Developments in Pediatric Psychopharmacology: Focus on Stimulants, Antidepressants, and Antipsychotics

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Most major psychiatric disorders have an onset in childhood or adolescence in a sizeable proportion of patients, and earlier onset disorders often have a severe and chronic course that can seriously disrupt sensitive developmental periods, with lifelong adverse consequences. Accordingly, psychopharmacologic treatments have been increasingly utilized in severely ill youth. However, the increased use of psychopharmacologic treatments in pediatric patients has also raised concerns regarding a potential overdiagnosis and overtreatment of youth, without adequate data regarding the pediatric efficacy and safety of psychotropic agents. Over the past decade, a remarkable number of pediatric randomized controlled trials have been completed, especially with psychostimulants, antidepressants, and antipsychotics. For these frequently used agents, effect sizes against placebo have typically been at least moderate, with most numbers-needed-to-treat well below 10 for response, indicating clinical significance as well. Nevertheless, data also point to a greater and/or different profile of susceptibility to adverse effects in pediatric compared to adult patients, as well as to a role for nonpharmacologic treatments, given alone or combined with pharmacotherapy, for many of the youth. Taken together, these results highlight the need for a careful assessment of the risk-benefit relationship of psychopharmacologic treatments in patients who cannot be managed sufficiently with nonpharmacologic interventions and for routine, proactive adverse effect monitoring and management. Although considerable progress has been made, there is still enormous need for additional data and funding of pediatric psychopharmacology trials. It is hoped that the field will acquire the necessary resources to propel pediatric clinical psychopharmacology to new levels of insight by linking it with, but not replacing it by, pharmacoepidemiologic and biomarker approaches and advances.

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As part of a series honoring the 50th anniversary of the Early Clinical Drug Evaluation Unit (ECDEU)–New Clinical Drug Evaluation Unit (NCDEU) Annual Meeting, this article will address the pharmacologic treatment of youth with psychostimulants, antidepressants, and antipsychotics. In the spirit of providing a synopsis of past achievements, current challenges, and outstanding solutions, we will also summarize the current evidence for the efficacy and safety of these major pharmacologic drug classes in youth, identify knowledge gaps, and outline future directions in the clinical use and research of these medications in pediatric patients.

PSYCHOTROPIC MEDICATION USE IN YOUTH: A DEBATED ISSUE

Despite increasing recognition that psychiatric disorders that are generally treated in adulthood often have an onset before age 18 years, including unipolar depression,[1] bipolar disorder,[2] and schizophrenia,[3] the use of psychopharmacologic medications in youth with these conditions has been controversial. Although data suggest that psychiatric disorders are often more severe, chronic, and unresponsive to therapies and associated with greater functional impairment and disease burden if their onset occurs during childhood or adolescence compared to adulthood,[1,3,4] a number of concerns have been raised regarding the number of psychotropic medication prescriptions received by children and adolescents and the appropriateness of the diagnoses used to justify such use. There has been significant debate about a potential overdiagnosis of psychiatric disorders in childhood, particularly of bipolar disorder,[5–7] as well as allegations of overmedicating behaviors of prescribers.[8–17] The concern is that psychotropic medications, especially antipsychotics, are used too early, before or instead of attempts to address the youngsters' psychiatric symptomatology with more resource-intensive psychotherapeutic, behavioral, and family interventions.[18] The debate has also been fueled by decades of prescribing despite a dearth of efficacy and safety data for major psychiatric drug classes in youth, resulting in a general need to rely on extrapolations from studies in adults.[19]

