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Atypical neuroleptics in child and adolescent psychiatry

Abstract Atypical neuroleptics have enriched our treatment programmes, especially in childhood and adolescent schizophrenia. This article reviews the use of atypical neuroleptics in children and adolescents with schizophrenic disorder. It considers the receptor binding profile and pharmacological properties, indications, side effects, clinical applications and trials of atypical neuroleptics in comparison to the classical neuroleptic haloperidol in adolescent schizophrenia. Special emphasis is placed on the most common atypical neuroleptics clozapine, olanzapine and risperidone since most studies are carried out with these compounds, especially with clozapine. More clinically controlled trials have to be conducted since only one was performed so far. The place of the atypical neuroleptics is discussed and further studies are necessary in order to differentiate the indications tested so far and to find out if the spectrum of indications can be broadened.

Key words Atypical neuroleptics – schizophrenia – child – adolescent – psychiatry

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Definition

Atypical neuroleptics are a group of chemically different compounds that are characterized by the following properties, which distinguish them from typical (classical) neuroleptics:

- A different receptor binding profile as compared to classical neuroleptics (lower binding to dopamine receptors, high affinity to 5-HT_{2A} and α_1 receptors) which is responsible for a different action.
- Low rate of extrapyramidal side effects (EPS) as a consequence of this receptor profile.
- Efficacy also with regard to negative symptoms in contrast to classical neuroleptics.
- Absence of hyperprolactinemia and a low rate of other adverse effects.

The first atypical neuroleptic clozapine was originally not thought to have an antipsychotic efficacy because of the absence of EPS. According to the dopamine hypothesis of schizophrenia (54), EPS was formerly thought to be essential for the antipsychotic efficacy. The different receptor binding profile involving the dopaminergic, serotoninergic, glutaminergic, and alpha-adrenergic systems led to new considerations and hypotheses on the aetiology of schizophrenia (23). For compounds that were considered to act according to this different mechanism the term "atypical neuroleptics" was introduced.

Receptor binding profile and pharmacological properties

We summarize here some biochemical properties of the atypical neuroleptics clozapine, olanzapine and risperidone, which are used now also in child and adolescent psychiatry (24, 27, 40). The other atypical neuroleptic agents quetiapine, sertindole and zotepine are currently mainly used in adult psychiatry and there is not sufficient experience concerning children

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and adolescents. Nevertheless we included them into some tables, because they might become clinically relevant in the near future.

Receptor binding profile

The receptor binding profile is demonstrated in Table 1. Haloperidol, listed in Table 1 for comparison reasons, was and is thought to induce its benefits by acting via the dopamine D_2 receptor binding affinity. Haloperidol shows in vitro and in vivo low K_D values for the D_2, D_3, and D_4 receptor. The atypical neuroleptics clozapine, olanzapine and risperidone, however, have a different binding profile. This led and still leads to speculations about the D_2 receptor theory of schizophrenia. Thus Sanyal et al. (43) suggested that the higher D_4/D_2 binding ratio of clozapine as compared with haloperidol is important for the therapeutic properties of clozapine and the other atypical neuroleptics. Other authors (for review see 32) favour the role of the high binding capacity for the serotonin receptors in this respect. PET studies in humans indicate that atypical neuroleptics show a higher in vivo occupancy of the serotonin 5-HT_2 receptor than the dopamine D_2 receptor, and this supports the role of the therapeutic contribution of the serotoninergic transmission in schizophrenia and may contribute to a lesser degree of EPS (21, 48). One of the major benefits of the atypical neuroleptics is their lower rate of EPS (4, 10, 34, 40). This might be due to the fact that atypical neuroleptics show only little effect on the nigrostriatal dopaminergic neurons (50), and also have a high 5-HT_{2A}/D_2 binding ratio (see Table 1). With in situ hybridization of neuropeptide mRNA it could be shown that haloperidol affects the output pathways of the striatum of the rat stronger than risperidone (33). Imaging studies in adult patients show that the threshold for EPS is approximately 80 % occupancy of D_2 receptors. In the usual clinical dose range, haloperidol, for instance, occupies between 70 and 90 % of the D_2 receptors, clozapine between 20 to 60 %, and olanzapine around 60 %. Olanzapine additionally occupies 80 % of the 5-HT_2 receptors at the 10 mg daily dose. If the dose is increased above the recommended daily maximum of 20 mg, the binding profile becomes very similar to that of standard neuroleptics, with the consequent risk of EPS and loss of its advantages (19).

