

Antipsychotic Medications in Children and Adolescents

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Antipsychotic medications are commonly prescribed to children and adolescents. These medications, however, are not only prescribed for young patients with psychosis, but are often prescribed for youths with a variety of psychiatric disorders. Despite the fact that psychiatric illness in the pre-adult era is not rare, few controlled clinical trials have examined the short-term safety and efficacy of these agents in youths with psychosis. There are even fewer data regarding the long-term safety and efficacy of these agents in psychotic children and adolescents. As new antipsychotics become available, the study of these agents in youngsters with a variety of psychiatric illnesses may become an exciting new avenue for research.
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Neuroleptics are among the psychotropic agents most frequently prescribed by child psychiatrists.¹ A review of the literature reveals that neuroleptics have been used to treat many psychiatric disorders in youngsters (Table 1). A discussion of the use of antipsychotic medications in these patients provides an interesting perspective, for reviews of these agents in adults typically focus on an individual diagnostic entity and not an age-defined population.

Despite the widespread use and potent action of these medicines, there is a relative paucity of studies of neuroleptics in children and adolescents when compared with studies in adults,² even though psychopharmacology research has demonstrated that children's and adolescents' responses to psychotropic medications may be significantly different than those of adults. For example, despite numerous placebo-controlled studies that have demonstrated the superiority of tricyclic antidepressants (TCAs) over placebo in adults with major depression, no controlled study has definitively demonstrated that TCAs are more effective than placebo for this disorder in children or adolescents. Therefore, it cannot be presumed that adolescents or children will respond to psychotropic treatment with the same direct effects or side effects as adults. In 1995, the determinants that contribute to these differences in response are not fully understood.

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Table 1. Psychiatric Diagnoses for Which Neuroleptics Have Been Used in Children and Adolescents

Schizophrenia
Mood disorders
Autism (pervasive developmental disorders)
Mental retardation
Tourette's syndrome (tic disorders)
Conduct disorder
Anorexia nervosa
Attention-deficit hyperactivity disorder
Personality disorders

In this article, we will review the research that has been performed regarding the use of antipsychotic agents in the young. This is a particularly timely topic because new atypical antipsychotic agents that are effective in the treatment of adults with serious psychiatric illness have recently been developed. A review of the literature may provide direction for promising areas of further investigation and point to the role that these new medications may have in the treatment of youngsters with psychiatric disorders.

SCHIZOPHRENIA

Schizophrenia in adults is a severe psychotic illness for which antipsychotic medications are routinely used. We have approached our neuropsychiatric research to assess how schizophrenia and other psychotic disorders in teenagers either resemble or differ from adult forms of these illnesses.³ In the course of our work on the neuropsychiatry of psychotic teenagers, we have observed that treatment is rarely studied.

One may presume that the reason that adolescents with psychotic illnesses are seldom studied is because teenagers rarely suffer from psychotic illnesses. Epidemiologic

Table 2. Controlled Clinical Trials of Neuroleptics in Pre-Adults With Schizophrenia

Author	Year	Subject		Medication		Placebo-Control	Comments
		Number	Age (y)	Drug	Mean Dose (mg/d)		
Pool et al ⁸	1976	75	13-18	Loxapine	87.5	Yes	Both active medications were superior to placebo
				Haloperidol	9.8		
Realmuto et al ⁹	1984	21	11-18	Thiothixene	16.2	No	Both medications were equally effective; side effects differed
				Thioridazine	178		
Spencer et al ¹³	1992 ⁷	12	5-12	Haloperidol	2.02	Yes	Active medication was superior to placebo

data, however, demonstrate that a significant number (10%–30%) of patients with schizophrenia develop psychosis prior to their eighteenth birthday.⁴⁻⁶ Another reason one might presume that schizophrenia is infrequently studied in youngsters is that its symptoms are very different in the young. However, current evidence⁷ shows that the symptoms that characterize schizophrenia in adults are similar to those in children and adolescents with the disorder, which is reflected in the lack of specific DSM-IV diagnostic criteria for schizophrenia in teenagers compared with adults.

