# Treatment Challenges and Safety Considerations for Antipsychotic Use in Children and Adolescents With Psychoses

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With increased prescribing of psychotropic medications to children and adolescents, more attention should be given to the safety and tolerability of these drugs in this population. Compared with adults, children are especially vulnerable to adverse effects, including extrapyramidal symptoms (EPS), sedation, weight gain, and prolactin elevation. The prevalence of EPS is much higher in children treated with conventional antipsychotics than in those given atypical antipsychotics. Sedation, which can be minimized through gradual dose escalation, is common with risperidone, olanzapine, quetiapine, and ziprasidone. The relative propensities for producing weight gain in children and adolescents are olanzapine > risperidone > quetiapine. All conventional and some atypical antipsychotics (e.g., risperidone) increase serum prolactin levels. Nonetheless, preclinical studies suggest that atypical antipsychotics may have neuroprotective effects in the central nervous system; further studies, especially in children and adolescents, are required to confirm these results.

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Because of their improved safety compared with conventional antipsychotics, atypical antipsychotics are increasingly being used in vulnerable patient populations, such as children and adolescents with psychoses. However, there are few randomized placebo-controlled clinical trials on the safety and tolerability of these agents in the pediatric population. This review covers some of the treatment challenges involved in prescribing atypical antipsychotics to children and adolescents. Various safety issues are covered, as well as the possibility of using atypical antipsychotics for the prevention of psychiatric conditions or in a neuroprotective capacity.

## DOSING AND PRESCRIBING ISSUES

### Pharmacokinetic Differences in the Pediatric Population

Appropriate dosing in children and adolescents is difficult because few clinical trials evaluating dosing have been carried out in this population. The pharmacokinetics of some drugs may be different in children and adolescents because of developmental issues. Drug uptake and distribution may be affected by age-related factors, such as active tissue growth and differences in the proportions of organ and tissue masses. For example, children have larger livers relative to body weight and may metabolize medications more efficiently than do adults. Consequently, children may require higher dosages relative to their body weight than do adults for drugs whose metabolism is primarily hepatic.[1] Furthermore, the proportion of adipose tissue and the degree of protein binding of drugs tend to be lower in children than in adults. Both of these factors can result in increased bioactivity from a given dose, in terms of both therapeutic and adverse effects.[2]

### Use of Antipsychotic Pharmacotherapy in Children and Adolescents

Antipsychotics are frequently prescribed to children and adolescents for off-label uses. A review of 100 charts[3] of children who had been treated with antipsychotics at various public inpatient facilities found that only 11.3% had a diagnosis of psychosis; the most common diagnoses were disruptive disorders (33.3%) and depression (24.0%). Furthermore, at discharge, 87% of the patients were receiving 2 or more psychotropic medications. The most common combinations were an atypical antipsychotic plus mood stabilizer (40%) and an atypical antipsychotic plus selective serotonin reuptake inhibitor (SSRI) (30%).

However, antipsychotics are not the most commonly prescribed psychotropic medications in children and adolescents. A survey conducted in 1995 showed that the

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most frequently prescribed psychotropics were stimulants, followed by SSRIs.[4] Similarly, a study of prescribing patterns conducted from 1992 to 1996 at office-based medical practices as determined by the National Ambulatory Medical Care Survey showed that prescriptions for psychotropic medications were given during 2.2% of all visits for patients up to age 19 years.[5] The most commonly prescribed psychotropic medications were stimulants (prescribed during 53.9% of visits), antidepressants (30%), mood stabilizers (12.7%), and antipsychotics (7.2%).

Another survey used the Medicaid managed care database of the Connecticut Department of Social Services to obtain data for the 1-year period ending June 30, 1999.[6] Of the 196,549 youths younger than 19 years, 9447 (4.8%) received at least 1 psychotropic medication. The most commonly prescribed psychotropics were stimulants (48.2%), antidepressants (23.9%), mood stabilizers (9.1%), and antipsychotics (7.7%). Among those who were prescribed psychotropics, 13.6% had multiple psychotropic pharmacotherapy (prescriptions for 2 or more different classes of psychotropic drugs during a 7-day period). The most common drug class combination was an antidepressant plus an antipsychotic (21.9%). An antipsychotic was prescribed in 41.9% of youths who received multiple psychotropic pharmacotherapy.

A population-based analysis of nearly 900,000 youths (aged under 20 years) enrolled in 2 U.S. health care systems examined ten 1-year cross-sectional data sets from 1987 through 1996.[7] During this 10-year period, the use of psychotropic medication in general increased 2- to 3-fold, and this pattern of increasing use also applied to antipsychotics. In another study in preschool children (aged 2 through 4 years), the prescribing of antipsychotics increased 1.2- to 1.5-fold over the 4-year period from 1991 to 1995.[8] These data support the notion that the use of psychotropic medications in young patients is growing.