Clozapine

Clozapine differs in the following ways from classical antipsychotics (13): greater arousal inhibition activity, no inhibition of apomorphine- or amphetamine-induced stereotypic behaviour, no induction of catalepsy, no dopaminergic or GABAergic supersensitivity on chronic administration, no depolarization or blocking of nigrostriatal dopamine neurons with chronic exposure. It shows moderate to high affinities for the D_1 and D_4, the serotoninergic 5-HT_2, the noradrenergic α_1 and α_2, the muscarinergic M and the histaminergic H_1 receptors. In addition, it shows affinity to the 5-HT_6 and 5-HT_7 receptors as well as other receptors (42).

Olanzapine

Olanzapine was developed as a consequence of research seeking an antipsychotic agent with a similar receptor-binding profile as clozapine, but without its adverse side effects, especially agranulocytosis. Olanzapine interacts with a broad spectrum of receptors, including moderate to high affinities for D_{1-4}, 5-HT_{2A+C}, α_1, M and H_1 receptors (see Table 1). In comparison with typical neuroleptics, the affinity of olanzapine for the family of dopamine receptors is relatively low and for the serotonin receptors relatively high. Similar to clozapine, this might go some way in explaining why olanzapine is more effective with regard to negative and mood symptoms in schizophrenic patients. The adverse effects of olanzapine can also be explained by its receptor-binding profile. The anticholinergic effects result from its interaction with muscarinic receptors, whereas sedation can be attributed to the effects at

Table 1 Radioreceptor binding profiles of atypical neuroleptics and haloperidol (adopted from (39))

	D1	D2	D3	D4	5-HT1A	5-HT2A	5-HT2C	α1	α2	M	H1
Clozapine	++	+(+)	+(+)	++	+	++(+)	++(+)	++(+)	++(+)	++(+)	++(+)
Olanzapine	++	++	++	++	+	+++	++	++	+	+++	+++
Risperidone	++	+++	+++	+++	+	+++	++	+++	+++	+	++(+)
Quetiapine	+	+(+)	+		+	+(+)		++(+)	+(+)	+	+++
Sertindole	++	+++	+++	++	+	+++		+++	+	+	+
Zotepine	+++	++(+)	++	++	+	+++		+++		++	++
Haloperidol	++	+++	+++	+++	+	++	+	++(+)	+	+	+

+ none or low affinity (KD > 100 nM); ++ moderate affinity (KD < 100 nM), +++ high affinity (KD < 10 nM)

histamine and adrenergic receptors. One of the most pronounced adverse effects is weight gain, which results from its antagonism at serotonin receptors. The reduced risk of EPS is due to the weak D_2 blockade, combined with the antimuscarinic action. This is important, because it suggests that, as a result of these properties, there might be a low risk for tardive dyskinesia. Compared with clozapine, the compound is characterized by a weaker action at the a-adrenergic receptors, which accounts for the decreased risk of orthostatic hypotension.

Risperidone

It is presumed that the antipsychotic activity is mediated through a combination of a D_2 receptor antagonism and a 5-HT_{2A} antagonism. Risperidone also binds with moderate to high affinities to D_{1-4}, 5-HT_{2A+C}, α_{1+2} and H_1 receptors (see Table 1). This slightly different receptor binding profile compared to clozapine and olanzapine is responsible for the different effects (see Table 2) and side effects of risperidone (see Table 3).

Pharmacological properties

All atypical neuroleptics reach their plasma peak level within a few hours. The major portion of the drug, however, is immediately metabolized and inactivated mostly by liver enzymes such as the cytochrome P450 system and/or by sulfation or glucoronidation, so that a number of different metabolites for each of these atypical neuroleptics can be detected in blood and urine (2, 11, 31, 45, 55).

Monitoring of the blood levels of the neuroleptics is an important and necessary tool to control the quality of the antipsychotic therapy with atypical neuroleptics (2, 11, 34). In our clinics this is standard for clozapine and its major metabolites (45, 47), and has now been introduced for olanzapine and its major metabolites (12). The serum levels of the drugs and their metabolites depend on several parameters, such as the activity of the cytochrome P450 system (e.g. poor or extensive metabolizers) but also on factors such as co-medication, smoking, sex, or age.

Clozapine

Clozapine, the first atypical neuroleptic, is a dibenzodiazepine derivative. It was developed by Wander through systematic variation of heterotricyclic compounds and introduced into clinical practice in 1972. The most serious side effect of bone marrow suppression and agranulocytosis delayed the acceptance of clozapine into common clinical practice but application of a monitoring protocol led to adequate protection from these side effects. The chemical structure is shown in Fig. 1. The main metabolites of clozapine (N-oxide-clozapine and N-desmethyl-clozapine) are likely to have only low pharmacological activity.

