1992[32]
	1	Acute psychosis, prolactinoma	16	4 mo	75	NA	Improved	Gonzales & Michanie, 1992[33]
	2	Schizophrenia	(14, 16)	12 mo	(300–400)	BPRS	2/2 improved	Mandoki, 1993[34]
	4	Schizophrenia (N = 4), tardive dyskinesia (N = 2)	(10–12)	(23–70 wk)	(150–300)	BPRS, CGI	4/4 improved	Mozes et al, 1994[35]
	2	Schizophrenia (N = 1), PDD (N = 1)	(13, 18)	18 mo	(250–550)	NA	2/2 improved	Jacobsen et al, 1994[36]
	1	Schizophrenia, developmental delay	13	15 mo	(400–500)	BPRS, CGI, AIMS	Improved	Towbin et al, 1994[37]
	1	Schizophrenia	15	140 wk	(300–550)	NA	Improved	Freedman, et al, 1994[38]
	1	Mood disorders, OCD	13	3 mo	(200–250)	NA	Improved	Fuchs, 1994[39]
	1	PDD, mood disorders	16.8	3 wk	350	NA	Improved	Atlas & Gerbino-Rosen, 1995[40]
	1	Schizophrenia, mild MR	14	5 mo	275	WISC-R, ACLT	Improved	Burke et al, 1995[41]
	2	Schizophrenia, tardive dyskinesia	(15, 16)	10–56 wk	(300–550)	BPRS, TDRS, AIMS BPRS	2/2 improved	Levkovitch et al, 1995[42]
	10	Schizophrenia (N = 4), mood disorders (N = 5), psychosis (N = 1)	(6–15)	6 wk	(75–225)	CGI, CGAS	10/10 improved	Kowatch et al, 1995[43]
	1	Schizophrenia	10	16 mo	325	BPRS, AIMS, SAS	Improved	MacEwan & Morton, 1996[44]
Risperidone								
Open trials	7	TD, OCD, chronic motor tics	12.9 (10–16)	11 wk	(1–2.5)	YGTSS, CY-BOCS	6/6 improved in tics (18%–66%), 1/3 improved in OCD	Lombroso et al, 1995[45]
	15[e]	TD, ADHD, OCD	(8–15)	4 wk	(0.5–9)	YGTSS	58% improved, 18% no change, 24% worse	Bruun & Budman, 1996[46]

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Table 1. (Continued)

Drug Trial	No. of Subjects	Diagnosis and Comorbidity*	Mean Age, y (range)	Treatment Duration	Mean Dose, mg/d (range)[a]	Outcome Measures†	Results	Reference
Risperidone								
Open trials (cont'd)	10	Schizophrenia	15.1 (11–18)	6 wk	6.6 (4–10)	PANSS, BPRS, CGI	9 improved, 1 no change; $p < .01$	Armenteros et al, 1997[47]
	6	PDD	7.3 (5–9.5)	8 wk	1.1 (0.75–1.5)	CPRS, OCS, CGI	6/6 improved; p = .001–.0001	Findling et al, 1997[48]
	6	PDD	10.7 (7–14)	5.2 mo (1 mo–2 y)	2.7 (1–6)	CGI, CPRS	4/6 improved	Perry et al, 1997[49]
	10	PDD	(4.5–10.8)	12 wk	1.3 (1–2.5)	CGI, Conners, CARS, AIMS	8/10 improved	Nicolson et al, 1998[50]
	18	PDD, MR	10.2 (5–18)	12 wk	1.8 (1–4)	CY-BOCS, Vineland	12/18 improved	McDougle et al, 1997[51]
Case reports	2	Schizophrenia	15	NA	(2–6)	NA	2/2 improved	Cozza & Edison, 1994[52]
	10	Mood disorders (N = 6), schizophrenia (N = 2), OCD, TD, PTSD	(7–17)	(6–12 wk)	(2–6)	WISC-R, CDI	100% improved	Mandoki, 1995[53]
	7	Schizophrenia (N = 3), PDD, ADHD, OCD, MR	(11–17)	(3–5 mo)	(1–6)	NA	6/7 improved	Simeon et al, 1995[54]
	6	ADHD, CD, mood disorders	(8–14)	1 mo	(1–3)	NA	6/6 improved	Fras & Major, 1995[55]
	1	Schizophrenia, ADHD	6	3 mo	2	NA	1/1 improved	Sternlicht & Wells, 1995[56]
	4	Schizophrenia	(12–17)	6 mo	(4–5)	CGI, BPRS, PANSS, AIMS	3/4 improved	Quintana & Keshavan, 1995[57]
	1[f]	Idiopathic segmental dystonia	17	3 mo	1.5	NA	Improved	Zuddes & Cianchetti, 1996[58]
	1	Schizophrenia	8	4 mo	(0.5–2)	CGAS, PANSS	Improved	Sourander, 1997[59]
	14	PDD	(9–17)	7 mo	(0.75–1.5)	CGAS, PANSS	13/14 improved	Fisman & Steele, 1996[60]
	1	Schizophrenia, OCD	13	5 mo	6	NA	Psychosis improved, OCD worsened	Dryden-Edwards & Reiss, 1996[61]
	1	Schizophrenia, prominent negative symptoms	15	8 mo	3	NA	Improved	Zuddas et al, 1996[62]
	20	PDD, MR, ADHD, ODD, developmental delay	(8–17)	(8–15 mo)	(1.5–10)	ABC, CGI, Conners	15 improved, 4 no change, 1 worsened	Hardan et al, 1996[63]
	2	Schizophrenia	8, 11	NA	2.5, 5.5	CGI	2/2 improved	Lykes & Cueva, 1996[64]
Olanzapine								
Retrospective study	8	Schizophrenia	NA	NA	(5–20)	CGI	8/8 as effective as clozapine	Mandoki, 1997[65]
Open trial	8	Schizophrenia	15.3 (6–18)	8 wk	17.5 (12.5–20) 0.27/kg (0.15–0.41)/kg	BPRS, SAPS, SANS, CGI	2/8 drug responders, 1/8 partial responder	Kumra et al, 1998[66]
Case report	2	PDD, MR, mood disorders	9, 10	5 wk, 9 wk	(5–20)	NA	2/2 75%–90% reduction in target behaviors	Horrigan et al, 1997[67]
Sulpiride								
Open trials	20	ADHD	(7–12)	NA	(50–100)	NA	10/10 improved	Chartier, 1974[68]
	16	School phobia	(9–17)	NA	100	NA	10/16 improved	Kazuhiko, 1975[69]
	27	Mood disorders, anxiety	(7–12)	4 wk	5/kg	CDI, BDI	59% improved	Nissen, 1981[70]
	10	Schizophrenia	NA	NA	(100–1000)	NA	8/10 improved	Dalery et al, 1984[71]
Case reports	1	PDD	18	15 mo	(800–1200)	BPRS	Improved	Scott & Eames, 1988[72]
	1	TD, OCD	8	12 wk	(75–225) 7/kg	NA	Worsened	Eggers et al, 1993[73]
	4	PDD	(4–24)	(4–48 mo)	(3.3–5/kg) (200–700)	NA	4/4 improved	Rothenberger, 1993[74]