## VULNERABILITY TO ADVERSE EFFECTS OF ANTIPSYCHOTIC DRUGS

The increase in the prescribing of psychotropic medications to children and adolescents indicates that more attention needs to be given to the safety and tolerability of these drugs in this population. As detailed in this section, compared with adults, the pediatric population is especially vulnerable to the development of many different types of adverse events.

The occurrence of adverse events may have a negative impact on patient compliance with pharmacotherapy. Compliance rates for children tend to be lower than those for adults, and adolescents are especially at risk for poor compliance because of control issues and defensive mechanisms, such as denial and acting out.[9]

The functioning of the central nervous system (CNS) may also be different in children than in adults because the various neurotransmitter systems develop at different times during childhood. For example, the dopaminergic and noradrenergic systems develop earlier than the serotonergic system.[2] Studies in animals suggest that developing neurotransmitter systems can be irreversibly altered by early inhibition or stimulation by pharmacologic agents.[10] In other experimental models, working memory may be impaired by a deficiency of dopamine type 2 ($D_2$) and $D_3$ receptors or by chronic use of antipsychotic drugs that block $D_2$ receptors.[11] These effects may help explain why children and adolescents are especially sensitive to adverse events affecting the CNS.

### Extrapyramidal Symptoms and Dyskinesias

In a literature review of studies of antipsychotics in children and adolescents, the incidence of extrapyramidal symptoms (EPS) was higher in younger patients than in adults.[12] Positron emission tomography receptor studies in adults show that the development of EPS is related to $D_2$ receptor occupancy.[13] The densities of $D_1$ and $D_2$ receptors in the striatum are highest in infancy and decrease during childhood. Thus, $D_2$ receptor densities are higher in children and adolescents than in adults. Because the absolute number of occupied receptors can be higher in the pediatric population than in adults, the probability of developing EPS may be increased.[12]

The prevalence of EPS is much higher in children treated with conventional antipsychotics than with atypical antipsychotics. For example, of 41 children, adolescents, and young adults withdrawn from chronic (conventional) antipsychotic treatment in a 1984 study, 18 developed tardive dyskinesia, withdrawal dyskinesia, or other withdrawal symptoms or transient behavior deterioration after termination of treatment.[14] In another study of 104 children and adolescents who were residents at a child psychiatric center,[15] the prevalence of parkinsonism, tardive dyskinesia, or akathisia among 61 patients receiving antipsychotics during the evaluation was 34% and was significantly associated with longer antipsychotic periods immediately before evaluation. At the same time, the prevalence of treatment-emergent tardive dyskinesia among 41 patients who had at some time taken antipsychotics for at least 90 consecutive days was 12%. These data illustrate the sensitivity of children and adolescents to the development of parkinsonism, akathisia, and tardive dyskinesia when they are treated with conventional antipsychotics.

Recent studies have examined whether atypical antipsychotics have a decreased risk of EPS compared with conventional antipsychotics. For example, a prospective study evaluated 102 seriously emotionally disturbed children and adolescents who were receiving conventional or atypical antipsychotics or both.[16] Probable tardive dyskinesia was observed in 5.9% of the youths treated with antipsychotics. Furthermore, the use of conventional antipsychotics was significantly associated with development

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of more frequent dyskinesia as compared with the use of atypical antipsychotics. Atypical antipsychotics cause less risk for EPS than do conventional antipsychotics in seriously emotionally disturbed children and adolescents.

A decreased incidence of EPS has been observed in children and adolescents treated with olanzapine and quetiapine compared with risperidone.[17] A retrospective chart review of 97 children and adolescents treated in an outpatient mental health clinic examined the comparative adverse events associated with the use of risperidone, quetiapine, and olanzapine.[18] Extrapyramidal symptoms occurred in 14 (19%) of 75 risperidone patients, 1 (6%) of 16 olanzapine patients, and 1 (4%) of 25 quetiapine patients.

### Sedation

The sedative effects of atypical antipsychotics may be particularly deleterious to the pediatric population because drowsiness can impair attention and learning at school. Sedation, which can be minimized by using gradual dose escalation, is a common adverse event observed with risperidone, olanzapine, quetiapine, and ziprasidone.[17,19] Transient mild sedation was observed in 11 children and adolescents with pervasive developmental disorder who were treated with risperidone.[20] Treatment with olanzapine is more likely to produce sedation in children and adolescents than in adults.[21] Somnolence was the most common adverse event related to quetiapine treatment among adolescents in an 8-week open-label study (4 of 15 patients)[22] and in a long-term open-label study (6 of 10 patients).[23] Although sedation appears to be a common adverse event in the acute and maintenance treatment of children and adolescents prescribed atypical antipsychotics, the degree of sedation that occurs does not usually interfere with drug therapy because the sedation is frequently transient and does not lead to drug withdrawal.[24]

### Weight Gain

Weight gain has a significant negative effect on the physical and emotional development of children and adolescents. In addition to being an important risk factor for serious medical conditions such as type 2 diabetes mellitus and cardiovascular disease, obesity also has a negative impact on the self-esteem of children and adolescents.