Under standard clinical doses, serum levels of clozapine are usually between 100–400 ng/ml. Olesen (34) suggested that serum levels of 400 ng/ml serum would be too high, and could account for serious side effects.

Olanzapine

Olanzapine, developed by Eli-Lilly, is a thienobenzodiazepine derivative. Its chemical structure (Fig. 1) and its receptor binding profile (Table 1) are quite similar to that of clozapine. Metabolites of olanzapine like N-desmethyl-olanzapine, 2-hydroxymethyl-olanzapine, and 4'-N-oxide-olanzapine do not have antipsychotic activity.

Catlow et al. (11) measured levels of olanzapine between five and 70 ng/ml in the plasma of steady-state adult patients

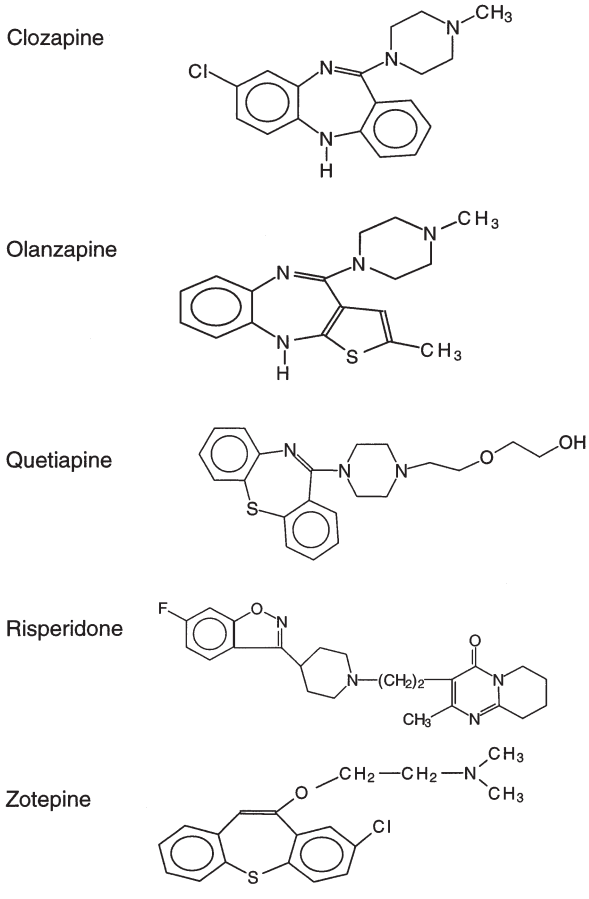

Fig. 1 Chemical structures of atypical neuroleptics

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receiving doses of 2.5 to 17.5 mg/day. In our own preliminary study we could confirm this blood level range in the serum of adolescent patients receiving olanzapine (12).

Risperidone

Risperidone is a benzisoxazole derivative and was developed by Janssen. It differs in its chemical structure from the aforementioned compounds (Fig. 1) and is closer related to haloperidol, although its receptor binding profile is quite different (Table 1). The primary metabolism of risperidone results in the formation of 9-hydroxy-risperidone, which shows a similar binding profile as compared to risperidone itself, whereas the metabolites of clozapine and olanzapine do not have such antipsychotic activity. For risperidone Olesen et al. (35) reported serum levels of 20–60 ng/ml (50–150 nmol/l) in 90 % of 22 adult patients treated with 6 mg/day risperidone.

Indications and contraindications

The main indications for atypical neuroleptics are the acute and maintenance treatment of schizophrenic disorders with an emphasis on the treatment refractory and chronic schizophrenic disorders. However due to the lower risk of extrapyramidal side effects (EPS) such as tardive dyskinesias there is a tendency to a wider range of indications for some of the atypical neuroleptics, e.g. clozapine has been shown to be effective in the treatment and relapse prevention of manic episodes and bipolar disorders (22, 51). Other possible indications might be pervasive developmental disorder, Tourette's disorder, obsessive-compulsive disorders and attention deficit disorder (for review of case reports see 52). However, these states and disorders have not yet been established as therapeutic indications. This is likely to occur, however, in the near future.

