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Child and Adolescent Psychiatry (M Singh and M Goldsmith, Section Editors)

Antipsychotics for Treatment of Adolescent Onset Schizophrenia: a Review

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Abstract

Purpose of Review Schizophrenia is a leading cause of disease burden in youth and can significantly impair an adolescent's peer and familial relationships and academic functioning. Therefore, safe and effective treatments are needed. This article reviews the pharmacological treatment of adolescents with schizophrenia, when possible, with a focus on the past five years of research.

Recent Findings There are relatively few randomized controlled trials (RCTs) and head-to-head trials informing selection of a medication in pediatric schizophrenia. However, recent literature focusing on the efficacy and tolerability of atypical antipsychotics has led to the Food and Drug Administration (FDA) approval of multiple agents, specifically risperidone, olanzapine, quetiapine, aripiprazole, paliperidone, and lurasidone, for the treatment of pediatric schizophrenia. Asenapine has also been studied in a large RCT within the past five years, but participants randomized to asenapine treatment did not do statistically significantly better than those assigned to receive placebo. Comparison RCTs on clozapine have indicated benefit in treatment-resistant pediatric schizophrenia, but at the cost of significant side effect burden. Common adverse events with atypical antipsychotics include weight gain, akathisia, hyperprolactinemia, and somnolence.

Summary Atypical antipsychotics remain first-line treatment for children and adolescents with early onset schizophrenia. However, further study is required to develop more effective and better tolerated treatment options, and in addition to pharmacologic management, current guidelines recommend combination treatment with psychotherapy and psychoeducation.

Introduction

Schizophrenia, when it occurs during adolescence, can have a profound detrimental impact on a patient's life. Besides the suffering that accompanies the symptoms of the disorder, schizophrenia can be associated with impairments in peer relationships, familial relationships, and academic functioning as well as an increased number of lifetime inpatient hospital days and hospital readmission [1, 2]. Adolescents who develop schizophrenia have significant functional impairment [3]. Overall, schizophrenia is one of the leading causes of disease burden in pediatric patients [4].

According to current nosology, the diagnostic symptom criteria for schizophrenia are the same in pediatric patients as it is in adults. The condition is characterized by hallucinations, delusions, "negative symptoms," and disorganized thinking and behavior [5].

Although schizophrenia is considered to be a rare condition in pre-adolescent aged children, a substantial number of patients, particularly males, develop symptoms of the condition during the second decade of life [6, 7]. When compared with schizophrenia that develops during adulthood, adolescent-onset schizophrenia is associated with worse outcomes in several domains. These areas include poorer social relationships, lack of independent living, and lack of employment [8].

For all these reasons, safe and effective treatments for patients with schizophrenia are needed. The purpose of this review is to describe what is known about the pharmacological treatment of adolescents with schizophrenia. Since the amount of study done on the topic of the pharmacotherapy of adolescent schizophrenia is much smaller when compared with the amount of research done on the use of medication in adults with schizophrenia, we have chosen to not simply focus on the past five years of research in this review.

Although the topic of this work is on medication treatment of adolescent schizophrenia, current guidelines note that other forms of intervention are recommended when caring for an adolescent with schizophrenia. These treatments include baseline and follow-up monitoring of symptoms, psychotherapeutic intervention, and in treatment resistant cases, electroconvulsive therapy (ECT) [9].

Medications

Risperidone

There have been no randomized trials published about risperidone in this population in the last five years. However, two landmark randomized controlled trials (RCTs) were published in 2009 and bear mentioning here, both completed by Haas et al. The first RCT compared very low doses of risperidone (0.15–0.6 mg) with typical treatment dosing (1.5–6 mg) in 257 subjects [10•]. This double-blind randomized controlled trial measured the baseline adjusted mean change in the Positive and Negative Syndrome Scale (PANSS) after 56 days of treatment with risperidone. There was statistically significant improvement in the total PANSS score in the group that received typical dosing when compared with very low dose risperidone. Adverse effects were more common in the typical treatment dose group, and included extrapyramidal side effects (EPS), hyperprolactinemia, and weight gain. Interestingly, even at very low doses of risperidone, 64% of patients had an increased prolactin level when compared with baseline. In the higher dose group, 97% of patients had an increase in prolactin level.