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Table 1. (Continued)

Drug Trial	No. of Subjects	Diagnosis and Comorbidity*	Mean Age, y (range)	Treatment Duration	Mean Dose, mg/d (range)[a]	Outcome Measures†	Results	Reference
Tiapride								
Controlled trials	27	Tics, TD	(7–18)	NA	NA	NA	Improved	Eggers et al, 1988[75]
	32	Cerebromotor disorders, dyskinesia	6–19	3 wk	(150–500)	Terman-Merrill test	NA	Forner-Valero et al, 1986[76]
Open trial	10	Stuttering	(10–17)	20 wk	(3–10/kg)	NA	Improved	Rothenberger et al, 1994[77]
Case report	5	Self-mutilation, MR	(8–16)	NA	NA	NA	4/5 improved	Descalzo & Masanes, 1985[78]
Amisulpiride								
Controlled trials	27[g]	Schizophrenia (N = 21), schizotypal (N = 6)	20 ± 4	6 wk	50 (N = 14), placebo (N = 13)	SANS, SAPS, BPRS, MADRS	21/27 improved in negative symptoms; 6/27 worse/dropped	Paillere-Martinot et al, 1995[79]
	9	PDD	(4–13)	15 wk	1.5 mg/kg vs placebo	CARS, BSE, PTQ, CPRS, DOTES	Improvement of withdrawal symptoms	Dollfus et al, 1992[80]
Remoxipride								
Open trial	7	TD	(15–18)	8 wk	(50–250)	TSGS, CGI, OTC, TSSL, VAS	7/7 improved	Buitelaar et al, 1995[81]
Clothiapine								
Case report	1	Schizophrenia	8	4 mo	(10–20)	CY-BOCS, CGI	Improved	Toren et al, 1995[82]

*Abbreviations, diagnosis: ADHD = attention-deficit/hyperactivity disorder, CD = conduct disorder, MR = mental retardation, NA = data not available, OCD = obsessive-compulsive disorder, ODD = oppositional defiant disorder, PDD = pervasive developmental disorders, PTSD = posttraumatic stress disorder, TD = Tourette's disorder.
†Abbreviations, outcome measures: ABC = Aberrant Behavior Checklist, ACLT = Allen Cognitive Level Test, AIMS = Abnormal Involuntary Movement Scale, BDI = Beck Depression Inventory, BHS = Bunney-Hamburg Scale, BPRS = Brief Psychiatric Rating Scale, BSE = Behavioral Summarized Evaluation, CARS = Childhood Autism Rating Scale, CDI = Children's Depression Inventory, CGAS = Children's Global Assessment Scale, CGI = Clinical Global Impression scale, Conners = Conners Rating Scale, CPRS = Children's Psychiatric Rating Scale, CY-BOCS = Children's version of the Yale-Brown Obsessive Compulsive Scale, DOTES = Dosage and Record Treatment Emergent Symptoms scale, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not available, OCS = NIMH Obsessive Compulsive Scale, OTC = Observed Tic Count, PANSS = Positive and Negative Syndrome Scale, PTQ = Parent Teacher Questionnaire, TDRS = Tardive Dyskinetic Rating Scale, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms, SAS = Simpson-Angus Scale for Extrapyramidal Side Effects, TSGS = Tourette's Syndrome Global Scale, TSSL = Tourette Syndrome Symptom List, VAS = Visual Analogue Scale, Vineland = Vineland Adaptive Behavior Scale, WISC-R = Wechsler Intelligence Scale for Children-Revised, YGTSS = Yale Global Tic Severity Scale.
[a]mg/kg are cited in Table 1 when available.
[b]Eight patients in open trials, 3 in blind trials.
[c]Clinical improvement exhibited a consistent linear relationship with plasma clozapine concentrations but not with clozapine dosage. No other data are available.
[d]No specific data are available about patient improvement with clozapine treatment.
[e]The study included 38 patients, 15 of them children and adolescents. All data (including dosage and results) refer to the whole sample.
[f]One case of 5 reported in study (others were adults).
[g]Study includes young adults as well.