Several studies have examined the weight gain produced by risperidone treatment. In a study conducted in 11 children and adolescents (aged 7–17 years) with pervasive developmental disorders who were treated with risperidone, weight gain was a frequent adverse event.[20] Six children experienced an average weight gain of 7.2 kg in 6 months. Weight changes associated with 6-month treatment with risperidone were investigated in 37 child and adolescent inpatients in a juvenile psychiatric institution.[25] Risperidone treatment produced statistically significant weight gain between baseline and endpoint that became apparent within 2 months of starting treatment; the mean rate of increase was 1.2 kg/month, and weight did not stabilize during the course of the study. Furthermore, treatment with risperidone for 6 months produced clinically significant weight gain in 78% of the children and adolescents compared with 24% of the 33 control inpatients with no exposure to antipsychotics. A pilot study conducted in children, adolescents, and adults with mental retardation and autism examined weight changes associated with risperidone treatment.[26] Over 1 year, mean weight gain was greater among 5 children and 6 adolescents (8.2 kg and 8.4 kg, respectively) than among 8 adults (5.4 kg). Furthermore, the weight gain from risperidone tends to be greater in persons with mental retardation than in persons with schizophrenia and a normal IQ.[26]

A higher risk of weight gain with olanzapine than with risperidone has been observed for children and adolescents.[17] A retrospective chart review of 97 patients treated with various atypical antipsychotics (quetiapine, risperidone, and olanzapine) revealed that weight gain was the most common adverse effect observed with all 3 antipsychotics.[18] The mean weight gain after 3 months was 3.9 kg with risperidone, 3.3 kg with quetiapine, and 6.4 kg with olanzapine.

Weight gain with quetiapine is generally less than that with olanzapine or risperidone.[17] In an open-label extension study in 10 adolescents who were treated with quetiapine (mean daily dose = 600 mg) for an average of 445 days, the mean change in body weight over 64 weeks was 6.8 kg.[23] The mean ± SD body mass index increased from 25.75 ± 1.4 kg/m$^2$ to 27.11 ± 3.0 kg/m$^2$ over the same period of time. Thus, treatment with quetiapine caused some weight gain over the course of 1 year. The relative propensities of different atypical antipsychotics for producing weight gain in children and adolescents are olanzapine > risperidone > quetiapine.[17]

Clinical studies, mainly in adult patients, of the newer atypical antipsychotics indicate that weight gain is not a significant problem with ziprasidone[27,28] or aripiprazole.[29,30] However, experience with these 2 agents in the pediatric population is limited; in one report, open-label use of ziprasidone in 12 young patients with autism or other pervasive developmental disorder did not lead to significant weight gain.[31]

### Prolactin Elevation

All conventional antipsychotics, risperidone, and olanzapine increase serum prolactin levels.[32] The adverse events associated with hyperprolactinemia (menstrual disturbance, galactorrhea, and sexual dysfunction) may be particularly distressing to adolescents.

Several studies have examined the effects of various atypical antipsychotics on serum prolactin levels in children and adolescents. In one study, 35 children and adolescents (mean age = 14 years) with early-onset psychosis were treated with haloperidol, clozapine, or olanzapine.[33]


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Serum prolactin levels increased above the upper limit of normal for 9 of 10 patients taking haloperidol, 7 of 10 patients given olanzapine, and 0 of 15 patients treated with clozapine after 6 weeks of treatment. In addition, treatment with olanzapine is linked to a greater risk of hyperprolactinemia in adolescents than in adults.[21]

Increased levels of prolactin have been observed in adolescents treated with risperidone but not in those treated with clozapine or quetiapine.[19] Prolactin levels were unchanged in an 8-week, open-label study of quetiapine in 15 adolescents with psychotic symptoms.[22] Data on prolactin levels were also examined from an open-label study in which 10 adolescents received quetiapine in dosages ranging from 50 to 800 mg/day over 21 to 27 days.[34] Plasma prolactin levels decreased from baseline for girls and remained unchanged for boys. Treatment with risperidone or olanzapine is more likely to elevate plasma prolactin levels in children and adolescents than treatment with clozapine or quetiapine.

## MONITORING RECOMMENDATIONS

Children and adolescents are generally more sensitive to adverse events than are adults; thus, more careful monitoring of these patients may be necessary during their treatment with atypical antipsychotics. Baseline measurements are needed for the body systems at risk for the development of antipsychotic-induced adverse events. The following baseline measurements may be useful: hematology values (leukocytes, platelets, hemoglobin), serum chemistry values (electrolytes, renal and liver function tests, thyroid hormones, prolactin, glucose), height and weight, and urine drug screen.[35] The physical examination should include a thorough baseline assessment of the extrapyramidal system, along with determination of whether there are any neurologic abnormalities that may confer an increased risk for dyskinesias.