The second RCT was a six-week study comparing low dose (1–3 mg) risperidone, high dose (4–6 mg) risperidone, and placebo in 160 patients [11•]. This trial showed significant improvement in the PANSS total score in both medication groups compared with placebo. The high dose group separated from placebo by day eight, while the lower dose group did not separate from placebo

until day 15. By day 43, the least squares estimate of mean change from baseline in PANSS total score was – 10.3 in placebo, – 23.0 in low dose groups, and – 23.7 in high dose groups ($p < 0.001$). Higher doses were associated with greater rates of adverse effects including EPS, dizziness, and hypertonia, while improvement in symptoms in both groups was clinically meaningful. The authors concluded that lower dose range of 1–3 mg risperidone might be optimal for an adolescent population. Table 1 reviews antipsychotics, including risperidone, that are approved by the US Food and Drug Administration (FDA) for treatment of schizophrenia in adolescents.

Olanzapine

Prior to the past five years, Kryzhanovskaya et al. evaluated the use of olanzapine in 107 patients with pediatric schizophrenia [12•]. This six-week study compared olanzapine with placebo. The mean daily dose was 11.1 mg. Patients on olanzapine compared with placebo had significantly greater improvement in the Brief Psychiatric Rating Scale for Children (BPRS-C) when compared with pre-treatment baseline. The treatment group separated from placebo by week two and maintained separation throughout the completion of the study. By six weeks, the change in BPRS-C scores in the treatment group was – 19.4, while in the placebo group was – 9.3 ($p = 0.003$). Adverse effects associated with olanzapine included weight gain, somnolence, headache, and increased appetite. This study indicated that response rates in adolescents taking olanzapine (38%) were lower compared with the response rate in adults (58–62%) [13•].

In more recent years, Stentebjerg-Olesen et al. (2015) conducted a post hoc analysis using the same study population from Kryzhanovskaya's 2009 RCT [14••]. This analysis found that improvement in the BPRS-C score was achieved predominantly in the first two weeks after initiating treatment and that 85.5% of improvement was achieved by the end of week three. This study also added to the current literature evidence that adolescents who have an early response to treatment (defined as a ≥ 20% reduction in BPRS-C score by week two) have significantly better outcomes than adolescents who have < 20% reduction in

Table 1. FDA-approved medications in the treatment of pediatric schizophrenia and recommended dosing

Medication	Year approved in the USA for adults	Year approved in the USA for children	Age, years	Starting dose	Target dose
Risperidone	1993	2006	13–17	0.5 mg daily	3 mg (effective dose range 1–6 mg)
Olanzapine	1996	2009	13–17	2.5–5 mg daily	10 mg daily (up to 20 mg daily)
Quetiapine	1997	2009	13–17	50 mg daily	400–800 mg
Aripiprazole	2002	2008	13–17	2 mg daily	10 mg daily (up to 30 mg daily)
Paliperidone	2006	2011	12–17	3 mg daily	3–6 mg daily (< 51 kg) 3–12 mg daily (> 51 kg)
Lurasidone	2010	2018	13–17	40 mg daily	40–80 mg daily

the BPRS-C total score by week two. A total of 70.2% of "early responders" achieved remission by the study endpoint whereas only 40.9% of study participants who were not in the "early responders" group achieved remission. Remission in this study was defined as a score of three or less out of seven BPRS-C indicators, as suggested by Andreasen et al's standardized schizophrenia remission criteria [15•].

Additionally, in 2003, Ross et al. completed a one-year open label study of 20 patients on olanzapine [16•]. At six months, the mean daily dose was 9.3 mg, and at one year, the mean daily dose was 10.4 mg. The outcome measures included the BPRS-C, Scale for the Assessment of Positive Symptoms (SAPS), and Scale for the Assessment of Negative Symptoms (SANS) which all showed statistically significant improvement by the study endpoint when compared with baseline. This study found significant variability in dosing, with effective dose ranging from 2.5 to 17.5 mg daily. For a few patients, the dose was briefly raised higher than 17.5 mg daily, but then was lowered again as there was no further benefit and only an increase in adverse effects. Due to the small sample size, weight gain was the only consistently observed adverse effect.