Table 2. Percentage of Patients With Adverse Side Effects to Clozapine[a]

	Blanz & Schmidt, 1993[21] (N = 57)		Frazier et al, 1994[22] (N = 11)		Remschmidt et al, 1994[24] (N = 36)[b]		Levkovitch et al, 1994[25] (N = 13)		Kumra et al, 1996[18] (N = 10)	
Side Effect	N	%	N	%	N	%	N	%	N	%
Tachycardia	37	65	3	27	2	5	…		7	70
Fatigue	29	51	7	63	…		4	31	9	90
Hypersalivation	20	35	8	72	…		1	7.7	7	70
Orthostatic hypotension	20	35	2	18	…		…		…	
Weight gain	…		7	63	…		…		…[c]	
Temperature rise	15	26	…		…		1	7.7	…	
Motor side effects[d]	9	16	…		5	14	…		…	
Enuresis	…		6	54	…		…		…	
Constipation	…		4	36	…		…		…	
Nausea	…		1	9	…		…		…	
Dizziness	…		1	9	…		…		…	
EEG alterations	14	25	…		16	44	…		…	
Seizures	1	1.7	…		…		…		2	20
ECG alterations	…		…		1	2.7	…		…	
Elevation of liver enzymes	…		…		1	2.7	…		1	10
Transient eosinophilia	…		1	9	…		…		…	
Leukopenia/ agranulocytosis	0	0	0	0	3	8.3	0	0	4	40
Stupor/delirium	1	1.7	…		1	2.7	…		…	
Insomnia	…		…		…		…		0	0
NMS	…		…		…		…		0	0

[a]Abbreviations: ECG = electrocardiogram, EEG = electroencephalogram, NMS = neuroleptic malignant syndrome. Symbol: … = data not available.
[b]Combination of clozapine (100 mg daily) and carbamazepine (400 mg daily).
[c]Weight gain (mean ± SD) of 0.90 ± 6.47 kg was noted, which did not differ significantly from weight gain for haloperidol-treated patients.
[d]Motor side effects include extrapyramidal symptoms, akathisia, tremor.

Other studies have found EEG changes in 10% to 44% of clozapine-treated children and adolescents, and clinical seizures have been documented as well.[18,22] Absence status seizures in an adolescent during long-term treatment with clozapine (550 mg/day) responded to a dose reduction (to 400 mg/day). Two patients in the double-blind clozapine trial[18] had clinically significant seizure activity without preexisting epilepsy. One experienced myoclonus at the end of week 4 while receiving 400 mg/day of clozapine, followed by a tonic-clonic seizure the next day. Clozapine dosage was reduced and anticonvulsants added. No further seizures occurred, but the EEG continued to show epileptiform spikes, and clozapine was discontinued. The second patient experienced bifrontal and posterior slowing on the EEG at week 5 of clozapine treatment. Four weeks later, this patient exhibited tonic-clonic seizures while receiving 275 mg/day of clozapine, which necessitated drug discontinuation.

Weight gain may be more problematic in adolescents than adults: the mean weight gain in 6 weeks for 12 clozapine-treated adolescents (mean week-6 dose = 366.7 mg/day) was 6.5 kg,[23] as opposed to 6.2 kg in adults treated for 16 weeks.[12] Unfortunately, the doses of clozapine administered to the adults were not specified.

Although no cases of agranulocytosis occurred, hematopoietic toxic effects are a major issue. Kumra et al.[18] reported on 5 patients receiving clozapine who experienced a decrease in the absolute neutrophil count to below 1500/mm^3. In 3 of them, the white blood cell count normalized spontaneously, but 2 had to be dropped from the double-blind protocol at week 4 after neutropenia recurred with rechallenge. Remschmidt et al.[24] described the appearance of neutropenia (2900 and 2500 neutrophils/mm^3) in 2 of 36 adolescents treated with clozapine. In these 2 cases, the neutropenia was managed by drug discontinuation.