Obtaining a baseline electrocardiogram (ECG) is recommended before starting treatment with risperidone, olanzapine, quetiapine, or ziprasidone.[36] The acceptable range for ECG parameters are as follows: PR interval < 200 ms, QRS duration < 120 ms, and QTc < 460 ms. After steady-state plasma drug concentrations have been achieved, a repeat ECG should be obtained to verify that these measurements remain within their acceptable limits.

## EARLY INTERVENTION AND PREVENTION OF PSYCHIATRIC DISORDERS AND PRODROMAL SYMPTOMS

### Earlier Versus Later Intervention

In various studies, the interval between onset of psychosis and initiation of treatment ranges from 0.4 to 3.2 years.[37] Prolonged untreated psychosis may lead to neurotoxicity and poorer clinical outcomes; and although no clear relationship has been demonstrated between the duration of untreated psychosis and the risk of relapse, early treatment may still be warranted in terms of reducing suffering and possibly improving long-term outcome.[37]

Several reasons have been put forward to explain the delay in the diagnosis and treatment of schizophrenia.[38] Concerns about false-positive or false-negative case identification have contributed to delayed or missed diagnoses. Diagnosis may also be impeded by concerns about causing needless worry and social stigmatization at a time when patients are showing only prodromal manifestations. Concerns about the effectiveness and safety of antipsychotic medications have contributed to hesitance in initiating pharmacotherapy. Finally, ethical concerns about research in pediatric patients have impeded the collection of scientific evidence relating to early-onset psychosis.

However, a significant change has occurred in the attitude of psychiatrists toward early treatment of psychotic disorders. Accumulating evidence from studies of first-episode schizophrenia suggests a correlation between earlier treatment and better prognosis.[38] Furthermore, the introduction of atypical antipsychotics that have better risk-benefit ratios than those of conventional antipsychotics makes it possible to consider early intervention in psychotic disorders.

Although some research suggests a positive correlation between the duration of untreated psychosis and cognitive deterioration,[39,40] other studies have not linked untreated psychosis to progressive biological toxicity affecting brain function.[41–43] For example, cognitive functioning during first-episode psychosis was measured in 156 patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder.[42] In these patients, the mean duration of untreated initial psychosis was 74.3 weeks. There were no statistically significant differences in most domains of neurocognitive functioning between patients grouped by longer-than-median versus shorter-than-median duration of untreated psychosis.

### Identification of Prodromal Symptoms of Psychiatric Conditions

***Schizophrenia.*** Among individuals with first onset of schizophrenia, neuropsychological and brain structural abnormalities may be developmental in origin. The following prodromal signs characterize the preschizophrenic stage: deviant development with delayed milestones, lower IQ, solitary play, excessive anxiety, and minor neurologic problems.[44] Preliminary findings from a pilot study in 54 adolescents and young adults suggest that the prodromal phase of schizophrenia consists of at least 3 progressive stages: attenuated negative or disorganized symptoms, attenuated positive symptoms, and symptoms that are schizophrenia-like in intensity but do not meet the diagnostic criteria for schizophrenia.[45] In the earliest

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Table 1. Potential Risks and Benefits of Identification in the Putatively Prodromal Phase of Schizophrenia[a]

| Identification Risks | Identification Benefits |
|---|---|
| Unnecessary anxiety, dysphoria, or both | Close monitoring of symptoms |
| Stigmatization, discrimination, or both by others | Early identification of psychotic disorder |
| Self-stigmatization | Reduced treatment delay |
| Avoidance of developmentally appropriate challenges | Reduced risk of hospitalization |
| | Reduced risk of behaviors that are harmful, stigmatizing, or both (eg, suicide attempts, violence, strange or bizarre responses) |

[a]Reprinted from Heinssen et al.[52] This information is in the public domain.

Table 2. Potential Risks and Benefits of Treatment in the Putatively Prodromal Phase of Schizophrenia[a]

| Treatment Risks | Treatment Benefits |
|---|---|
| Unnecessary monitoring | Reduced distress from presenting symptoms |
| Unnecessary medication exposure | Reduced distress from prodromal symptoms |
| Medication adverse effects | Attenuation of full-blown psychosis |

[a]Reprinted from Heinssen et al.[52] This information is in the public domain.

prodromal stage, treatment with antidepressants appears to be as beneficial as treatment with atypical antipsychotics.