Quetiapine

No RCTs looking solely at quetiapine were published over the past five years in this patient group; however, in 2012, Findling et al. published a placebo-controlled RCT evaluating the efficacy of quetiapine for the treatment of schizophrenia in adolescents [17•]. This study compared placebo with quetiapine dosed at 400 mg daily or 800 mg daily in 220 participants. By the six-week study endpoint, there was a statistically significant improvement in PANSS scores in both the 400 mg and 800 mg dose groups when compared with placebo. The most notable difference between the medication groups was that significant divergence from placebo was achieved at day 14 in the 800 mg group and not until day 21 for the 400 mg group. Adverse effects associated with quetiapine included increases in total cholesterol and triglycerides, as well as somnolence, headache, dizziness, EPS, and sedation. Sedation was the most common reason for discontinuing medication.

Ziprasidone

In 2013, Findling et al. published a double-blind, placebo-controlled RCT followed by an open label extension (OLE) examining the efficacy of ziprasidone for the treatment of adolescents with schizophrenia [18•]. The study evaluated 283 participants age 12–17 with a diagnosis of schizophrenia per the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). The RCT portion of the study occurred from the start of the study through week six, followed by a 26-week open label extension. The primary endpoint was measured as the change in the Brief Psychiatric Rating Scale–Anchored (BPRS-A) from baseline to week six in the RCT. In the OLE, the BPRS-A, Clinical Global Impression-Severity scale (CGI-S), and Children's Global Assessment Scale (CGAS) were followed over the course of the study. Statistical analysis was done in two groups, the modified intent to treat (mITT) group which included every randomized patient who participated, and the per protocol (PP) group which included only patients who did not stray significantly from the study protocol. In the mITT group, at the end of the six-week RCT,

mean BPRS-A scores were not statistically different in the ziprasidone group compared with the placebo group, and both groups showed a decrease in scores from baseline to week six. However, in the PP group, there was a statistically significant improvement in the BPRS-A in the drug group compared with the placebo group ($p = 0.03$). During the OLE, BPRS-A scores continued to decrease throughout the study time period. Thus, only patients who completed the RCT in the per-protocol group experienced statistically significant improvement in symptoms based on BPRS-A scores. Those who completed the OLE did have some decrease in the BPRS-A scores over the course of the study though statistical significance and p values were not reported. Mean modal dose of ziprasidone in the RCT was 135.8 mg in patients weighing 45 kg or more, and 65.3 mg in patients weighing less than 45 kg. In the OLE, mean modal dose in the 45 kg or greater group was 125 mg and in the less than 45 kg group was 64.8 mg. The most common adverse effects were somnolence and EPS in the ziprasidone group when compared with placebo.

Aripiprazole

In 2008, Findling et al. published a double-blind, placebo-controlled RCT comparing placebo with aripiprazole at doses of 10 mg or 30 mg daily in a sample of 302 participants [19•]. Both aripiprazole doses were more effective than placebo and showed statistically significant reduction in the PANSS total score by the six-week study endpoint. However, there was a different rate of response between dosing groups; the 10 mg group did not separate from placebo until week six, while the higher dose group separated at weeks one, three, four, five, and six. Adverse effects included EPS, tremor, and somnolence. There was no statistically significant weight gain in any of the groups. Prolactin levels decreased in patients on aripiprazole compared with placebo ($p = 0.003$ for 10 mg; $p < 0.0001$ for 30 mg).

Correll et al. completed a 52-week randomized, placebo-controlled withdrawal study examining aripiprazole; the results of which were published in 2017 [20••]. This study included 146 participants and was completed in three stages including a 4–6-week cross-titration from other oral antipsychotics, followed by stabilization on oral aripiprazole from weeks 7–21, and finally a 2:1 randomization to aripiprazole or placebo until week 52. The primary endpoint was time from randomization to exacerbation of psychotic symptoms or impending relapse of psychotic symptoms. Treatment with aripiprazole was associated with a significantly longer time to exacerbation of psychotic symptoms or impending relapse when compared with placebo ($p = 0.016$). The dose range of aripiprazole was 10–30 mg, and the average dose during the double-blind maintenance treatment was 19.2 mg. Adverse effects during the stabilization phase (weeks 7–21) were most commonly akathisia, insomnia, weight gain, tremor, headache, and somnolence. During the double-blind maintenance phase, there was no statistically significant difference between the proportion of patients who reported adverse events (AEs) in the aripiprazole group (65.3%) compared with the placebo group (68.8%). Insomnia occurred in a higher proportion of the placebo group ($p = 0.009$), but other two-sided p values evaluating rates of AEs between active medication and placebo were not significant. See Table 2 for a summary of RCTs evaluating the use of