Clozapine-induced obsessive-compulsive symptoms, noted earlier in adults,[32] have also been reported in children.[35] There has been 1 case report of acute pancreatitis in an adult[84] and 1 in an adolescent.[85]

Growing evidence suggests that chronic treatment with typical neuroleptics may be responsible for the increase in basal ganglia volume found on magnetic resonance imaging (MRI) brain studies. Frazier et al.[86] studied the effect of clozapine on the striatal morphology in 8 adolescents (mean age = 15.1 ± 2.3 years) with childhood-onset schizophrenia before and after 2 years of clozapine therapy and compared the findings with 8 matched controls. The mean ± SD duration of typical neuroleptic therapy before the first scan was 24.8 ± 19.4 months. Results indicated a larger caudate volume in the patients at the initial scanning, a decrease between scans, and no significant difference from controls at termination of treatment. The authors concluded that caudate enlargement occurs in patients with childhood-onset schizophrenia who are taking typical neu-

Table 3. Percentage of Children and Adolescents With Adverse Effects to Risperidone[a]

	Lombroso et al, 1995[45] (N = 7)		Bruun & Budman, 1996[46] (N = 15)[b]		Mandoki, 1995[53] (N = 10)		Armenteros et al, 1997[47] (N = 10)		McDougle et al, 1997[51] (N = 18)	
Side Effect	N	%	N	%	N	%	N	%	N	%
Weight gain	7	100	…		…		8	80	12	67
Fatigue/sedation	4	57.1	7	18	…		8	80	6	33
Motor side effects[c]	2	29	6	15	6	60	6	60	0	0
Photophobia	1	15	…		…		…		…	
Light-headedness	…		7	18	…		…		…	
Headache	…		2	5	…		…		…	
Weakness	…		1	3	…		…		…	
Insomnia	…		1	3	…		…		…	
Depression	…		1	3	4	40	…		…	
Anxiety	…		1	3	…		…		…	
Aggressive behavior	…		1	3	…		…		…	
Galactorrhea	…		…		1	33[d]	…		…	

[a]Symbol: … = data not available.
[b]These percentages reflect the total population treated (38 adults and children); side effects were not broken out by age.
[c]Motor side effects include extrapyramidal symptoms, akathisia, tremor.
[d]1 of 3 girls in the study developed galactorrhea.

roleptics, but not clozapine, and that it is secondary to medication exposure.

Risperidone

Seven open trials (total 72 patients) and 13 case studies (total 70 patients) have been published on the use of risperidone in children and adolescents with tic disorders, schizophrenia, and pervasive development disorders. (The study of Vanden Borre et al.[87] in mentally retarded patients with persistent behavioral disturbances was not included here because the data were not reported separately for the children.)

Tic disorders. In the first open trial, Lombroso et al.[45] investigated the short-term (11-week) safety and efficacy of risperidone (1–2.5 mg/day) in the treatment of chronic motor tic disorder or Tourette's disorder in 7 patients (mean age = 12.9 ± 1.9 years), 3 with a comorbid diagnosis of obsessive-compulsive disorder (OCD). Risperidone appeared to be effective in reducing tic frequency and intensity. One of the 3 children with OCD had a substantial improvement, while the other 2 showed no change. Thirty-eight Tourette's disorder patients, 15 of them aged 8 to 15 years, participated in the second open-label trial.[46] All were refractory to conventional neuroleptics. Although the results were not reported separately for the pediatric population, the 58% improvement rate suggests that risperidone is a promising alternative therapeutic agent in Tourette's disorder. (The most dramatic case was that of a 15-year-old girl with severe symptoms who had already been treated unsuccessfully with 13 other agents; the severity of her symptoms lessened considerably during risperidone treatment.) Eighteen percent of the patients showed no appreciable change, 3% showed a worsening of the tics, and 21% discontinued treatment because of intolerable side effects (mostly EPS).

Schizophrenia. The short-term beneficial effect and safety of risperidone were demonstrated in an open pilot study in 10 adolescents with schizophrenia (11–18 years old) given 4–10 mg/day (0.05–0.17 mg/kg/day) for 6 weeks,[47] as well as in several case studies (N = 15).[52–54,56,57,59,64]

Pervasive developmental disorders. Four recent open-label studies of risperidone with mean doses ranging from 0.75 to 2.7 mg/day (0.03–0.06 mg/kg/day) in a total of 40 children and adolescents (4.5–18 years old) with pervasive development disorders (and comorbid mental retardation) all showed substantial improvement in interfering behavioral symptoms.[41,49–51] In addition, 3 case studies of 27 children with pervasive development disorders reported good results.[54,60,63]

Other childhood psychiatric disorders. There is some preliminary evidence of the effectiveness of risperidone for ADHD (N = 19),[54–56,63] mood disorder (N = 8),[53,55] conduct disorder (with comorbid ADHD) (N = 4),[55] OCD (N = 3),[53,54] mental retardation (N = 17),[51,54,63] and idiopathic segmental dystonia (N = 1).[58] Doses were 0.5–10 mg/day; the doses used for OCD and conduct disorder, like for pervasive development disorders and Tourette's disorder, were usually lower than those for schizophrenia. The follow-up periods varied from 4 weeks to 15 months. The mean time to therapeutic response in all studies was 4 weeks. However, risperidone was ineffective in 3 of 4 children with OCD[45,54] and exacerbated incapacitating obsessive-compulsive symptoms in a 13-year-old boy with schizophrenia and OCD.[61]

Adverse effects. Table 3 presents the adverse effects of risperidone reported in 4 open trials and 1 case study (total 60 patients). In the first, Lombroso et al.[45] found that all 7 adolescents with Tourette's disorder complained of weight gain of 3.6–6.3 kg, and 4 of fatigue. Two experi-

enced motor side effects, which responded to a dose reduction, and 1 had photophobia, which resolved spontaneously. Side effects reported in Bruun and Budman[46] (38 adults and children) included light-headedness and sedation (18%), akathisia/agitation (15%), dystonic reactions (5%), headache (5%), and weakness, insomnia, depressed mood, anxiety, and aggressive behavior (1 patient each, 3%). These percentages reflect the total population; side effects were not broken out by age.