Another reason that therapeutic trials with antipsychotic agents may have been previously rare in teenagers with psychotic illnesses may be due to the fact that typical antipsychotic medications may be associated with the same significant side effects seen in adult patients. Hesitation to study medications with potentially serious side effects may partially explain why so few studies of neuroleptics have been performed in adolescents.

When one considers the sizable number of youngsters who suffer from schizophrenia, it becomes apparent that antipsychotic medications are not being carefully examined in a large and potentially vulnerable population. With the recent availability of the atypical antipsychotic agents, clozapine and risperidone, new, promising therapeutic options have become available for adults with psychotic illness. In adults, there is evidence that atypical antipsychotic medications may be associated with fewer extrapyramidal symptoms (EPS) than typical neuroleptics. If atypical antipsychotic medications have a similar side effect profile in pre-adults, these antipsychotics may have a significant advantage over their predecessors for young patients. It will be important to see what roles these agents may have in the treatment of children and adolescents.

A MEDLINE search of the literature on acute treatment of schizophrenia in children and adolescents revealed only three controlled clinical trials that have examined the safety and efficacy of typical antipsychotic agents in children or adolescents with schizophrenia (Table 2). In addition, we were unable to find any studies on maintenance treatment. Since compliance (or noncompliance) can have a profound effect on treatment in teenagers, we were surprised that we could not locate a single study that evalu-

ated the use of depot neuroleptics in children or adolescents with psychotic illnesses.

The first report is of a double-blind, placebo-controlled study that was performed by Pool et al.⁸ in 75 adolescents with schizophrenia. The patients were randomly assigned to receive either placebo, loxapine, or haloperidol for 4 weeks. Doses of medications could be adjusted on the basis of clinical response to a maximum of 200 mg/day of loxapine or 16 mg/day of haloperidol. The authors found that both loxapine and haloperidol were superior to placebo in reducing psychotic symptoms in this population. The most common neuroleptic-induced side effects noted by the investigators were pseudoparkinsonism and sedation. Pseudoparkinsonism occurred in 73% of patients who received neuroleptics as compared with 4% of the patients receiving placebo. Twenty-five percent of patients receiving placebo were reported as being sedated at least once during the study, whereas 81% of the patients who received loxapine and 52% of the patients who received haloperidol experienced some degree of sedation during this study.

This original work was followed by a study by Realmuto et al.⁹ who performed a comparison of thiothixene and thioridazine in 21 adolescents with schizophrenia diagnosed by DSM-III criteria. Patients were administered medication for a period of 4–6 weeks. The authors found that both medications had equal therapeutic efficacy as measured by the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impression (CGI) scale. Despite finding similar therapeutic response, the authors cited different rates of adverse effects for each medication. Fifty-four percent of patients treated with thiothixene experienced EPS while no patients treated with thioridazine experienced any EPS. Only patients treated with thioridazine experienced dizziness (25%) and orthostatic hypotension (13%). Drowsiness was present in 75% of the patients treated with thioridazine and 54% of the patients treated with thiothixene. Of interest was the authors' observation that response was good despite the fact that most participants had an insidious onset of schizophrenia.

We are aware of no other controlled clinical medication studies in adolescents with schizophrenia. Although other controlled studies that were performed before 1980 de-

scribed investigations into the therapeutic efficacy of antipsychotic agents in children with psychosis or schizophrenia.^{10,11} It is likely that many of the subjects in these studies suffered from autism or another pervasive developmental disorder and not schizophrenia.¹² To our knowledge, there has been only one published article that has reported preliminary data from an ongoing double-blind, placebo-controlled crossover study that is examining the efficacy of haloperidol in children with schizophrenia.¹³ This article described data from 12 subjects aged 5–11 years who met DSM-III-R criteria for schizophrenia. The authors reported that haloperidol (the dose of which was adjustable based on clinical response) was found to be superior to placebo in treating psychotic symptoms in these children.

When compared with studies in adults, the number of studies that have been performed in young patients with schizophrenia is miniscule. From these studies, it appears that typical antipsychotics are effective in ameliorating symptoms and improving functioning in youngsters with psychotic illness. Of note, high degrees of side effects were reported to be associated with neuroleptic treatment. Yet studies such as fixed-dose trials to investigate thresholds of lowest effective dose have not been performed.