Table 2. Selected randomized controlled trials of antipsychotics in the treatment of pediatric schizophrenia from 2015 to 2019, with study characteristics, efficacy, and tolerability

Study	Active medication	Study design	*N*	Mean dose ± SD (range)	Duration of study	Efficacy (primary efficacy measures)	Side effects
Correll et al., 2017	Aripiprazole	Double-blind placebo controlled RCT	146	19.2 ± 6.7 mg (10–30 mg daily)	52 weeks	Treatment with aripiprazole was associated with statistically and clinically significantly longer time to exacerbation of psychotic symptoms, HR = 0.46, 95% CI = 0.24–0.88 (PANSS, CGI-I)	*Common AEs*: akathisia, insomnia, weight gain, headache, somnolence *SAEs*: 3.1% (vs 12.5% in placebo); no deaths, NMS, changes in glucose/prolactin levels, or seizures *Discontinuation due to AE*: 20.4% (vs 39.6% in placebo)
Matsumoto et al., 2018	Aripiprazole	Double-blind RCT	106	(2 mg, 6–12 mg, or 24–30 mg daily)	6 weeks	The 6–12 mg and 24–30 mg groups did not achieve a ≥ 5 point difference vs the 2 mg group at 6 weeks (PANSS)	*Common AEs*: nausea, akathisia, insomnia, somnolence *SAEs*: 2.8%; suicide attempt ($n = 2$), worsening psychosis ($n = 1$), anxiety (n = 1) *Discontinuation due to AEs*: $n = 2$ in 2 mg group, $n = 3$ in 6–12 mg group, $n = 5$ in 24–30 mg group
Goldman et al., 2017	Lurasidone	Double-blind, placebo controlled RCT	326	59.8 mg (40 or 80 mg daily)	6 week	Least-square mean change in PANSS from baseline to week 6 was – 18.6 ($p < 0.001$) with lurasidone 40 mg, – 18.3 ($p < 0.001$) with lurasidone 80 mg, and – 10.5 with placebo (PANSS, CGI-S)	*Common AEs*: nausea, nausea, anxiety, somnolence; clinically meaningful weight gain was not greater than placebo *SAEs*: 3.6% in 40 mg group and 1.9% in 80 mg group (vs 8.0% in placebo), no deaths or suicidal behavior/ attempts *Discontinuation due to AEs*: suicidal ideation ($n = 1$ in 40 mg group)
Findling et al., 2015	Asenapine	Double-blind placebo controlled RCT followed by OLE	306	RCT 7.6 mg (2.5–5 mg BID) OLE 8.7 mg daily	8 weeks (26 week OLE)	There was no statistically significant difference between either asenapine group (2.5 mg BID or 5 mg BID) and placebo on primary efficacy endpoint (PANSS)	*Common AEs*: weight gain and sedation. Akathisia, fasting glucose elevation, and EPS were more common in 5 mg BID group than placebo. *SAEs*: 3.1% in 2.5 mg BID group and 2.8% in 5 mg BID group (vs 2.9% in placebo), mostly

Table 2. (Continued)

Study	Active medication	Study design	*N*	Mean dose ± SD (range)	Duration of study	Efficacy (primary efficacy measures)	Side effects
							worsening psychosis, no deaths or suicidal behavior/attempts *Discontinuation due to AEs*: 6.1% in 2.5 mg BID group, 7.5% in 5 mg BID group, 2.9% in placebo
Dogterom et al., 2018	Asenapine	Study 1: double-blind placebo controlled RCT Study 2: open label			Study 1: 40 Study 2: 30	(1–10 mg BID)	Study 1: 12 days Study 2: 8 weeks
N/A	*Common AEs*: Somnolence, dysgeusia, oral						paresthesia/hypoesthesia and dizziness. A total of 23% of patients experienced dystonia in study 2 *SAEs*: none *Discontinuation due to AEs*: none attributable to study medication
Pagsberg et al., 2017	Quetiapine, aripiprazole	Double-blind RCT	113	Quetiapine ER 451.8 ± 198.8 mg (50–800 mg daily) Aripiprazole 14.6 ± 6.9 mg (2.5–30 mg daily)	12 weeks	Mean changes in score were not statistically significantly different between quetiapine and aripiprazole groups at week 12 (PANSS)	*Common AEs*: quetiapine led to more weight gain. Aripiprazole led to more sedation and initial akathisia *SAEs*: no statistically significant difference between groups *Discontinuation due to AEs*: 22% of quetiapine ER group vs 35% in aripiprazole group
Jensen et al., 2018	Quetiapine, aripiprazole	Double-blind RCT	113	Quetiapine ER (50–800 mg daily) Aripiprazole (2.5–30 mg daily)	12 weeks	See Pagsberg et al. above	Quetiapine ER treatment was related with a statistically significant increase in QTc (+ 6.8 ± 20.2 ms), vs no significant increase in aripiprazole group. There was no significant correlation between dose and prolongation of QTc.
Savitz et al., 2015	Paliperidone, aripiprazole	Double-blind RCT	228	Paliperidone ER 6.75 ± 1.8 mg (3–9 mg daily)	26 weeks	There was no significant difference in the change in total primary outcome scores from baseline to day 56 between	*Common AEs*: akathisia, headache, somnolence, tremor, weight gain in paliperidone ER;