Six of the 10 children reported by Mandoki[53] acquired EPS during risperidone treatment, 4 requiring treatment with anticholinergic agents. These patients were started on a relatively aggressive regimen wherein the dose was increased by 0.5 mg b.i.d. each day. Another unexpected finding was dysthymia in 4 of the 10 children within 3 months of starting risperidone.[53] Two of them met the DSM-IV criteria for major depression and required an antidepressant. One of 3 adolescent girls developed galactorrhea. None of the children showed side effects commonly reported in adults treated with risperidone, such as insomnia, anxiety, agitation, dizziness, rhinitis, hypotension, and nausea.

Armenteros et al.[47] reported on mild somnolence in 8 of their 10 patients with schizophrenia. The somnolence subsided within 2 weeks. Two patients had acute dystonic reactions, 3 had parkinsonism, and 1 had mild orofacial dyskinesia; weight gain was noted in 8 patients (mean = 4.85 kg). McDougle et al.[51] also reported transient sedation in 6 of 18 patients and weight gain in 12.

The weight gain reported in many studies[37,59,88,89] was also supported by Penn et al.[90] who studied 2 adolescents with schizophrenia and no past medical problems or history of obesity or eating disorders. After 52 and 38 weeks on risperidone treatment, the patients gained 46.4 and 25.1 kg, respectively. A serotonergic mechanism has been proposed as the cause of the weight gain associated with atypical antipsychotics.

Another interesting finding was the onset of nocturnal enuresis, noted 2 to 4 weeks after the start of risperidone in 5 of 50 patients investigated by Took and Buck.[91] None of the 5 patients (10–14 years old) had a history of enuresis, and all had been concomitantly treated with a selective serotonin reuptake inhibitor (SSRI).

Kumra et al.[92] suggested that long-term risperidone treatment may be associated with hepatotoxicity in pediatric patients. They reviewed the charts of 13 psychotic children admitted to the National Institute of Mental Health (NIMH) and treated with risperidone, and found 2 who presented with obesity, liver enzyme abnormalities, and confirmatory evidence of fatty liver. The authors suggested that weight and liver function need to be carefully monitored during risperidone therapy.

Feeney and Klykylo[93] reported a case of tardive dyskinesia that developed during risperidone treatment in an adolescent female (with an affective disorder). Since the patient was concomitantly treated with methylphenidate, tics should be included in the differential diagnosis. Rowan and Malone[94] described the emergence of a Tourette-like syndrome in a child on abrupt withdrawal of risperidone. They suggested that the tics represented an episode of withdrawal dyskinesia. A single case of risperidone-induced neuroleptic malignant syndrome was reported in an adolescent boy.[95] Finally, Edleman[96] reported on risperidone-related acute leukocytopenia in a 15-year-old boy.

Olanzapine

Olanzapine is a novel atypical neuroleptic displaying affinity at the dopaminergic (D_1–D_4) and serotonergic ($5\text{-}HT_2$, $5\text{-}HT_3$, $5\text{-}HT_6$), muscarinic (subtypes 1–5), adrenergic (α_1), and histaminergic (H_1) receptors, very similar to clozapine. Many studies are emerging on the efficacy of olanzapine in adults, and recently a few reports on its use in children and adolescents have appeared as well.[65–67] Mandoki[65] conducted a retrospective evaluation of the medical records of 8 children and adolescents who were switched from clozapine to olanzapine (5–20 mg/day); only individuals responsive to and stable on clozapine therapy were included and were pleased to be relieved of the discomfort and inconvenience of the weekly blood collections. Olanzapine was found to be at least as effective as clozapine, and like clozapine, it was not associated with EPS. Kumra et al.[66] examined the efficacy of olanzapine for treatment-refractory childhood-onset schizophrenia in 8 patients (6–18 years old) in an 8-week open-label trial. Olanzapine doses were initiated at 2.5 mg every other day in patients weighing ≤ 40 kg or 2.5 mg every day in patients weighing > 40 kg. The mean ± SD dose of medication at the sixth week of treatment was 17.5 ± 2.3 mg/day (range, 12.5–20 mg/day) or 0.27 ± 0.11 mg/kg/day (range, 0.15–0.41 mg/kg/day). At week 8, there was a 17% improvement in the Brief Psychiatric Rating Scale (BPRS) score of the group. Two patients (25%) were drug responders, and 1 (12.5%) was a partial responder. The authors compared their results with data from 15 patients (also 6–18 years old) who had undergone a 6-week open-label trial with clozapine using the identical rating instruments in the same treatment setting. Fifty-three percent of the clozapine-treated patients met the "drug responder" criteria of Kane et al.,[11] whereas none of the patients treated with olanzapine did so. The authors suggested that clozapine is superior to olanzapine for the treatment of neuroleptic-nonresponsive childhood-onset schizophrenia.