For children and adolescents the main indications are:

- Acute schizophrenic psychosis characterized by delusions, hallucinations, thought disorder, aggressive and acting-out behaviour
- chronic and therapy-refractory schizophrenic psychosis and
- symptom suppression and prophylaxis of relapse in acute and chronic schizophrenic psychosis during long-term treatment.

Common contraindications for the use of atypical neuroleptics include acute intoxications with sedative agents (antidepressants, analgesics, hypnotics, tranquilizers), and alcohol. Patients with leukopenia should not be medicated with tricyclic neuroleptics (mainly clozapine). If drugs with high anticholinergic properties are used, pylorus stenosis, glaucoma and prostatic hypertrophy must be excluded. Parkinson's syndrome, seizures, allergic reactions, diseases of the haematological system, hypotension or cardiovascular diseases, liver and kidney diseases, prolactin-dependent tumours, asthma or bronchospasm and pheochromocytoma are further restrictions. The effects of atypical neuroleptics are shown in Table 2.

Clozapine

Absolute contraindications include known dysfunctions and disease of the haematological system, co-medications with substances that carry a risk of bone marrow suppression (with the exception of leukopenia induced by chemotherapy), allergic hypersensitivity reactions against clozapine, acute intoxication or psychosis induced by agents with adverse CNS effects (especially alcohol, antidepressants or other neuroleptics, tranquilizers, hypnotics and opiates), severe cardiovascular, liver, gastrointestinal or renal disease, jaundice, intestinal atonia, and therapy-refractory epileptic seizures.

Relative contraindications are glaucoma, co-medication with

Table 2 Effects of atypical neuroleptics and haloperidol (adopted from (39))

	Sedation	Anticholinergic	Extrapyramidal reaction	Positive symptoms	Negative symptoms	Usual oral dose
Clozapine	+++	+++	+	+++	+++	25–600 mg/day
Olanzapine	++	++	+	+++	+++	5– 20 mg/day
Risperidone	+	+	+	+++	+++	1– 12 mg/day
Quetiapine	+	+(+)	+(+)	+++	+++	150–750 mg/day
Sertindole	+	+	+	+++	+++	16– 24 mg/day
Zotepine	++	++	+(+)	+++	+++	75–300 mg/day
Haloperidol	+	+	+++	+++	++	2– 20 mg/day

+ none or low; ++ moderate; +++ high

Table 3 Side effects of atypical neuroleptics and haloperidol (adopted from (39))

	Acute dystonia	Parkinsonian effects	Acute akathisia	Tardive dyskinesia	Hyperprolactinemia	Seizures	Weight gain	Sexual dysfunctions	Orthostatic hypotension	Other cardiovascular effects	Liver enzyme elevation	Agranulocytosis	NMS
Clozapine	+	+	+	+	+	+++	+++	+	++(+)	+++	+	+++	+
Olanzapine	+	+	+	+	+	+	++	+	+	+	+	+	
Risperidone	++	++	+	+(+)	++	+	+(+)	+	+	+	+	+	+
Quetiapine	+	+	+		+	+	++	+	+	+	+	+	
Sertindole	+	+	+		+	+	++	++	++	++	+	+	
Zotepine	+	+	+			+++	+++			++(+)	++	+	
Haloperidol	+++	+++	+++	++(+)	+++	++	+	+(+)	+	+	+	+	+

+ none or low; ++ moderate; +++ high

other substances that are known to induce leukopenia (e.g. carbamazepine, thioridazine), pregnancy, brain dysfunction, prostate adenoma, allergic reactions to other medications and combinations with depot neuroleptics, especially from the tricyclic type.

Olanzapine

Absolute contraindication is glaucoma.

Relative contraindications include symptomatic prostate adenoma, intestinal obstruction with liver enzyme elevations, liver disease or hepatotoxic medication, low counts of leukocytes, bone marrow depression or toxicity and seizures.

Risperidone

Absolute contraindication is hyperprolactinemia not induced by medication.

Relative contraindications include seizures, prolactin-dependent tumours, severe cardiovascular disease, alterations in blood cell counts, liver and kidney disease and Parkinson's syndrome.