In a retrospective survey designed to characterize symptoms in the prodromal stage of schizophrenia, the parents of 17 children with childhood-onset schizophrenia or schizoaffective disorder indicated that the most common initial manifestations were developmental delays, learning disabilities, problems at school (11 children), and behavioral problems, such as tantrums, aggression, opposition, and attention-deficit/hyperactivity symptoms (11 children).[46] The parents first suspected problems when their children were 1.5 to 7 years old, and clinical assessments were performed when the children were 2 to 11 years old. The mean age at onset of psychotic symptoms was 8.6 years, and the mean age at diagnosis of schizophrenia or schizoaffective disorder was 10.5 years.

A retrospective study examined 110 children and adolescents (aged 10–17 years) with first-episode psychoses.[47] First psychotic episodes occurred earlier in 61 patients with schizophrenia than in 49 patients with other psychoses (14.1 vs. 14.7 years; $p = .07$), and premorbid social impairment was more severe in the schizophrenia group.

The risk of developing schizophrenia is 48% for identical twins, 17% for fraternal twins, 13% for offspring, and 9% for siblings of a person with schizophrenia, reflecting the declining degree of gene sharing associated with this order of relationships.[11] A model was developed to estimate the probability that screening family members of patients with schizophrenia would detect individuals who would subsequently also develop the disease.[48] However, the results suggested that the number of new cases obtained by this procedure was low—approximately 19 new cases of schizophrenia per year per 10,000 relatives screened.

***Psychoses in general.*** To assess selected environmental events as possible risk factors for psychosis, mothers whose children had been diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder were interviewed by telephone.[49] There were statistically significant differences between cases (N = 264) and controls (N = 528) for the following variables: fever during pregnancy, complications during delivery, city or suburban residence at birth, cat ownership between birth and age 13 years, and breast-feeding.

Individuals at high risk for developing psychosis (nonspecific symptoms in patients with schizotypal personality disorder or a first-degree relative with a psychotic disorder and patients with subthreshold or brief transient psychotic symptoms) were assessed monthly and observed for 12 months or until the development of psychosis.[50] Of these individuals, 20 (40.8%) of 49 developed a psychotic disorder within 12 months. The following were highly significant predictors of psychosis: a long interval between onset of symptoms and contact with psychiatric services; poor level of function at intake; and presence of low-grade psychotic symptoms, depression, and disorganization.

***Bipolar disorder.*** Seventeen studies were reviewed that examined children and adolescents who had at least 1 parent with bipolar disorder.[51] The studies suggest that the children of parents with bipolar disorder have an increased risk for developing mood and other disorders. For example, the rates of mood disorders in offspring ranged from 5% to 67% and the rates of other psychopathology ranged from 5% to 52% compared with lower rates in the offspring of healthy volunteers (0%–38% and 0%–25%, respectively).

## Ethical Issues

Early intervention in persons who are not psychotic but show prodromal symptoms or are considered at high risk for schizophrenia but who are not psychotic presents ethical issues. There are benefits and risks associated with early identification (Table 1) and early treatment (Table 2) of schizophrenia. The risks include unnecessary anxiety (for false-positives) and stigmatization. The medical benefits accrue mainly for individuals who are true positives.

There appears to be a consensus that the benefits outweigh the risks in studies on reducing the duration of untreated psychosis,[53] although pre-onset detection and prophylactic intervention are still controversial. However, even if the biological toxicity hypothesis is not confirmed, subthreshold prodromal symptoms may produce a psychosocial burden that justifies intervention in receptive patients.[54]


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### Results of Clinical Early Intervention Studies

Early intervention programs treat patients with first-episode psychosis, patients with attenuated positive symptoms suggesting early psychosis, and patients with known genetic risk and at least moderate functional impairment.[54] A pilot study of short-term (8–12 weeks) treatment with low-dose (1.0–1.8 mg/day) risperidone was conducted in 5 patients (aged 15–20 years; mean age = 15.6 years) with prodromal symptoms and a family history of schizophrenia and 11 patients (aged 16–35 years; mean age = 23.9 years) with first-episode schizophrenia.[55] Among the 4 prodromal and 6 first-episode patients who completed the study, adverse events were minor and transient, and performance on tests of verbal learning improved significantly (from 30% to 100%) and comparably in both groups. Furthermore, the severity of thought and behavior disturbance ratings decreased by 30%. This study suggests that treatment with a low-dose atypical antipsychotic is feasible and can produce positive cognitive changes. However, these results need to be confirmed in randomized clinical trials with larger samples and longer follow-up times.

In a Dutch study of 97 adolescent and young adult patients with first episodes of psychoses, the patients had a relatively short duration (mean time = 5.4 months) of untreated psychosis.[56] After 3 months of inpatient treatment, 76 patients participated in 12 months of outpatient follow-up. By conservative criteria, the psychotic relapse rate was low (15.8%) over the 15-month intervention program. Seventy-three of the patients were then followed up for 5 years, and data available for analysis in 71 patients showed that the initial low relapse rate was not maintained: over the course of 60 months, 52% of the patients had 1 or more psychotic relapses, 25% developed chronic positive symptoms, and only 23% did not have another psychotic episode. These results show that early intervention may therefore improve short-term but not long-term outcome in schizophrenia.