The development of atypical antipsychotic agents for the treatment of schizophrenia in adults is an important advance in the pharmacotherapy of this disorder. Clozapine has been shown to be an effective treatment for adult patients who are not responsive to other antipsychotic treatments. There are several open-label reports that have described clozapine as an effective treatment for neuroleptic-resistant psychosis in youngsters with schizophrenia.^{14–16}

Risperidone, the first atypical antipsychotic medication approved for general use, has been shown to be effective in the treatment of adults with schizophrenia and may have a significant clinical advantage over previous antipsychotic agents, as studies have reported that risperidone is associated with fewer EPS than neuroleptics. This improved side effect profile is an important advantage for risperidone. As can be seen from previous studies of children and adolescents with schizophrenia, typical antipsychotic agents may be associated with very high rates of EPS. Practicing clinicians have noted that adolescents seem especially prone to dystonia, which can have a long-term impact on acceptability of antipsychotic treatment. The improved side effect profile of risperidone makes it a theoretically promising drug for potential use in youngsters with psychotic illnesses.

Since risperidone may be both effective and associated with fewer side effects than neuroleptics in patients with schizophrenia, several adolescents with schizophrenia who received treatment at the residential treatment center of Parmadale Family Services, Parma, Ohio, were offered a therapeutic trial of risperidone. A chart review¹⁷

of patients treated at Parmadale Family Services with risperidone has been completed. BPRS ratings were performed at baseline and endpoint for six of these patients. The mean baseline BPRS score for this cohort was 47.8, and the mean endpoint BPRS score was 28.0. Only one of the six patients was switched to another antipsychotic due to lack of therapeutic efficacy. The only adverse events noted included sedation and mild parkinsonism. This latter effect was found to be treated effectively by simply lowering the risperidone dose. Our preliminary experience indicates that risperidone may hold promise for the treatment of adolescents with schizophrenia. As more youngsters are treated with risperidone, it will be important to see if this improved side effect profile is generalizable.

MOOD DISORDERS

Psychosis can complicate both depression and mania in children, adolescents, and adults. Although it is generally accepted that antipsychotics can serve as useful adjuncts to mood-stabilizing medications, we were unable to identify any studies that systematically assessed the use of antipsychotic medications in children or adolescents with mood disorders.

One explanation that may account for the lack of studies may be due to the controversy in the diagnosis of psychosis in children and adolescents. Concerns were initially raised by Carlson and Strober¹⁸ that adolescents with bipolar illness were being misdiagnosed with schizophrenia. Although recent research indicates that diagnostic accuracy has improved, bipolar disorder is still often underdiagnosed in this age group.¹⁹ Since much of the research done on youths with bipolar disorder has focused on both diagnostic concerns and the potential salutary effects of lithium, the investigation of these important considerations may have detracted from the execution of clinical trials into the use of neuroleptics in this population.

As far as the atypical antipsychotic agents are concerned, there is evidence that clozapine may be effective for adult patients with refractory mood disorders.²⁰ A recent case report of a 13-year-old boy who suffered from refractory bipolar illness and obsessive-compulsive disorder noted that he responded to treatment with a combination of clozapine, clomipramine, and lithium after failing previous therapeutic trials of typical antipsychotic agents given concomitantly with mood-stabilizers and anti-obsessional agents.²¹ We could not locate any reports regarding the use of risperidone in children or adolescents suffering from mood disorders with psychotic features.

Since young patients with mood disorders may suffer from psychosis, research is needed on the use of antipsychotic agents in this population. An important avenue of investigation may be the examination of comparing the safety and efficacy of the atypical antipsychotics with the traditional therapies for these youngsters. Some investiga-

tors have reported recently that an exacerbation of manic symptoms may be associated with risperidone monotherapy.²² Others have failed to find a worsening of mania in patients who were treated with a combination of risperidone and a mood-stabilizer.²³ Investigators of risperidone for teenagers with bipolar disorder may consider including a mood-stabilizing drug in future clinical trials.

