

Second-Generation Antipsychotic Drugs for Children and Adolescents

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The effectiveness and safety of antipsychotics have not been fully established in children and adolescents. Many antipsychotics approved for use in adults are prescribed off-label to children and adolescents. We investigated the effectiveness and tolerability of antipsychotics for children and adolescents with schizophrenia and bipolar disorder. A literature review of the empirical evidence regarding the use of antipsychotics, particularly second-generation antipsychotics, in children and adolescents showed that these drugs were safe and effective for this population. Antipsychotics were similarly effective for treatment of schizophrenia and bipolar disorder in children and adolescents. When prescribing antipsychotics to this population, clinicians should consider adverse events and the discontinuation rate in treated patients. However, the current evidence shows a lack of consensus regarding the use of antipsychotics in children and adolescents. (*J Nippon Med Sch* 2021; 88: 10–16)

Key words: antipsychotics, children, adolescents, effectiveness, tolerability

Introduction

Although there are serious concerns about the proper use of psychotropic drugs, the effectiveness and safety of antipsychotics have not been established in children and adolescents. Thus, many antipsychotics are now prescribed off-label to this population.

Studies performed between 1990 and 2010 were compiled in the American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameters for the Use of Atypical Antipsychotic Medications in Children and Adolescents, but data collected after 2010 were not included. We therefore reviewed studies of the use of second-generation antipsychotics (SGAs) to determine the effectiveness and tolerability of these drugs for children and adolescents.

Methods

Only a few studies have comprehensively compared the effectiveness and tolerability of first-generation antipsychotic (FGA) and (SGA) drugs in children and adolescents. With the exception of some special cases requiring intravenous administration, SGAs are usually the first-line antipsychotics for adults. Studies of SGA use in chil-

dren and adolescents are outlined below. Because studies conducted between 1990 and 2010 have already been compiled in the AACAP Practice Parameters for the Use of Atypical Antipsychotic Medications in Children and Adolescents¹, only studies published between January 1, 2010 and May 30, 2017 were included in this study.

A literature search was performed using the PubMed database. We narrowed the search by using delimiters and filters, including English language only and human studies published in medical journals during this period and used the Boolean operators, child “OR” adolescent “AND” drug name (eg, clozapine). This study focused primarily on schizophrenia and bipolar disorder and excluded case reports. Studies of children younger than 6 years were also excluded. Nine antipsychotic drugs (clozapine, olanzapine, risperidone, quetiapine, aripiprazole, paliperidone, asenapine, perospirone, and blonanserin) approved in Japan were included in our search; however, few studies evaluated perospirone, blonanserin, and clozapine use in adolescents.

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Results

Effectiveness in Children and Adolescents

Schizophrenia

A long-term study² and a short-term, double-blind, randomized controlled trial³ (RCT) compared the effects of olanzapine, risperidone, and molindone in patients with early-onset schizophrenia (EOS) spectrum disorders. There was no significant difference in effectiveness or discontinuation rate among the three drugs. A meta-analysis of the use of antipsychotics in patients with EOS compared eight FGAs and SGAs with placebo⁴. The meta-analysis included 11 studies ($n = 1,714$) and assessed the effectiveness of aripiprazole, haloperidol, molindone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone by using the positive and negative syndrome scale (PANSS). All drug treatments resulted in significant improvement in PANSS total score at week 6, but the improvement was significant only for molindone, olanzapine, and risperidone.

Another meta-analysis⁵ compared the effectiveness of the antipsychotics olanzapine, risperidone, and aripiprazole in adolescents with schizophrenia (age, 13-17 years; $n = 666$). All treatments resulted in significant improvement, as measured by PANSS. To determine the effectiveness of antipsychotics for 2,158 children with EOS, we analyzed data from 12 trials (duration, 6-12 weeks) of patients aged 8-19 years who received eight antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone)⁶. Change in PANSS score was comparable among all antipsychotics (low- to moderate-quality evidence) except ziprasidone (very low- to low-quality evidence), and all antipsychotics except ziprasidone and asenapine (low- to moderate-quality evidence) were superior to placebo (low- to high-quality evidence). Positive change in PANSS and additional effectiveness outcomes were comparable among antipsychotics. This meta-analysis showed that most antipsychotics (except for ziprasidone and perhaps asenapine) had comparable effectiveness in the treatment of EOS.