Side effects

If we look at the side effect profile, which is shown in Tables 3 and 4, the differences between the group of atypical neuroleptics in comparison to the typical high-potency neuroleptic

Table 4 Novel neuroleptics: most common side effects (%) (according to (37))

Drug	N	Dosage	Reference
Clozapine Somnolence (24) Tachycardia (17) Constipation (16) Dizziness (14)	126	600 mg/day (mean peak dose)	Kane J, Honigfield G, Singer J et al. (1998) Clozapine for the treatment-resistant schizophrenic. Arch Gen Psychiatry 45: 789–96
Olanzapine Somnolence (30) Dizziness (9) Constipation (8) Weight gain (8)	64	7.5–12.5 mg/day (dose range)	Tollefson GD, Beasely CM, Tran PV et al. (1994) Olanzapine: a novel antipsychotic with a broad spectrum profile. Society of Biological Psychiatry, Philadelphia, PA, 19–21 May 1994
Risperidone Headache (16) Rhinitis (16) Insomnia (13) Agitation (11) EPS (11)	64	6 mg/day	Marder SR and Meibach RC (30)

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haloperidol become evident. Clozapine, for instance, is characterised by the absence of or very low extrapyramidal side effects (EPS), but bears a risk of epileptic seizures, leads to a remarkable weight gain in many patients and causes also, to some extent, orthostatic hypotension and other cardiovascular effects. The highest danger may be its effect on the haematopoetic system, leading to agranulocytosis as the most severe complication. This complication can, however, be avoided by a careful blood count monitoring.

Olanzapine and quetiapine seem to have the lowest rate of side effects, but the efficacy with regard to positive and negative symptoms of schizophrenia in comparison to clozapine is still underinvestigated. Risperidone may cause EPS as parkinsonism and tardive dyskinesia and is also characterized by causation of hyperprolactinemia and, to some extent, also weight gain, but has no adverse effects with regard to hypotension and other cardiovascular effects.

Clozapine

The most common side effects include alterations in blood cell counts like leuko-, granulocyto- and thrombocytopenia as well as agranulocytosis (first symptoms are like a cold). In the first weeks of treatment with clozapine, leukocytosis or eosinophilia may occur. Other common side effects are fever (in case of high fever consider a neuro-malignant syndrome (NMS)), EEG alterations, seizures, headache, tiredness, muscle pain and vertigo. In case of higher doses or quick enhancement of dose delirious states, tremor, akathisia, myoclonus and rigor may occur. Further side effects may be hypersalivation (mainly during night), dry mouth, altered sweat secretion, alterations of accommodation, tachycardia, orthostatic hypotension, ECG alterations, gastro-intestinal disorders (e.g. nausea, vomiting, constipation, seldom ileus), asymptomatic liver enzyme elevation, urine incontinence, bladder dysfunction, skin reactions, weight gain, sedation, thromboembolism due to sedation, and hyperglycaemia with its symptoms. In some cases hypertension, cholestasis, hepatitis, dysphagia, acute pancreatitis, priapism, acute nephritic syndrome, and CK elevation are seen. Rarely hepatic necrosis, arrhythmia, pericarditis, myocarditis and aspiration may occur.

Olanzapine

The most common side effects include drowsiness and weight gain. Sometimes vertigo, increase of appetite, periphreral oedemas, orthostatic hypotension, weak anticholinergic reactions like constipation and dry mouth, asymptomatic liver enzyme elevation, EPS, increase of prolactin plasma level, alterations of blood cell counts like leuko- and thrombocytopenia may occur. Rarely skin reactions, light irritability reactions, NMS, and increase of CK values are seen.

Risperidone

The most common side effects are drowsiness, agitation, fear, headache, somnolence, weakness, dizziness, concentration disturbances, constipation, dyspepsia, nausea, vomiting, abdominal pain, visual disorders, priapism, erectile dysfunction, ejaculation disorder, orgasm disorder, urine incontinence, rhinitis, skin reactions, and other allergic reactions. Sometimes vertigo, orthostatic hypotension, tachycardia, hypertension, EPS, weight gain, oedema, elevation of liver enzymes and increase of prolactin level may occur. Rarely NMS or hypothermia, and seizures are seen.

Clinical applications

The reported rate of non-responders in adult psychiatry is similar to that found in child and adolescent psychiatry, where about 40 % of the children and adolescents with schizophrenia do not respond to classical neuroleptic medication (38). In general there is a lack of controlled studies on the use of atypical neuroleptics in children and adolescents. The only controlled trial has been conducted with clozapine. Concerning the efficacy of risperidone and olanzapine only open trials and case reports are available (Table 5). There are even less data on the other atypical neuroleptics (for review see 52).