Table 2. (Continued)

Study	Active medication	Study design	*N*	Mean dose ± SD (range)	Duration of study	Efficacy (primary efficacy measures)	Side effects
				Aripiprazole 11.6 ± 3.0 mg (5–15 mg daily)		paliperidone ER and aripiprazole groups (PANSS)	worsening schizophrenia and somnolence in aripiprazole. Paliperidone ER group had more dystonia and hyperkinesia, prolactin increase, weight gain *SAEs*: $n = 7$ in both groups; worsening psychosis was higher in paliperidone ER group *Discontinuation due to AEs*: 4.4% in paliperidone ER group (oculogyric crisis, lethargy, anxiety, galactorrhea, rash)

SD standard deviation, *RCT* randomized controlled trial, *ER* extended release, *PANSS* positive and negative syndrome scale, *CGI-S* clinical global impression of severity, *CGAS* Children's Global Assessment Scale, *C-SSRS* Columbia-Suicide Severity Rating Scale, *ROC* receiver operating characteristics curve, *BPRS-C* brief psychiatric rating scale-children, *Tmax* time of peak concentration, *Cmax* maximum serum concentration, *AUC* area under the curve, *TEAE* treatment-emergent adverse event, *AE* adverse event, *SAE* serious adverse event, *NMS* neuroleptic malignant syndrome, *EPS* extrapyramidal symptom, *OLE* open label extension

antipsychotics for treatment of schizophrenia in adolescents published within the past five years.

More recently, a 2018 double-blind randomized dose-comparison study and OLE by Matsumoto et al. explored the safety and efficacy of aripiprazole in 106 adolescents with schizophrenia in Japan [21••]. Study groups were divided by dose, receiving 2 mg, 6–12 mg, or 24–30 mg of aripiprazole daily. In the six-week-randomized control portion of the study, the difference between response in each group based on least square mean change PANSS score from baseline to endpoint was not statistically significant, even in the highest dose groups compared with the 2 mg group. After the 6-week randomization was completed, the study continued as an open-label extension for 52 weeks. During the open-label extension, improvement in PANSS scores was maintained and there was continued improvement noted, though *p* values were not reported in the study results. Adverse effects were frequent, 20% or more of patients experienced nausea, akathisia, insomnia, and somnolence in the first six weeks. More than 20% of patients in the open-label extension experienced nasopharyngitis. One patient had worsening psychotic symptoms, one had worsening anxiety, and two attempted suicide; however, no deaths occurred.

Paliperidone

In 2011, Singh et al. completed a RCT comparing paliperidone with placebo in 200 patients [22•]. Dosing in this paper was divided into six categories: low (1.5 mg), medium (3 mg), and high (6 mg) dose for patients weighing 29–51 kg, and low (1.5 mg), medium (6 mg), and high (12 mg) dose for patients weighing 51 kg or more. The results from this study showed that the mean change in PANSS total score for patients in the 51 kg or greater category was greater compared with placebo in all dose groups. In the lower body weight category, the mean change in PANSS total score was only greater than placebo in the medium treatment group. Ultimately, doses of paliperidone ER less than 3 mg were not effective in reducing symptoms of schizophrenia, but dose ranges from 3 to 12 mg were effective. Most common adverse effects included somnolence, insomnia, akathisia, and headache. Adverse effects occurred in 59% of patients in the placebo group, 50% of those in the low dose group, 60% of those in the medium dose group, and 75% in the high dose group.