An open-label multicenter study of participants enrolled for 6-12 months, including two double-blind RCTs, assessed adolescents with EOS treated with risperidone⁷. PANSS scores had significantly improved after treatment, as compared with baseline. A 6-week placebo-controlled trial used PANSS scores to confirm the effectiveness of quetiapine in adolescents with EOS⁸. A 6-week multicenter, double-blind, randomized, placebo-controlled, parallel-group study of adolescents with EOS assessed

the effectiveness of extended-release paliperidone⁹. The patients were randomly assigned to placebo or one of three extended-release paliperidone groups (low-, medium-, and high-dose) on the basis of body weight. That study showed a significantly greater improvement in final PANSS score in the medium-dose extended-release paliperidone group than in the placebo group. Furthermore, an RCT of the effectiveness of aripiprazole and paliperidone in adolescents with schizophrenia assigned patients to two treatment periods (8 weeks of acute-phase treatment and 18 weeks of maintenance treatment)¹⁰. Patients with schizophrenia and a PANSS score of 60-120 were assigned to the paliperidone group or aripiprazole group. PANSS scores did not significantly differ for the two drugs at day 56 and day 182. In another 2-year open-label trial of adolescents with schizophrenia, treatment with paliperidone was started¹¹ and showed effectiveness during the maintenance therapy period. A double-blind, controlled trial of asenapine in patients with EOS compared the effectiveness of asenapine 5 mg/day and 10 mg/day with a placebo group¹². Asenapine was confirmed to be safe but did not show effectiveness.

Bipolar disorder

Analysis of effectiveness for bipolar disorder in children and adolescents showed positive results only for the manic and mixed phase. In a double-blind RCT of patients with bipolar disorder, risperidone had a more immediate effect than valproic acid on manic episodes. However, there was no significant difference in the ultimate effectiveness of these drugs¹³. In a multicenter RCT of risperidone, lithium, and valproic acid as initial therapy for management of bipolar I disorder, risperidone showed higher effectiveness than lithium and valproic acid¹⁴. Mixed models for repeated measures analysis revealed a significant difference between risperidone and placebo groups. A 3-week, double-blind, placebo-controlled study showed that quetiapine was efficacious for children and adolescents with mania¹⁵. A double-blind, controlled trial that used the Young mania rating scale (YMRS) score to evaluate aripiprazole after 4 weeks of treatment in children with manic or mixed episodes confirmed its effectiveness¹⁶. After 4 weeks, patients completing the acute treatment continued to receive ≤ 26 weeks of double-blind treatment. That study confirmed the effectiveness of aripiprazole¹⁷. In a 3-week double-blind controlled trial of patients in the manic phase or mixed state of bipolar I disorder, patients were assigned to placebo or asenapine 2.5 mg twice daily, 5 mg twice

daily, or 10 mg twice daily, and effectiveness was assessed with the YMRS¹⁸. Asenapine yielded significantly higher YMRS scores at all doses, as compared with the placebo group.

The above effectiveness outcomes of SGAs in children and adolescents (except those from meta-analyses) are summarized in **Table 1**.

Safety Data in Children and Adolescents

Olanzapine

To determine the safety of antipsychotics for 2,158 adolescents with EOS, we analyzed 12 trials (duration, 6-12 weeks) of patients aged 8-19 years receiving eight antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone)⁶. Weight gain was primarily associated with olanzapine; extrapyramidal symptoms (EPS) and akathisia were associated with molindone; and prolactin increased with risperidone, paliperidone, and olanzapine. Serious adverse side effects, discontinuation of treatment, sedation, insomnia, and change in triglycerides did not differ among antipsychotics. The adverse reaction profiles among the investigated antipsychotics were consistent with prior findings in adults.