Clozapine

In some countries the treatment guidelines for clozapine require that the patients have failed to respond to or have not tolerated standard neuroleptic medications. In Germany and in the USA for example, two other standard neuroleptic agents have to be tested before clozapine treatment may be introduced. Because of the risk of agranulocytosis, the absence of any haematological anomaly (number of white blood cells more than 3500/mm^3, normal differential blood count) is required. Before initiating treatment patients must have a baseline white blood cell and differential count. During treatment white blood cell count has to be monitored (frequency and duration depends on country, e.g. USA: weekly during the entire treatment and four weeks after discontinuation, UK: weekly during first 18 weeks and at least at two-week intervals for the first year, then at least every four weeks and for four weeks after discontinuation, Germany: weekly for the first 18 months and subsequently every four weeks). In addition, total and differential blood counts have to be administered if any symptoms or hints of an agranulocytosis occur.

In our clinic, clozapine is applied to adolescent patients in a dose range of 100 to 600 mg/d or even wider (41, 45, 47). This is in accordance with the therapy protocols from other

Table 5 Reports on the use of clozapine, olanzapine and risperidone in children and adolescents with schizophrenia (modified according to (52))

No. of subjects (Drug trial)	Diagnosis and comorbidity	Mean age y (range)	Treatment duration	Mean dose mg/d (range)[a]	Outcome measures	Results	Reference
Clozapine							
10 (Controlled trial)	Schizophrenia	14.4 ± 2.9	6 wk + 30 ± 15 mo	176 ± 149	BPRS, CGI, BHS, SAPS, SAS, AIMS	Positive + negative symptoms improved, clozapine > haloperidol (p = .04–.002)	Kumra et al. (24)
21 (Open trial)	Schizophrenia	18.1 (57 % < 18)	133 d	352 (150–800)	Symptom checklist	80% improved	Siefen & Remschmidt (49)
57 (Open trial)	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. (44), Blanz & Schmidt (5)
11 (Open trial)	Schizophrenia	(12–18)	6 wk	370 (125–900)	BPRS, CGAS, BHS, SAPS, SANS, AIMS	> 50% improved	Frazier et al. (18), Gordon et al. (20)
36 (Open trial)	Schizophrenia	(14–22)	154 d	330 (50–800)	SANS, SAPS	75 % improved, 8 % no change, 17% worse	Remschmidt et al. (40)
13 (Open trial)	Schizophrenia	16.6 (14–17)	NA	240	BPRS	77% improved	Levkovitch et al. (26)
6 (Open trial)	Psychosis with TD or PTSD	NA	NA	300	NA	6/6 improved	Mandoki (28)
11[b] (Open trial)	Schizophrenia	14.1 (6–18)	6 wk	350	BPRS, BHS	Improved[c]	Piscitelli et al. (36)
31 (Open trial)	Schizophrenia	NA	NA	NA	NA	Improved	Abczynska et al. (1)
20 (Open trial)	Schizophrenia	(14–22)	30 wk	307 (75–600)	BPRS, SAPS, SANS	Improved[d]	Schulz et al. (46)
11 (Open trial)	Schizophrenia	11.3 (9–13)	16 wk	230 (200–300)	PANSS, BPRS, CGI	4/11 improved	Turetz et al. (53)
Olanzapine							
8 (Retrospective study)	Schizophrenia	NA	NA	(5–20)	CGI	8/8 as effective as clozapine	Mandoki (29)
8 (Open trial)	Schizophrenia	15.3 (6–18)	8 weeks	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. (25)
Risperidone							
10 (Open trial)	Schizophrenia	15.1 (11–18)	6 weeks	6.6 (4–10)	PANSS, BPRS, CGI	9 improved, 1 no change; p < .01	Armenteros et al. (3)

Abbreviations: *AIMS* Abnormal Involuntary Movement Scale, *BHS* Bunney-Hamburg Scale, *BPRS* Brief Psychiatric Rating Scale, *CGAS* Children's Global Assessment Scale, *CGI* Clinical Global Impression scale, *NA* not available, *PANSS* Positive and Negative Syndrome Scale, *PDD* pervasive develpomental disorder, *PTSD* postraumatic stress disorder, *SANS* Scale for the Assessment of Negative Symptoms, *SAPS* Scale for the Assessement of Positive Symptoms, *SAS* Simpson-Angus Scale for EPS, *TD* Tourette's disorder, [a]mg/kg are cited when available, [b]8 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 available. [d]No specific data are available about patients improvement with clozapine treatment.

groups (24, 25). Olesen (34) reviews that for adults the range in clozapine application is from 50-900 mg/d.