A randomized controlled trial compared 2 interventions, needs-based psychotherapy alone and in conjunction with preventive therapy with low-dose risperidone (mean dosage = 1.3 mg/day) plus cognitive-behavioral therapy, in 59 patients at risk for progression to first-episode psychosis.[57] The patients were treated for 6 months and then provided with needs-based intervention. After 6 months of treatment, 10 (36%) of 28 patients who received only needs-based intervention progressed to first-episode psychosis compared with 3 (9.7%) of 31 patients who also received risperidone ($p = .03$). After a 6-month follow-up period, 3 additional patients who were treated with risperidone became psychotic, and the difference between the 2 interventions was no longer statistically significant. Thus, treatment with low-dose risperidone appeared to delay the onset of psychosis but may not have prevented it completely.

An intervention study is currently in progress at the Yale University (New Haven, Conn.) Prevention Through Risk Identification Management and Education (PRIME) clinic. The PRIME trial has enrolled 35 patients in a randomized, double-blind, placebo-controlled study. Patients are randomly assigned to low dosages (5–15 mg/day) of olanzapine plus supportive psychotherapy or placebo plus psychotherapy. Patients receive 1 year of treatment and 1 year of follow-up. The investigators conducting the trial believe that all patients benefit from careful monitoring and stress management psychotherapy and that those who receive active medication may also benefit in terms of amelioration of prodromal symptoms and prevention of conversion to psychosis.[54] However, the results of this study are not yet available.

How these various findings and considerations apply to child and adolescent patients with psychosis is unclear at this point. It could be argued that earlier identification and treatment could lead to better eventual outcomes. Alternatively, younger patients showing clear psychotic phenomenology could be representative of a group with a poorer prognosis. Further research is needed. For children and adolescents with psychosis, it is also unclear whether the effects of early intervention are greater than those in adults, and, if so, whether the effects are related to age at onset or duration of illness, or both.

## POSSIBLE NEUROPROTECTIVE EFFECTS OF MEDICATION

Preclinical studies of various medications such as atypical antipsychotics, mood-stabilizing drugs (e.g., lithium), and anticonvulsants (e.g., topiramate) suggest that these drugs may have neuroprotective effects in the CNS. These drugs have been studied for their effects on various proteins, such as neurotrophins, and on neurogenesis (Table 3).[58–71] In children and adolescents, developmental neuroprotective actions may be more marked.

### Neurotrophins

Neurotrophins are secretory proteins that regulate long-term survival and differentiation of neurons.[72] However, neurotrophins have recently been shown to play an important role in synaptic development and plasticity in different neuronal populations. For example, brain-derived neurotrophic factor (BDNF) has been shown to exert both presynaptic and postsynaptic effects in the modulation of hippocampal long-term potentiation, a cellular model for learning and memory.

The neurotrophin hypothesis of psychosis postulates that changes in the expression of neurotrophins could contribute to neural maldevelopment and disturbed neural plasticity that may be associated with schizophrenic psychoses.[73] In a test of this hypothesis, BDNF and neurotrophin-3 (NT-3) levels in postmortem brain

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**Table 3. Summary of Selected Preclinical Studies of Antipsychotics and Neuroprotection**