Risperidone

An open-label multicenter study of participants enrolled for 6-12 months, including two double-blind RCTs, was performed in adolescents with EOS treated with risperidone⁷. Adverse symptoms were observed in more than 10% of the patients. A multicenter RCT of the use of risperidone, lithium, and valproic acid as initial therapy for management of bipolar I disorder found that risperidone resulted in severe metabolic abnormalities¹⁴. A systematic review¹⁹ of associations between SGAs and prolactin-related adverse events in pediatric patients showed that risperidone, olanzapine, and two doses of paliperidone were associated with an increase in prolactin level as compared with baseline. A prospective observational study analyzed sex, pubertal status, risperidone dosage, psychiatric diagnosis, and personal/family history of genetic diseases in relation to serum prolactin levels at baseline and after 3-months of risperidone treatment²⁰. Mean serum prolactin level was significantly higher after 1 month of treatment. Moreover, a 1.5-year follow-up study of bone mass reduction in boys administered risperidone for ≥ 6 months showed a significant decrease in bone mass in the group receiving continuous risperidone²¹.

Aripiprazole

A meta-analysis⁵ assessed the comparative safety of the

antipsychotics olanzapine, risperidone, and aripiprazole in adolescents with schizophrenia (age, 13-17 years; $n = 666$). Weight gain was higher in patients treated with olanzapine. Risperidone treatment was associated with a significant increase in the incidence of akathisia, tremor, and dystonic events, as compared with control. A high-dose aripiprazole regimen was associated with higher incidence of tremor and Parkinsonism than in control patients. Treatment with aripiprazole 10 mg daily was associated with the lowest incidence of EPS and resulted in no significant weight gain.

Paliperidone

A meta-analysis of 55 studies ($n = 5,423$) compared aripiprazole, haloperidol, molindone, olanzapine, paliperidone, pimozide, quetiapine, risperidone, and ziprasidone with placebo, to assess the risk of QTc interval prolongation (mean age, 12.8 years)²². The risk of QTc interval prolongation in healthy adolescents was low; however, caution is warranted because of the interaction of individual risk factors in patients with cardiac complications. An RCT assessed the tolerability of aripiprazole and paliperidone in adolescents with schizophrenia by dividing the study period into an 8-week acute-treatment phase and 18-week maintenance-treatment phase¹⁰. Patients with schizophrenia and a PANSS score of 60-120 were assigned to the paliperidone group or aripiprazole group. Both drugs were tolerated in adolescents with schizophrenia.

Asenapine

In a 3-week double-blind controlled trial of patients in the manic phase or mixed state of bipolar I disorder¹⁸ asenapine was adequately tolerated, in terms of adverse reactions. In a 50-week open-label study, safety was assessed by evaluating adverse reactions²³. Asenapine had adequate tolerability in children with bipolar I disorder.

The above safety outcomes of SGAs in children and adolescents (except for those of meta-analyses) are summarized in **Table 2**.

Discussion

To evaluate the effectiveness of treatments for schizophrenia in young people, six drugs (olanzapine, risperidone, quetiapine, aripiprazole, paliperidone, and asenapine) were studied. Although there were differences in the number of reports, all drugs except asenapine were effective. Four drugs have been studied to assess the effectiveness of antipsychotics for bipolar disorder: risperidone, quetiapine, aripiprazole, and asenapine. All were effective against bipolar disorder. However, the deciding

Table 1 Summary of reported efficacy outcomes of second-generation antipsychotic (SGA) drugs in children and adolescents