Adverse effects. Olanzapine is moderately well tolerated[66]; the most common treatment-induced adverse effects were increased appetite (N = 6), constipation (N = 5), nausea/vomiting (N = 6), headache (N = 6), somnolence (N = 6), insomnia (N = 7), difficulty concentrating (N = 5), sustained tachycardia (N = 6), transient elevation of liver transaminase levels (N = 7), and increased agitation (N = 6). An average weight gain of 3.4 ± 4.1 kg

was observed during the 6-week trial of olanzapine, and 7 of the 8 patients required benzodiazepine treatment for agitation or insomnia; 1 patient was dropped from the olanzapine trial at week 6 because of increased agitation and worsening of psychosis. No cases of neutropenia, abnormal EEG changes, or seizures were noted during the open olanzapine trial; abnormal movements and EPS were minimal, and no change in the total score on the Abnormal Involuntary Movements Scale (AIMS) or the Simpson-Angus Scale was noted. The authors concluded that the strengths of olanzapine are its relatively safe side effect profile and enhanced therapeutic effects in some children with schizophrenia. They suggested olanzapine as a good first-line agent for the treatment of childhood-onset schizophrenia.

Horrigan et al.[67] reported on the efficacy of olanzapine in 2 children with pervasive development disorders. Olanzapine was well tolerated with no side effects except for mild initial sedation. London[97] reported on new-onset manic symptoms in a 16-year-old patient with pervasive development disorders and a history of cyclic variations in mood who had been treated with 7.5 mg of olanzapine.

Sulpiride

Sulpiride, a substituted benzamide with mainly D_2 antagonist effects, acts as an atypical neuroleptic. Although EPS, tardive dyskinesia, and tardive dystonia have been reported in association with sulpiride, their incidence appears to be lower than that with conventional neuroleptics.[88] Sulpiride has been available in Europe, Israel, and Japan since 1969; it is not currently available in the United States.

The 4 open-label clinical trials (N = 73) and 3 case studies (N = 6) on the use of sulpiride in children and adolescents are summarized in Table 1. Indications for treatment were ADHD,[68] school phobia,[69] schizophrenia,[71] pervasive development disorders,[72–74] Tourette's disorder and OCD,[73] and depressive and anxiety symptoms.[70] The rationale for using sulpiride in the treatment of school phobia and anxiety and isolation symptoms, according to the authors, was the putative antidepressive effect of the drug.[69] The sulpiride dose was higher for the schizophrenia and pervasive development disorders patients (100–1200 mg/kg) than for those with ADHD and school phobia (50–100 mg/kg). Eggers et al.[73] reported an exacerbation and provocation of tics with sulpiride in an 8-year-old child, though Robertson et al.[88] found that 59% of their 63 Tourette's disorder patients (mean age = 29.3; range, 10–68 years) receiving sulpiride (200–1600 mg/daily) showed beneficial effects. The latter work is not included in Table 1 because the data were not reported separately for the younger subjects, nor was the number of participating children and adolescents specified. Currently, the major indication for sulpiride treatment is schizophrenia. Its role in the treatment of ADHD, school phobia, and mood and anxiety disorders remains doubtful.

Adverse effects. Sulpiride was generally well tolerated, and EPS were rarely reported[88,89]; other side effects were drowsiness, depression, akathisia, weight gain, amenorrhea, and galactorrhea.[70,72,88]

Tiapride

Tiapride, another substituted benzamide derivative with selective D_2 antagonism, appears to have a preferential affinity for extrastriatal dopamine receptors.[77] It is sometimes used in the treatment of persistent tardive dyskinesia in adults.[98] Tiapride is marketed in the European community, but is not available in the United States. In contrast to sulpiride, tiapride has no antipsychotic effects. It was found to improve severe stuttering in 10 children (10–17 years old) treated in a 20-week open study (low baseline dose of 3 mg/kg/day followed by 10 mg/kg/day and an observational off-medication period).[77] Tiapride also reduced tic severity in 27 children aged 7–18 years treated in a placebo-controlled or double-blind crossover trial.[75] There were no adverse effects on neuropsychologically measurable cognitive parameters.

Amisulpride

We found 2 trials with amisulpride in children and adolescents, including the double-blind placebo study of Paillere-Martinot et al.,[79] in which the data were not reported separately for adults and adolescents, but all the patients were young (mean ± SD age = 20 ± 4 years). Amisulpride significantly improved negative symptoms in 8 of the 27 schizophrenic patients, particularly avolition, attentional impairment, and retardation. In 4, however, positive or negative symptoms worsened. Side effects included very mild EPS (12/14), insomnia, and excitement or somnolence (8/14). Dollfus et al.[80] compared the clinical efficacy of amisulpride and bromocriptine in a randomized, double-blind, crossover trial in 9 children with autism and severe mental retardation. Bromocriptine showed distinct beneficial effects on attention deficit and hyperactivity symptoms, whereas amisulpride improved predominantly negative symptomatology (behavioral inhibition and withdrawal symptoms). Both drugs were generally well tolerated, and side effects were mild (insomnia, excitation, agitation). Amisulpride is not available in the United States.