| Study | Antipsychotic | Method | Results | Conclusions |
|---|---|---|---|---|
| Hashimoto et al[58] | Lithium | Rat and mouse cerebral cortical neurons in cell culture<br>Cell viability measured | Pretreatment with lithium protected neurons from glutamate excitotoxicity in wild-type mice but not in BDNF knockout mice | The BDNF pathway may be involved in the neuroprotective effect of lithium |
| Bai et al[59] | Haloperidol<br>Clozapine<br>Olanzapine | Rat hippocampus<br>28-day drug administration<br>In situ hybridization | Haloperidol ↓ BDNF mRNA expression in CA1 and dentate gyrus<br>Clozapine and olanzapine ↑ BDNF mRNA expression in the CA1, CA3, and dentate gyrus regions of the hippocampus | Typical and atypical antipsychotics differentially regulate BDNF mRNA expression in hippocampus |
| Chlan-Fourney et al[60] | Haloperidol<br>Clozapine<br>Risperidone | Rat hippocampus<br>In situ hybridization<br>Northern blot analysis<br>Chronic and acute administration of drugs | Chronic (19-day) but not acute administration of antipsychotics altered hippocampal BDNF mRNA levels<br>Low doses of risperidone and clozapine were without effect | Long-term down-regulation of hippocampal BDNF mRNA may be associated with side effects rather than clinical efficacy |
| Xu et al[61] | Quetiapine | Chronic immobilization-stressed rats<br>Western blot analyses<br>Immunohistochemistry | Pretreatment with quetiapine attenuated the stress-induced ↓ in BDNF protein in the hippocampus<br>Quetiapine also attenuated ↓ BDNF immunoreactivity in hippocampal pyramidal and dentate granular neurons | Chronic administration of quetiapine could have neuroprotective effects on hippocampal neurons |
| Riva et al[62] | Haloperidol<br>Chlorpromazine<br>Clozapine<br>Quetiapine<br>Olanzapine | Subcutaneous injections of drugs in rats<br>Western blot analyses | Clozapine ↑ FGF-2 mRNA and protein in striatum<br>Other drugs did not alter the expression of FGF-2 | FGF-2 has neurotrophic activity; thus, clozapine may have neuroprotective potential |
| Li et al[63] | Olanzapine | PC12 cell cultures<br>cDNA probes<br>Cellular RNA measured | Olanzapine ↑ SOD1 gene expression and ↓ p75 gene expression | Up-regulation of SOD1 mRNA and blockade of p75 mRNA are associated with reduced cell death, suggesting that olanzapine may have neuroprotective potential |
| Parikh et al[64] | Haloperidol<br>Clozapine<br>Risperidone<br>Olanzapine | Chemical analyses on rat brain homogenates | Chronic haloperidol ↓ SOD and catalase activity<br>Atypical antipsychotics did not change levels of antioxidant enzymes | Chronic administration of haloperidol, but not of atypical antipsychotics, induced oxidative stress |
| Ichikawa et al[65] | Quetiapine<br>Iloperidone<br>Melperone | Rats<br>DA and ACh assays | The 3 atypical drugs preferentially increased DA and ACh release in the MPC compared with the nucleus accumbens | The effects on ACh release may be related to the improved cognition seen with some atypical antipsychotics |
| Ichikawa et al[66] | Haloperidol<br>Sulpiride<br>Thioridazine<br>Clozapine<br>Risperidone<br>Olanzapine<br>Ziprasidone | Rats<br>ACh assay | Atypical antipsychotics (clozapine, olanzapine, risperidone, ziprasidone) ↑ ACh in MPC<br>Typical antipsychotics (haloperidol, sulpiride, thioridazine) did not affect ACh release in MPC<br>No antipsychotic affected ACh release in nucleus accumbens or striatum | The difference in atypical and typical antipsychotics in their ability to increase cortical ACh release may contribute to their different effects on cognition |
| Wakade et al[67] | Haloperidol<br>Risperidone<br>Olanzapine | Rats fed drugs in drinking water for 20 days<br>Immunohistochemistry | Atypical antipsychotics ↑ newly divided neurons in subventricular zone<br>Haloperidol had no effect | The neurogenesis stimulated by atypical antipsychotics in adult brain might explain the improved cognition seen with these drugs |
| Angelucci et al[68] | Haloperidol<br>Risperidone | Immunocytochemistry<br>Rat brains | Both antipsychotics ↓ BDNF in frontal cortex, occipital cortex, and hippocampus | Alterations of BDNF levels could be a mechanism of action of antipsychotic drugs |
| Angelucci et al[69] | Haloperidol<br>Risperidone | Rat brains<br>Radioimmunoassay<br>Enzyme-linked immunosorbent assay<br>29-day drug administration | Both antipsychotics ↑ NGF-LI levels in hypothalamus but ↓ levels in striatum and hippocampus<br>Haloperidol ↑ NPY-LI levels in occipital cortex<br>Risperidone ↑ NPY-LI levels in occipital cortex, hippocampus, and hypothalamus | The effects of antipsychotic drugs on levels of NYP-LI and NGF-LI may be important in their therapeutic properties |
| Bai et al[70] | Clozapine<br>Quetiapine<br>Risperidone | PC12 cell cultures<br>Cell viability measured<br>Northern blot analyses | All 3 drugs improved cell viability after serum withdrawal<br>Atypicals ↑ SOD1 gene expression and ↓ p75NTR mRNA expression | The atypical antipsychotics may have neuroprotective effects through modulation of SOD1 and p75NTR expression |
| Gruber and Mathe[71] | Haloperidol<br>Risperidone | Rat brains<br>28-day drug administration<br>Radioimmunoassay | Haloperidol ↑ NPY-LI in hypothalamus and occipital cortex<br>Haloperidol and risperidone ↓ NPY-LI in ventral striatum | Haloperidol and risperidone selectively affected levels of neuropeptide Y in brain tissue and microdialysates |

Abbreviations: ACh = acetylcholine, BDNF = brain-derived neurotrophic factor, DA = dopamine, FGF = fibroblast growth factor, MPC = medial prefrontal cortex, mRNA = messenger RNA, NGF-LI = nerve growth factor-like immunoreactivity, NPY-LI = neuropeptide Y-like immunoreactivity, p75 = low affinity nerve growth factor receptor, p75NTR = p75 neurotrophin receptor, SOD = superoxide dismutase.
Symbols: ↓ = decreased, ↑ = increased.