AUTISTIC DISORDER

Significant behavioral disturbances (e.g., stereotypies and hyperactivity) can complicate the management of patients with autistic disorder. Haloperidol has been described as being effective in ameliorating many of these problematic behaviors in double-blind, placebo-controlled studies.^{24,25} A recent open-label study has reported pimozide may also be a useful agent in this disorder.²⁶ Unfortunately, EPS and acute dystonic reactions may complicate the use of typical antipsychotic agents in this population.^{24,25}

Risperidone may be a promising new agent for the treatment of autistic disorder. The safety and pharmacokinetics of a single dose of risperidone in six children aged 3–7 years with autistic disorder has been described.²⁷ At a dose of either 0.015 or 0.030 mg/kg, the only adverse effect that was found was sedation, which appeared to be dose-related. The half-life of risperidone and 9-hydroxyrisperidone was approximately 30%–35% shorter for children than for adults.

We have found from our clinical experience at the Rainbow Autism Center (University Hospitals of Cleveland, Cleveland, Ohio) that risperidone may be safe and useful in patients with autistic disorder who could not tolerate or had suboptimal clinical response to therapeutic trials with other antipsychotic agents. This finding has led us to perform an open-label, dose-finding study that is systematically examining the safety and efficacy of risperidone in children with autistic disorder (Findling RL, Maxwell K, Wiznitzer M. Manuscript in preparation).

OTHER DISORDERS

Antipsychotic agents are used for other disorders that are commonly found in children and adolescents who receive psychiatric attention. Patients with mental retardation who suffer from a variety of behavioral difficulties have been described as being helped by antipsychotic medications. Short-term use of these medications may be complicated by acute dystonic reactions and EPS. In addition, long-term use of antipsychotic medications also carries an association with a risk of tardive dyskinesia. These adverse reactions may limit the usefulness of antipsychotics in this population. For this reason, clinicians may prescribe therapeutic trials with other medications in hopes of avoiding these side effects.

There are reports^{28–33} that typical antipsychotic agents may be helpful for youngsters with conduct disorder, attention-deficit hyperactivity disorder (ADHD), and the other diagnoses listed in Table 1. Again, concerns regarding acute effects and long-term side effects have led clinicians away from the typical antipsychotics and toward other pharmacologic interventions.

CONCLUSION

The disorders for which antipsychotic agents are often prescribed in adults (such as schizophrenia, bipolar disorder, and major depression with psychotic features) are present in children and adolescents. Although the limited data that are available regarding treatment of these disorders in youngsters suggest usefulness of antipsychotics, the paucity of studies precludes drawing clear conclusions.

In schizophrenia, clozapine appears safe and effective for neuroleptic nonresponders. Risperidone also shows promise as a possible frontline therapy for schizophrenia, although reports of experiences with risperidone are just beginning to emerge. Risperidone may also prove to be a useful pharmacologic treatment for autistic disorder.

Since the traditional antipsychotic medications are widely used in children and adolescents, the possibility of studying new antipsychotic agents in youngsters is an exciting avenue for potential research. In addition, since children and adolescents may respond differently to pharmacotherapy than adults, explorations into the factors that may lead to differences in response should also be undertaken.

One factor that may play a role in explaining variations in treatment response between adults and youngsters is pharmacokinetics and pharmacodynamics. The pharmacokinetics and pharmacodynamics of a medicine may be quite different in youngsters when compared with adults. Therefore, treatment failures or apparent declines in therapeutic efficacy may be more of a reflection of developmental changes in biodisposition rather than medication tolerance. Few studies have examined the pharmacokinetics of this class of medicines in this age group. Clinical trials that examine the relationships between pharmacokinetics, pharmacodynamics, and treatment response may eventually help determine why treatment successes or failures occur with psychotropic medicines in this age group.

The number of pharmacologic studies that have been performed in child and adolescent psychiatry has been quite small.² Despite this fact, antipsychotic agents are used for many indications in child and adolescent psychiatry. As new atypical agents that potentially have fewer short- and long-term side effects become marketed, significant improvements in treatment for youngsters with a variety of psychiatric disorders may become available. The systematic evaluation of these new agents in both

children and adolescents may eventually lead to better care for youngsters who suffer from potentially debilitating mental illnesses.

Drug names: clozapine (Clozaril), clomipramine (Anafranil), haloperidol (Haldol and others), loxapine (Loxitane), pimozone (Orap), risperidone (Risperdal), thioridazine (Mellaril and others), thiothixene (Navane).

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