Remoxipride

Remoxipride is a D_2 antagonist with more selective affinity for the mesolimbic dopaminergic system. Only 1 open-label trial of remoxipride (50–250 mg/day in 7 adolescents with Tourette's disorder) has been published.[81] The 3-phase design included a 3-week baseline placebo wash-in period, an 8-week active treatment period, and a 3-week placebo wash-out period. Illness ratings improved in 6 patients, and tic ratings decreased in all 7. A mean weight gain of 1.1 kg was noted. Adverse effects were

transient and mild and included nonspecific electrocardiographic changes (N = 3), muscle rigidity (N = 2), concentration problems (N = 1), akathisia (N = 1), fatigue (N = 1), and nocturnal enuresis (N = 1).

Remoxipride was withdrawn from the market in 1994 because it induces aplastic anemia.

Clothiapine

Clothiapine is a dibenzothiazepine, closely related to clozapine in its broad receptor-affinity profile. It has antagonistic activity at the D_1, D_2, 5-HT_{1A}, 5-HT_{2A}/5-HT_{2C}, and 5-HT_3 receptors.[99] Although clothiapine was found to be effective in one 8-year-old schizophrenic child,[82] de novo compulsive symptoms emerged shortly after initiation of treatment. This finding has also been reported for clozapine.[35] Clothiapine is marketed in Israel, Italy, Belgium, and South Africa. It is not approved for use in the United States.

THERAPEUTIC APPLICATIONS

Clinical studies of atypical neuroleptics in children and adolescents are accumulating. In the present review, we have listed the results by drug (clozapine, risperidone, olanzapine, sulpiride, tiapride, amisulpride, remoxipride, and clothiapine). Here, we summarize some of the data according to the disorders treated.

Schizophrenia

A total of 227 schizophrenic subjects aged 6–22 years who failed at least 2 previous neuroleptic trials were treated with clozapine.[18–25,27,30,31,35,43,44] Clinically significant improvements in both positive and negative symptoms were noted. However, only 1 study (10 subjects) followed a double-blind controlled design.[18] Risperidone has been administered in 1 open pilot study of 10 adolescents with schizophrenia, where it appeared to be effective and well tolerated,[47] and in 16 neuroleptic-resistant children and adolescents with schizophrenia (individual case reports) in whom there were improvements in positive and negative symptoms.* Nevertheless, the availability of many successful reports on clozapine and risperidone in children and adolescents with schizophrenia may not accurately reflect the drugs' clinical effectiveness because of publication bias favoring positive findings. Further substantiation is needed in larger controlled studies. Moreover, children given risperidone show an unexpectedly high rate of EPS, weight gain, and dysphoria,[47,53] all of which appear to be dose-dependent.

Few reports were found on the use of other atypical neuroleptics in the pediatric population with schizophrenia. One study described a trial with sulpiride in 10 young patients,[71] and one with amisulpride in 27 patients.[79] Some primary negative symptoms may be directly affected by low doses of amisulpride.[79] Olanzapine was retrospectively evaluated in 8 children and adolescents with schizophrenia and found effective.[65] An open-label trial of olanzapine in childhood-onset schizophrenia provided preliminary evidence of the efficacy of olanzapine for some children and adolescents with treatment-refractory schizophrenia.[66]

Mood Disorders

Only 9 children and adolescents with mood disorders are reported to have been treated with clozapine.[21,39,40,43] Five subjects with bipolar disorder resistant to extensive trials with lithium or carbamazepine combined with typical neuroleptics showed improvement in both mood symptoms and aggressive behaviors.[43] Risperidone was used to treat severe aggression in 8 children and adolescents with bipolar disorders[53,55]; all showed overall clinical improvement in target symptoms. However, in the study by Mandoki,[53] 4 of the 6 patients with bipolar disorder developed dysphoric mood within 3 months of starting risperidone treatment. Two of them met the criteria for major depression and required the addition of an antidepressant. In adults, risperidone has been shown to have an antidepressant activity, probably owing to its 5-HT_2 antagonistic activity.[100] It is not clear whether the differing effects of the drug on mood are due to inherent systemic differences in children and adults.

Pervasive Developmental Disorders

Four case reports have been published on the use of clozapine for children with pervasive developmental disorders[2,36,40]; all showed symptomatic improvement. In the 4 open clinical trials with risperidone (0.75–4.0 mg/day) in 40 children and adolescents with pervasive developmental disorders,[41,49–51] 30 exhibited an improvement in interfering behavioral symptoms. The most common side effects were weight gain and sedation. In addition, 14 case reports have been published on the use of risperidone in children with pervasive developmental disorders[54,60,63]; 24 of the 27 children had symptomatic improvement. Rothenberger[74] reported that sulpiride clearly reduced self-injurious behavior in 4 autistic patients, and Dollfus et al.[80] found that amisulpride was beneficial for predominant negative symptomatology (behavioral inhibition and withdrawal symptoms) in 9 autistic children. Olanzapine was well tolerated and associated with a rapid improvement in target behaviors in 2 children with pervasive developmental disorders.[67]

Obsessive-Compulsive Disorder

Clozapine is known to induce obsessive-compulsive symptoms in adults,[101] and may also do so in children.[35] Risperidone, too, exacerbated incapacitating obsessive-

*References 52, 53, 56, 57, 59, 61, 62, and 64.