Study	Age (years)	Study design	Subjects (N)	Efficacy Outcomes	Dosage of SGA drugs
Findling RL et al. [12]	8-19	Long term study, up to 44 additional weeks, followed by a short-term, double-blind, randomized controlled trial	Early-onset schizophrenia spectrum disorders (54)	No agent demonstrated superior efficacy.	molindone 10-140 mg/day, olanzapine 2.5-20 mg/day, risperidone 0.5-6 mg/day
Pandina G et al. [7]	13-17	6- to 12-month open-label, multicenter study	Schizophrenia (264)	Subjects who were enrolled for 12 months demonstrated continued efficacy, as determined by reductions in Positive and Negative Syndrome Scale (PANSS) total and factor scores, as well as by improvement in global clinical status and overall functioning.	Risperidone 2-6 mg/day
Findling RL et al. [8]	13-17	6-week placebo-controlled study	Schizophrenia (220)	Quetiapine 400 and 800 mg/day provided significant improvements in symptoms associated with schizophrenia in adolescent patients, including the primary efficacy measure of PANSS total score change.	Quetiapine 400-800 mg/day
Singh J et al. [9]	12-17	6-week multicenter, double-blind, randomized, placebo-controlled study	Schizophrenia (201)	The mean (SD) change in PANSS total score from baseline to endpoint was significant for the paliperidone extended-release (ER) medium-treatment versus placebo.	Paliperidone 1.5-12 mg/day
Savitz AJ et al. [10]	12-17	Randomized controlled trial	Schizophrenia (228)	Paliperidone ER did not demonstrate superior efficacy to aripiprazole in treating adolescent schizophrenia. Both drugs showed clinically meaningful improvements in symptom and functional measurements.	Aripiprazole 2-15 mg/day, Paliperidone 3-9 mg/day
Savitz A et al. [11]	12-17	2-year open-label trial	Schizophrenia (400)	Paliperidone ER exhibited efficacy in the maintenance treatment of schizophrenia in adolescents.	Paliperidone 1.5-12 mg/day
Findling RL et al. [12]	12-17	8-week double-blind trial and a 26-week open-label extension	Schizophrenia (306)	Although improvements in PANSS total score at day 56 of the acute phase were numerically greater for both asenapine 2.5 and 5 mg b.i.d. than for placebo and were maintained in the open-label extension (OLE), the primary end-point did not achieve statistical significance in the acute phase.	Asenapine 5-10 mg/day
Pavuluri MN et al. [13]	8-18	Double-blind randomized controlled trial	Bipolar disorder (66)	Risperidone group had more rapid improvement than the divalproex group, although final scores did not differ significantly between groups.	Risperidone 0.5-2 mg/day
Geller B et al. [14]	6-15	Multicenter, randomized, controlled trial	Bipolar I disorder (279)	Risperidone was more efficacious than lithium or divalproex sodium for the initial treatment of childhood mania.	Risperidone 0.25-6 mg/day
Pathak S et al. [15]	10-17	3-week double-blind placebo-controlled trial	Bipolar I disorder (277)	Quetiapine was significantly more effective than placebo in improving manic symptoms in youth.	Quetiapine 400-600 mg/day
Mankoski R et al. [16]	10-17	4-week double-blind controlled trial	Bipolar I disorder (296)	Seven of the 11 Young mania rating scale (YMRS) line items showed a statistically significant improvement in both aripiprazole treatment groups versus placebo.	Aripiprazole 10-30 mg/day
Findling RL et al. [17]	10-17	Randomized, double-blind, 30-week, placebo-controlled trial	Bipolar I disorder (210)	Aripiprazole 10 mg/day and 30 mg/day was superior to placebo. Despite the benefits of treatment, completion rates were low in all treatment arms.	Aripiprazole 10-30 mg/day
Findling RL et al. [18]	10-17	3-week double-blind controlled trial	Bipolar I disorder (403)	All asenapine doses versus placebo were superior based on change in YMRS.	Asenapine 5-20 mg/day

Table 2 Summary of reported safety outcomes of second-generation antipsychotic (SGA) drugs in children and adolescents