Asenapine

At the time of this publication, the FDA has approved several antipsychotics including asenapine for the management of acute manic or mixed episodes in pediatric bipolar disorder. However, asenapine does not currently have an indication for pediatric schizophrenia, indicative of insufficient evidence supporting its use for this diagnosis in youth.

The largest RCT of asenapine in pediatric schizophrenia to date is a randomized, double-blind placebo-controlled trial with an open-label extension study by Findling et al. with 306 study participants randomized to placebo, asenapine 2.5 mg twice daily, or asenapine 5 mg twice daily for 8 weeks [23••]. This was followed by a 26-week flexible-dosing open label extension study in which participants were on an average dose of 8.7 mg daily. Notably, in the acute phase, both asenapine groups did not separate from placebo based on PANSS scores. Common AEs included weight gain and sedation, and there was more

akathisia, fasting glucose elevation, and EPS in the higher-dose asenapine group compared with placebo. These findings on asenapine efficacy contrast with a separate study published by Findling et al. in the same year examining the use of asenapine in pediatric bipolar disorder, which found that all doses of asenapine from 2.5 to 10 mg twice daily resulted in greater reduction in Young Mania Rating Scale and Clinical Global Impression for use in bipolar illness (CGI-BP) severity scores compared with placebo [24••].

Lurasidone

There currently exists one published RCT examining the efficacy and safety of lurasidone in the management of schizophrenia in youth. This trial by Goldman et al. (2017) randomized 326 participants ages 13–17 with schizophrenia to placebo, lurasidone 40 mg daily, or lurasidone 80 mg daily for six weeks [25••]. Both 40 and 80 mg doses of lurasidone were efficacious compared with placebo in the treatment of psychosis, based on PANSS and CGI-S scores. Lurasidone was also well tolerated, with the majority of AEs mild or moderate in severity, and the incidence of serious AEs and study discontinuation was lower in the lurasidone group in comparison with placebo. The most common AEs observed were nausea, somnolence, akathisia, vomiting, and sedation. Also, of note, there were no clinically significant differences noted in body weight, lipids, and blood glucose between lurasidone and placebo. This study contributed to the FDA approval of lurasidone for schizophrenia in adolescents aged 13–17.

Comparison studies

Clozapine

Clozapine has not been studied in RCTs in adolescent schizophrenia over the past 5 years; however, there are several previously published RCTs that are worth noting. In 1996, Kumra et al. completed a double-blind randomized controlled trial comparing clozapine and haloperidol in 21 treatment resistant patients [26•]. Though this study had limited power due to a small sample size, results indicated that clozapine is more effective than haloperidol in improving depression, thinking disturbances, and withdrawal. Additionally, it leads to greater total improvement on the BPRS and CGI. Adverse effects including drowsiness, hypersalivation, and drop in absolute neutrophil count (ANC) were statistically more common in the clozapine group, while patients taking haloperidol had a higher rate of insomnia. The authors noted that based on follow-up telephone interviews, maximal effects of clozapine may not be seen until between months 6–9 of treatment.

Clozapine has also been compared with olanzapine in two separate RCTs published in 2006 [27•] and 2008 [28•]. In 2006, Shaw et al. compared clozapine at a mean final dose of 327 mg and olanzapine at a mean final dose of 18.1 mg. Multiple outcome measures were tracked including the CGI-S, SANS, SAPS, Brief Psychiatric Rating Scale 24 question version (BPRS-24), and Bunney-Hamburg rating scales. Patients entering the study were tapered off of medication for 1–4 weeks, then had a period of 1–3 weeks off medication before being randomized to olanzapine or clozapine. After eight weeks of treatment, the clozapine treatment group experienced statistically significant improvement in

all outcome measures from both baseline admission and baseline antipsychotic-free scores. The olanzapine treatment group only had statistically significant improvement when comparing endpoint outcomes with baseline medication-free scores, but not when compared with baseline admission scores. Adverse effects occurred in both treatment groups though more patients in the clozapine group experienced adverse effects. Specifically, patients on clozapine experienced more hypertension and supine tachycardia. This study had a sample size of 25, and therefore was underpowered to notice small differences between the medications; however, there was a statistically significant improvement in negative symptoms for patients on clozapine compared with olanzapine.