Efficacy in short-term treatment From studies in adult schizophrenics, it is evident that clozapine treatment has at least the same or a superior antipsychotic effect as compared to conventional neuroleptics. In some studies, clozapine was superior with regard to symptom reduction in severe and acute schizophrenic patients. Other studies demonstrated a superiority of clozapine as compared to chlorpromazine with regard to a reduction of negative symptoms such as emotional withdrawal and flattened affect, measured by BPRS scores (15). As the guidelines do not allow to use clozapine as a first-choice drug, most patients have been treated before with at least two other typical or atypical neuroleptics.

Only one controlled trial has assessed the efficacy of clozapine in child and adolescent psychiatry. 21 (mean age 14.4 ± 2.9 years) adolescents with treatment refractive early-onset schizophrenia received either clozapine (mean [± SD] final daily dose 176 ±149 mg) or haloperidol (mean final daily dose 16 ± 8 mg) in a six week double-blind parallel comparison. Clozapine was found to be superior to haloperidol on all measures of psychosis and showed a striking superiority for both positive and negative symptoms (24).

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Efficacy in maintenance treatment Studies in adult schizophrenia concerning maintenance treatment have been especially interesting because the majority of the patients were non-responders to conventional neuroleptics. These studies demonstrate the superior efficacy of clozapine as maintenance treatment in therapy-refractory psychoses, treated by classical neuroleptics. Beyond that, it could be demonstrated that clozapine was effective in reducing recurrence rates and duration of hospitalization. The superior efficacy of clozapine, although not its effects on recurrence and hospital stay, has also been demonstrated in adolescents suffering from chronic schizophrenia (46, 47).

Treatment recommendations and practical guidelines Treatment recommendations are, in general, the same as in adult psychiatry and have to respect the guidelines of the producing company (6). We have modified these guidelines slightly for the younger age group of patients with early-onset schizophrenia. These guidelines emphasize that the clozapine dosage must always be adjusted individually for each patient. The lowest effective dose should be used, which should be assessed by careful titration. Administration is usually oral, parenteral administration is only available for intramuscular injection using the same dosages and is rarely used. In most cases, intramuscular injections can be replaced by oral administration after a few days.

Some general recommendations for clozapine treatment in childhood and adolescent-onset schizophrenia have been formulated by a consensus conference of 13 German child and adolescent psychiatrists who have special expertise in clozapine treatment (16). The main principles of this consensus conference were as follows:

- clozapine treatment is recommended in acute early-onset schizophrenia under clinical conditions
- clozapine treatment should be tried when at least one traditional neuroleptic agent administered for four to six weeks in an adequate dosage has failed to improve test positive and/or negative symptomatology,
- clozapine is also indicated with the occurrence of intolerable side effects of classical neuroleptics,
- clozapine is also effective in chronic schizophrenia and
- no recommendation can as yet be given for relapse prevention because of inadequate data

Olanzapine

Olanzapine is given in an order of magnitude lower dosage than clozapine. For olanzapine the literature for adolescent schizophrenics is rare, but adult patients are treated in general with doses between 5 and 20 mg/d.

In a recent study, Kumra et al. (25) treated eight patients with early-onset schizophrenia with olanzapine. The mean age of the group was 15.3 years, the mean duration of illness 4.6 years. The group was exceedingly ill, demonstrated by the rating score on the Brief Psychiatric Rating Scale of 53.2 ± 15.3 at baseline. The patients were described as being treatment-refractory after having used on average 2.3 different neuroleptic medications at intake. Four subjects had previously been responsive to clozapine; however, this medication had to be discontinued because of adverse side effects. The treatment period lasted for up to eight weeks. The dosage was titrated on a weight-adjusted basis up to a maximum of 20 mg daily. The results of this trial demonstrated a significant improvement in symptomatology indicated by a 17 % improvement of the BPRS, a 27 % improvement on the Scale for the Assessment of Negative Symptoms and a 1 % improvement on the Scale for the Assessment of Positive Symptoms. In terms of the Clinical Global Impression Scale, three patients were rated as much improved and two as minimally improved. In the others there was either no change or they became even worse. In a follow-up investigation (follow-up interval three to 14 months), half of the subjects continued olanzapine medication, the other half discontinued treatment, because of an inadequate response. The adverse side effects were quite marked: six out of eight patients suffered increased appetite, nausea, vomiting, headache, somnolence, sustained tachycardia and increased agitation. In five patients, constipation and concentration problems were observed, and seven out of eight patients suffered from insomnia and showed elevations of liver transaminase levels.

In conclusion, the effect of olanzapine in this group of patients was not very impressive, and the adverse side effects were quite substantial. In particular, a weight gain after a six-week period of treatment of 3.4 ± 4.1 kg is quite striking and would be a particular problem for adolescents.