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tissue from patients with schizophrenia were determined by enzyme-linked immunoassay.[74] When compared with controls, patients had significantly increased BDNF levels in cortical areas and significantly decreased levels in the hippocampus. In addition, NT-3 levels in frontal and parietal cortical areas were significantly lower in patients than in controls. These findings tend to support the neurotrophin hypothesis of schizophrenic psychosis.

The neurotrophin hypothesis suggests that increasing the level of BDNF expression may counteract some of the pathologic changes that occur during the development of schizophrenia. Consequently, drugs that increase BDNF levels may provide some degree of neuroprotection. For example, the BDNF pathway may be involved in the neuroprotective effects of lithium.[58] Various in vitro studies have shown that atypical antipsychotics alter BDNF levels in the hippocampus and may provide neuroprotection.[59–61]

Another neurotrophin that has been investigated is fibroblast growth factor (FGF-2). In a study in rats, only clozapine increased FGF-2 expression in the rat brain.[62] Other atypical antipsychotics (quetiapine and olanzapine) and conventional antipsychotics were ineffective in altering FGF-2 expression.

### Gene Expression

Drugs can also exhibit neuroprotective characteristics by inducing the expression of various genes. For example, p75 is a low-affinity neurotrophic receptor that plays a role in neuronal apoptosis, and superoxide dismutase (SOD) is an enzyme that inactivates free oxygen radicals and reduces oxidative stress. Thus, increasing SOD levels and decreasing p75 activity are both associated with reduced cell death. In a cell culture model, olanzapine increased SOD expression and decreased p75 expression.[63] However, in another study in whole rat brain homogenates, haloperidol produced oxidative stress by decreasing SOD activity; at the same time, olanzapine, risperidone, and clozapine had no effect on SOD.[64]

### Cholinergic System

Acetylcholine has an important function in maintaining cognition.[75,76] Consequently, enhancing cholinergic transmission in the CNS may result in improved cognition. Atypical antipsychotics, but not conventional antipsychotics, have been shown to increase the release of acetylcholine in the rat medial prefrontal cortex.[65,66] Patients with schizophrenia have shown improvements in cognition after treatment with some atypical antipsychotics,[77–80] and improved cholinergic neurotransmission may contribute to this benefit.

### Neurogenesis

Another mechanism by which a drug may exert neuroprotective effects is by stimulating the formation of new neurons in the brain. The atypical antipsychotics risperidone and olanzapine increased the number of newly divided neurons in the subventricular zone of rats, in contrast to the conventional antipsychotic haloperidol, which had no effect on neurogenesis.[67] This stimulation of neurogenesis by atypical antipsychotics might help explain the improved cognition observed with these drugs.

## CONCLUSIONS

Although the atypical antipsychotics are not free of adverse events, their improved tolerability compared with conventional antipsychotics has led to their increased use in children and adolescents. Pediatric patients are more vulnerable than are adults to the development of many different types of adverse events, such as EPS, sedation, weight gain, and elevated prolactin levels. The prevalence of EPS is higher in children treated with conventional antipsychotics than with atypical antipsychotics. Among the atypical antipsychotics, the propensity for producing EPS is greater with risperidone than with olanzapine or quetiapine. Sedation is a common adverse event observed with risperidone, olanzapine, quetiapine, and ziprasidone. The relative propensities for producing weight gain in children and adolescents are olanzapine > risperidone > quetiapine. All conventional and some atypical antipsychotics (i.e., risperidone, olanzapine) increase serum prolactin levels.

Studies of patients experiencing their first episode of psychosis have demonstrated that pediatric patients typically remain undiagnosed and untreated for up to 3 years. Prolonged untreated psychosis can have serious effects because of a direct neurotoxicity. Preventing this biological toxicity is one of the rationales for early treatment of schizophrenia and other psychotic disorders. A pilot study suggests that pretreatment with a low dosage of an atypical antipsychotic is feasible and can produce positive cognitive changes in patients in the prodromal stage of schizophrenia.

Preclinical studies of atypical antipsychotics suggest that these drugs may have neuroprotective effects in the CNS. Atypical antipsychotics have been shown to increase the expression of some neurotrophins (e.g., BDNF), enhance cholinergic neurotransmission in the medial prefrontal cortex, increase the expression of antioxidant enzymes, and induce neurogenesis. All of these effects could improve neuronal survival in the early stages of psychotic disorders such as schizophrenia, and further study of these effects in vulnerable pediatric populations is warranted.

*Drug names:* aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

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