In 2008, Kumra et al. compared clozapine with "high-dose" olanzapine in 39 patients participating in this double-blind RCT. Mean final dose of clozapine in this trial was 487.5 mg, and mean final dose of olanzapine was 26.2 mg. Patients responded to clozapine at a higher rate (66%) compared with patients who were taking olanzapine (33%). Response was defined in this study as a decrease in BPRS score by 30% or more, and a CGI improvement rating of either "very much" or "much" improved between baseline and the 12-week study endpoint. In addition to known side effects of weight gain, hyperlipidemia, and hyperglycemia in both medications, serious adverse effects were noted in four patients on clozapine, including constipation leading to bowel obstruction, polyuria and impaired glucose tolerance, 7-lb weight gain in seven weeks, and increased fasting glucose consistent with drug-induced diabetes. Olanzapine was associated with one serious adverse effect in a patient who experienced neutropenia.

Olanzapine, Risperidone, and Molindone

The multisite treatment of early onset schizophrenia spectrum disorders (TEOSS) study was a randomized controlled trial comparing three antipsychotics [29•]. This double-blind study compared molindone (10–140 mg daily), olanzapine (2.5–20 mg daily), and risperidone (0.5–6 mg daily) in a sample of 116 patients. Sikich et al. published the original eight-week RCT; after which, patients who improved were eligible to continue, blinded, on their study medications for an additional 44 weeks [30••]. Primary outcome was responder status by week eight. Responders were defined as having a CGI improvement of "very much" or "much" improved, having a 20% or greater reduction in PANSS total score, and continuing on the study drug for eight weeks. By the eight-week endpoint, response was observed in exactly half of patients treated with molindone, 34% of patients taking olanzapine, and 46% of patients on risperidone. There was no statistically significant difference between responses in the different treatment groups. Common adverse effects included sedation, irritability, and anxiety. Molindone was associated with statistically more akathisia than the other treatment groups, while olanzapine was associated with higher rates of weight gain and increased appetite, and risperidone with constipation. As noted in previous RCTs, in this study, symptom reduction was most notable within the first two weeks of treatment [14••]. Findling et al's 44-week randomized extension noted that only 12% of youth were still taking medication by the end of the study, indicating a strong need to develop medications that are better tolerated [30••].

Quetiapine and Aripiprazole

In a multicenter double-blind randomized control trial studying 113 subjects ages 12–17, Pagsberg et al. looked at patients over the course of 12 weeks who were taking either quetiapine ER or aripiprazole [31••]. Dosing was increased as clinically indicated; quetiapine ER doses ranged from 50 to 800 mg daily and aripiprazole doses ranged from 2.5 to 30 mg daily. Mean dose of quetiapine ER was about 426 mg and mean dose of aripiprazole was about 13 mg. Overall, there were no significant differences between either group on mean PANSS positive symptoms score at 12 weeks. The biggest improvement in symptoms was noted by two weeks on medication, while there was a smaller improvement in symptoms by week four. PANSS scores did not improve significantly between weeks 4 and 12. Patients on quetiapine ER experienced more sedation and weight gain, while patients on aripiprazole experienced more initial akathisia.

Jensen et al. looked at the change in QT interval during treatment with quetiapine ER vs aripiprazole [32]. This trial used the same patient sample noted above, and evaluated the primary outcome of change in QT. There was no significant correlation found between the dose of either medication and prolongation of QTc interval. QTcH (defined as QTc calculated using Hodges formula) and heart rate did increase significantly with quetiapine ER, though changes were small and not clinically significant in patients who were otherwise healthy. QTcH and heart rate were unchanged in patients who took aripiprazole.

Paliperidone and Aripiprazole

Savitz et al. completed a double-blind randomized trial comparing paliperidone ER at a dose of 3–9 mg daily with aripiprazole at a dose of 5–15 mg daily in 228 patients [33••]. The initial study hypothesis was that paliperidone ER; a full D2 receptor antagonist would show superiority compared with aripiprazole, a partial D2 receptor agonist. Mean decrease in PANSS score on both medications by day 56 was about 20 points. By day 182, PANSS scores had decreased another 5–6 points on average for the paliperidone group, and another 6–7 points on average for the aripiprazole group. Forty percent of the study participants were in remission (defined as a score of less than or equal to three on PANSS items P1, P2, P3, N1, N4, N6, G5, and G9 at days 56 and 182) during the last four months of the 26-week study. Both medications led to statistically and clinically significant improvement; neither was superior when measured at day 56 and at day 182. Adverse effects occurred in 77% of participants on paliperidone; most common were akathisia, headache, somnolence, tremor, and weight gain. A total of 66.7% of participants in the aripiprazole group experienced adverse effects; most common was worsening psychotic symptoms, followed by somnolence. Five patients in the paliperidone ER group discontinued the study due to treatment emergent adverse effects, while no patients in the aripiprazole group discontinued for this reason.