Study	Age (years)	Study design	Subjects (N)	Safety Outcomes	Dosage of SGA drugs
Pandina G et al. [7]	13-17	6- to 12-month open-label, multicenter study	Schizophrenia (264)	Adverse symptoms (eg, somnolence, headache, weight gain, increased muscle tone, insomnia, tremors, and mental derangement) were observed in more than 10% of the subjects; moreover, prolactin-related adverse reactions were observed in 9% of subjects.	Risperidone 2-6 mg/day
Geller B et al. [14]	6-15	Multicenter, randomized, controlled trial	Bipolar I disorder (279)	Risperidone resulted in severe metabolic abnormalities.	Risperidone 0.25-6 mg/day
Druyts E et al. [19]	10-18	Systematic review selected six randomized controlled trials and five observational studies	Schizophrenia or schizophrenia spectrum disorder (1,772)	Risperidone, olanzapine, and two doses of paliperidone (3-5 mg/day and 6-12 mg/day) were associated with increased prolactin levels, as compared with baseline.	Clozapine 25-900 mg/day; Olanzapine 2.5-20 mg/day; Risperidone 0.15-6 mg/day, 25-50 mg biweekly; Quetiapine 200-800 mg/day; Aripiprazole 10-30 mg/day
Margari L et al. [20]	8-17	Prospective observational study	Early-onset schizophrenia spectrum psychosis (34)	The mean serum prolactin levels significantly increased after 1 month of treatment and were higher in pubertal or post-pubertal girls and in patients treated with risperidone (1 mg/day).	Risperidone 0.25-4 mg/day
Calarge CA et al. [21]	7-17	1.5-year follow-up study	Medically healthy boys (94)	A significant decrease in bone mass was shown in the group treated with continuous risperidone.	-*
Savitz AJ et al. [10]	12-17	Randomized controlled trial	Schizophrenia (228)	The most frequent adverse symptoms reported in the paliperidone-treated group were akathisia, headache, drowsiness, tremors, and weight gain. Both drugs were tolerated in adolescents with schizophrenia. Both drugs were tolerated in adolescents with schizophrenia.	Aripiprazole 2-15 mg/day, Paliperidone 3-9 mg/day
Findling RL et al. [18]	10-17	3-week double-blind controlled trial	Bipolar I disorder (403)	Asenapine was adequately tolerated in terms of adverse reactions. However, asenapine induced an increase in body weight and fasting insulin levels.	Asenapine 5-20 mg/day
Findling RL et al. [23]	10-17	50-week open-label study	Bipolar I disorder (321)	Asenapine was adequately tolerated in children with bipolar I disorder. The most frequent adverse symptoms were drowsiness and hypersomnia.	Asenapine 5-20 mg/day

*Not clear in report

factor in determining the most effective drug was not clear in schizophrenia or bipolar disorder.

Safety data confirmed clear differences in the side effect profiles of the drugs. As there are side effects associated with olanzapine, such as metabolic abnormalities and weight gain⁶, it is not commonly used as a first-line

drug for the treatment of EOS. Although some long-term studies have confirmed the safety of olanzapine, it is still likely to cause weight gain. Risperidone increases the risks of hyperprolactinemia, metabolic abnormalities, neurological adverse events, and loss of bone mass. Quetiapine is rarely selected as a first-line treatment be-

cause of the high incidence of quetiapine-related obesity and lipid abnormalities²⁴. However, because only a few EPS cases have been reported²⁵, we believe that quetiapine is efficacious and safe for selected patients. These studies of quetiapine included patients younger than age 6 years and were thus not included in the present results. Although high-dose aripiprazole was associated with higher incidence of tremor and Parkinsonism, treatment with aripiprazole 10 mg daily resulted in the lowest incidence of EPS and no significant weight gain⁶. Paliperidone did not differ from aripiprazole in tolerability¹⁰. However, additional studies of the effectiveness and safety of paliperidone are needed. A subsequent 50-week open-label trial concluded that asenapine had adequate tolerability²³. However, the evidence is conflicting, thus indicating that further study of asenapine effectiveness and safety is needed.

Therefore, drugs for adolescents should be selected on the basis of the antipsychotic side effect profiles (eg, low-dose aripiprazole was associated with the lowest incidence of EPS and resulted in no significant weight gain⁵). Studies of risperidone reported side effects such as sedation and drowsiness⁷; however, risperidone is somewhat effective for patients requiring sedation and should be actively prescribed for patients with strong psychomotor stimulation. Olanzapine should be prescribed after a thorough study of the effects of metabolic abnormalities and weight gain.

Our research has several limitations. The number of studies of children and adolescents are fewer than those of adults, and the evidence is thus limited. No study has compared adolescent and adult patients. In addition, indications such as autism spectrum disorder have not been investigated.

In conclusion, SGAs had similar effectiveness in the treatment of children and adolescents with schizophrenia and bipolar disorder. When selecting SGAs for this population, clinicians should consider the potential adverse effects and discontinuation rates in their patients.

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