Risperidone

Several investigations in adult patients have demonstrated a significant improvement of positive and negative symptoms comparable to the efficacy of haloperidol. For risperidone doses of 1–12 mg/d are reported (for review see 14). In a meta-analysis it has been proposed that risperidone might have a higher efficacy than haloperidol in the improvement of negative symptoms (8). Flynn et al. (17) conducted an open trial on treatment resistant schizophrenics (mean treatment duration: 12.1 weeks). 57 patients were treated with clozapine at a mean dose of 420 mg; 29 received risperidone, at a mean dose of 7.75 mg. Their results indicated a better improvement of positive and negative symptoms in those treated with clozapine compared to risperidone. However, risperidone appeared to be more effective than the typical neuroleptics on both positive and negative symptoms and on global psychopathology. In a controlled trial of 86 treatment refractive schizophrenic

patients, risperidone has been shown to be as effective on positive and negative symptoms as clozapine (7).

Until now there has been no controlled study on the use of risperidone in children and adolescents. Only one open trial has assessed its efficacy (3). Risperidone produced clinically and statistically significant improvement in 10 schizophrenics on the Positive and Negative Symptom Scale for schizophrenia, the Brief Psychiatric Rating Scale, and the Clinical Global Impression at a mean daily dosage of 6.6 mg (range 4 to 10 mg). The reported side effects in this study included: mild somnolence during dose finding (8 of 10 subjects), acute dystonic reaction (2/10), parkinsonism (3/10), mild oro-facial dyskinesia (1/10), blurred vision (1/10), impaired concentration (1/10), and weight gain (8/10, mean weight gain 4.85 kg). Throughout the study, electrolytes, blood cell count, liver enzymes, and ECG remained within normal limits. Several case studies also suggest a good efficacy of risperidone in child and adolescent schizophrenia (for review see 52). Side effects (see Tables 2 and 3) and receptor binding profile (Table 1) suggest that risperidone may be more related to the typical neuroleptics. Thus, due to the dose-dependence of EPS, it has been questioned whether risperidone can really be called an atypical neuroleptic (9). It has been demonstrated that dosages of 10 mg/day or more cause EPS, which can be avoided by the administration of dosages below 6 mg/day (30).

Conclusions

- Atypical neuroleptics belong meanwhile to the spectrum of pharmaco-therapeutic interventions in child and adolescent psychiatry. In spite of the relative lack of empirical studies, especially controlled studies, there is ample evidence that these groups of pharmacological agents have, where indicated, favourable effects and less adverse effects than classical neuroleptics. The most frequently used atypical neuroleptics in child psychiatry are clozapine, olanzapine and risperidone. For the other atypical neuroleptics, listed up in some tables of this article, there are no systematic studies in child psychiatry so far. Only a few case reports are available.
- Main indications of atypical neuroleptics are acute schizophrenic episodes, chronic and therapy-refractory schizophrenic psychoses and prophylaxis of relapses in acute and chronic schizophrenia. For other indications (e.g. affective disorders, manic states, autism, Tourette's disorder) there is less empirical evidence.
- One of the major questions is the use of atypical neuroleptics as a medication of first choice. This is not possible for clozapine, which according to the guidelines require lack of response or non-tolerance of at least two standard neuroleptic medications. Olanzapine and risperidone can, in principle, be used as medications of first choice, but it is not clear if their antipsychotic effect in acute states of schizophrenic psychoses is comparable, especially on positive symptoms, to classical neuroleptics such as haloperidol.
- A careful monitoring of effects and side effects has to be carried out during all treatment phases. The major danger of clozapine treatment is granulocytopenia respectively agranulocytosis. These adverse effects can be avoided by a careful monitoring regime. Other adverse effects include weight gain, which applies also to olanzapine, hypersalivation and anticholinergic effects. The absence of EPS and the relative efficacy also on negative symptoms, however, are great advantages. Risperidone seems to be effective on positive and negative symptoms also in adolescent schizophrenia, but is known to cause EPS in the higher doses range in a quite substantial proportion of the patients.
- It is imperative that children and adolescents who are treated with atypical neuroleptics and their parents should be informed about the disorder and the effects and side effects of the medication.

In conclusion, atypical neuroleptics have enriched our treatment programmes, especially in childhood and adolescent schizophrenia. Further studies are necessary in order to differentiate the indications tested so far and to find out if the spectrum of indications can be broadened.

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