Table 4. Major Indications, Dosages, and Adverse Effects of the Currently Available Atypical Neuroleptics in the United States (Clozapine, Olanzapine, and Risperidone) for Children and Adolescents[a]

Variable	Clozapine	Olanzapine	Risperidone
Major indications	Resistant schizophrenia	Schizophrenia, PDD	Schizophrenia, PDD, tic disorders
Dose range (mg/kg/d)	0.34–7.53	0.15–0.41	0.03–0.17
Major adverse effects	Seizures, agranulocytosis, hypersalivation, enuresis	Weight gain, transient elevation of liver enzymes	EPS, weight gain, dysphoria

[a]Abbreviations: EPS = extrapyramidal symptoms, PDD = pervasive developmental disorders.

compulsive symptoms in one 13-year-old boy with schizophrenia and OCD,[61] and clothiapine led to the de novo emergence of compulsive symptoms in a drug-naive 8-year-old schizophrenic child.[82] These 3 atypical neuroleptics—clozapine, risperidone, and clothiapine—all possess strong 5-HT_2 antagonistic activity; the results suggest that this receptor subtype may play a role in the pathophysiology of OCD. However, McDougle et al. reported that clozapine monotherapy resulted in neither improvement nor worsening of obsessive-compulsive symptoms in 12 adults with treatment-refractory OCD.[102,103] They also found that the addition of risperidone to the treatment regimen in fluvoxamine-refractory adult OCD patients led to significant improvement in obsessive-compulsive symptoms.[104] In the younger population, only one patient with mood disorder and OCD has been described, and his psychotic symptoms responded well to the addition of clozapine without concomitant worsening of the obsessive-compulsive symptoms.[39] Risperidone treatment was, however, ineffective in 3 of 4 children with OCD.[45,54] A possible explanation for these discrepancies is a heterogeneity of OCD whose subtypes may be associated with different neurotransmitter dysregulation; for example, schizophrenia-related OCD that worsens with 5-HT_2 antagonism versus primary OCD that improves with 5-HT_2 antagonism.

Tourette's Disorder

Two open trials[45,46] (22 children and adolescents) have demonstrated that risperidone (0.5–9 mg/day) is a good anti-tic agent in youth with Tourette's disorder. Sulpiride (200–1600 mg/day) was found effective in 60% of 63 Tourette's disorder patients, some of them under 18 years old[88]; however, 1 case report described an exacerbation of tics with sulpiride in a child.[73] Another substituted benzamide, tiapride, was found effective as an anti-tic agent in a placebo-controlled double-blind trial with 27 children. Remoxipride also showed some benefit in 7 adolescents with Tourette's disorder.[81]

CONCLUSION

The most commonly used atypical neuroleptics in children and adolescents at present are clozapine, olanzapine, and risperidone. These agents are compared in Table 4. Most of the published studies on the use of atypical neuroleptics in children and adolescents point to the efficacy of clozapine for drug-resistant schizophrenia. Studies of risperidone and olanzapine in young schizophrenic patients are just emerging, and these, too, indicate a possible effectiveness, though pediatric patients seem to have a greater propensity than adults for side effects, particularly EPS, weight gain, and dysphoria. There is some evidence of the efficacy of risperidone in aggressive bipolar disorder and some preliminary findings on its use in tic disorders and pervasive developmental disorders. Some studies have shown contradictory effects of atypical neuroleptics on OCD symptomatology.

At present, there is insufficient evidence of poorer therapeutic effect of one or more of these agents compared with the others, although it has been suggested[66] that clozapine may be superior to olanzapine for drug-resistant childhood-onset schizophrenia. Children and adolescents were not compared in any study, so no comments can be offered regarding possible drug-induced childhood developmental changes or any significant effects of the drug action or the therapeutic efficacy on development.

The fact that almost all of the studies published to date were open, uncontrolled clinical trials of relatively short-term treatment in small groups of patients seriously limits the conclusions that can be drawn. There are no estimates of the risk of tardive dyskinesia, neuroleptic malignant syndrome, or other possible side effects. Furthermore, young patients may require lower and gradually increasing doses of atypical neuroleptics[105] to reduce the risk of side effects and to enable better tolerance and compliance. Thus, systematic assessments of dose-response and dose-risk relationships for atypical neuroleptics in children are still needed. Extreme caution should be taken in generalizing results from the adult to the pediatric population. Further research will provide clinicians with a more reasonable and responsible basis for the treatment of children and adolescents with atypical neuroleptics. Many novel compounds that may be as effective as clozapine, only without agranulocytosis and other troublesome side effects, will soon be available for children and adolescents (e.g., quetiapine, ziprasidone). The full clinical profiles of these atypical neuroleptics and their indications remain to be determined in rigorous, double-blind placebo-controlled trials.

It seems that the currently available atypical neuroleptics are almost ready for general use for treating schizophrenia, and perhaps pervasive developmental disorders,

in children and adolescents. Their application for nonpsychotic disorders, such as Tourette's disorder, ADHD, mood disorders, and OCD, merits further investigation. Since atypical neuroleptics are associated with fewer EPS, they may soon become the first-line treatment in children and adolescents with schizophrenia and pervasive developmental disorders.

Drug names: bromocriptine (Parlodel), carbamazepine (Tegretol and others), clozapine (Clozaril), fluvoxamine (Luvox), haloperidol (Haldol and others), methylphenidate (Ritalin), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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