Discussion

Antipsychotic medications are the primary treatment modality in pediatric schizophrenia. This article reviews recent updates and important contributions

to the literature that can help guide treatment decisions and medication management for clinicians tasked with treating children and adolescents with psychosis.

Current guidelines recommend multi-modal treatment approaches, and suggest that the combination of psychotherapy and psychoeducational interventions along with medication management is most effective [9]. However, until recently, there were scant data regarding medication treatment of youth with schizophrenia, and approaches to pharmacologic management of pediatric schizophrenia were largely based on adult literature. Within the past few years, several clinical trials have been conducted which both inform evidence-based dosing and demonstrate the efficacy of newer antipsychotic agents compared with placebo, thus expanding our armamentarium of possible treatment options for patients. In addition, clinical trials have demonstrated that some medications which have efficacy in adults may not be efficacious in the pediatric population [24••].

In medications with demonstrated efficacy, RCTs examining both higher and lower doses have determined that generally lower evidence-based doses have equivalent efficacy when compared with higher evidence-based doses, while higher doses frequently are associated with greater side effect burden [10•, 11•, 16•, 21••, 22•]. However, there is also some evidence to suggest that psychotic symptom reduction is more rapidly achieved with higher antipsychotic doses [17•, 19•], and that early response may be predictive of superior outcomes [14••].

In selecting a medication, there is a relative paucity of head-to-head trials. For treatment-resistant pediatric patients with schizophrenia, clozapine has been demonstrated in comparison RCTs to have distinct superiority in pediatric patients. This agent, however, is also associated with a high relative side effect burden including significant risk for serious hematological side effects [26•–28•].

Based on the extant data, it appears that agents other than clozapine with proven efficacy have equivalent salutary effects but differ in regard to tolerability [29•–31••, 33••]. Despite the fact that none of these medications stands out as a clear first line agent, recent literature has contributed significantly to the evidence base regarding efficacy and tolerability of antipsychotic medications in pediatric schizophrenia, thereby allowing clinicians to make more informed, thoughtful decisions about treatment for their patients.

The information presented in this review article helps guide treatment and also identifies gaps in our knowledge of medications used in early onset psychosis. Future research with longer-term studies and head-to-head trials will be required so that the best evidence-based treatment choices can be made for this vulnerable patient population.

Compliance with Ethical Standards

Conflict of Interest

Dr. Nadia Zaim declares that she has no conflict of interest.

Dr. Amanda Sun declares that she has no conflict of interest.

Dr. Findling is a consultant for Acadia, receives grants from and is a consultant for Aevi, receives grants from and is a consultant for Akili, receives grants from and is a consultant for Alcobra, receives grants from and is a consultant for Allergan, is a consultant for Amerex, has an honoraria from Am Acad CAP, receives royalties from American Psychiatric Press, is a consultant for Arbor, is a consultant for Bracket, has an honoraria from Daiichi-Sankyo, is a consultant for Epharma Solutions, receives grants from Forest, is a consultant for Genetech, is a consultant for Ironshore, is a consultant for KemPharm, is a consultant for Luminopia, receives grants from and is a consultant for Lundbeck, is a consultant for Merck, receives grants from and is a consultant for NIH, receives grants from and is a consultant for Neurim, is a consultant for Noven, is a consultant for Nuvelution, is a consultant for Otsuka, receives grants from PCORI, receives grants from Pfizer, is a consultant for Physicians Postgraduate Press, is a consultant for Purinix, is a consultant for Receptor Life Sciences, receives grants from and is a consultant for Roche, receives personal fees from Sage, receives grants and is a consultant for Shire, receives grants and is a consultant for Sunovion, receives grants and is a consultant for Supernus Pharmaceuticals, receives grants from Syneurx, is a consultant for Teva, is a consultant for Touchpoint, is a consultant for Tris, and receives grants from and is a consultant for Validus, outside the submitted work.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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