DEVELOPMENTAL PSYCHOPHARMACOLOGY: DIFFERENCES THAT MATTER

The debate about the appropriateness and potentially underrecognized risks of psychotropic medication use in youth is accentuated by findings suggesting that psychotropic medications may have developmentally dependent effects that differ from those observed in adults. For example, research has suggested that tricyclic antidepressants are much less effective in youth than in adults.[20] Furthermore, a syndrome of paradoxical hyperactivity, agitation, and/or aggressiveness has been described in response to treatment with benzodiazepines or antihistamines, in a small subgroup of susceptible youth.[21,22] Similarly, pharmacokinetic differences have also been identified. Compared to adults, children

and adolescents have active tissue growth, increased reproductive hormone release during adolescence, a higher ratio of liver organ-to-tissue mass, greater intracellular and extracellular tissue water and glomerular filtration rates, lower protein binding, and reduced fat tissue mass.[23] Clinically, these differences usually mean that for some medications higher doses per kilogram weight are required in pediatric populations than in adults to achieve similar efficacy and that more frequent dosing per day may be required in younger children. In addition to other less well-known pharmacodynamic aspects, these pharmacokinetic differences between children and adolescents and adults might be one reason for a generally observed greater likelihood of a number of adverse effects in youths than in adults. For example, these quantitative differences include higher rates of nausea and activation with antidepressants[24]; higher rates of sedation, weight gain, prolactin elevation, and withdrawal dyskinesia with antipsychotics[24–26]; greater weight gain with mood stabilizers[26]; and higher rates of sudden cardiac death during stimulant treatment,[27] although the latter finding has not always been confirmed[28] and may be related to a greater prevalence of inborn structural and functional cardiac abnormalities in youth compared to individuals with attention-deficit/hyperactivity disorder (ADHD) who survived into adulthood.[29]

However, in addition to these quantitative differences, some adverse events might also differ qualitatively. In addition to the already described paradoxical agitation in response to benzodiazepines and sedatives, other examples include dysphoria in response to psychostimulants[30] and suicidal thoughts or behaviors in response to antidepressants.[31] While these qualitatively different responses do not affect all patients, there appear to be subgroups of patients who possibly either are genetically predisposed to metabolize these medications differently, leading to metabolites with different biological activity,[32] or differ in terms of receptor configuration and downstream pathways, due to an immaturity of the central nervous functioning or isolated pathway alterations. Taken together, the potential for age-dependent quantitative and qualitative differences in efficacy and adverse event profiles in youth compared to adults points toward the urgent need for carefully conducted large and long-term trials of psychotropic mediations in pediatric patients.

DEVELOPMENTS IN PEDIATRIC PSYCHOPHARMACOLOGY

Due to worries regarding insufficient knowledge about the complex and potentially enduring effects of psychotropic medications taken during periods of enormous biological and psychological development, it is important to evaluate how far the field of pediatric psychopharmacology has come and which gaps still need to be addressed.[33] Over the past 40 years, the field of pediatric psychopharmacology has evolved from an unduly long reliance on case reports and uncontrolled case series[33] to the conduct of methodologically problematic crossover and open-label studies and, more recently, to larger cohort studies and adequately powered, randomized, placebo-controlled and, less so, active comparator trials.[3,26,31,34,35] More recently, multisite studies have been conducted that compare the efficacy and safety of psychotherapy with a pharmacologic treatment and the combination of both treatment modalities against placebo.[36] Moreover, more complex equipoise randomization designs, placebo run-in phases, discontinuation designs, and large practical and adaptive trials are slowly entering the area of pediatric psychopharmacology. However, despite the fact that, like in adults, polypharmacy with psychotropic medications is common in youth with severe psychiatric disorders,[24,37,38] trials comparing different pharmacologic augmentation and combination strategies are scarce.

Due to the wide range of development and psychopathology encountered during childhood and adolescence, the validity and reliability of assessments can be affected in this population. Therefore, the development and validation of age-appropriate rating scales and determination of age-dependent thresholds for abnormal values and severity levels are necessary. Given that in psychiatry patient and clinician support measures will not yield to surrogate endpoints until our understanding of fundamental biology has progressed significantly,[39] this process is even more important. Moreover, questions and tasks must be age-appropriate and sometimes gender-appropriate (particularly in adolescence) and may not always be uniformly applicable.

Regarding side effect assessments, a review of 196 pediatric psychopharmacology articles published over more than 2 decades revealed that there was no common method used for eliciting or reporting adverse event data.[40] This appropriately prompted an increased focus on standardized assessment methods for acute and long-term adverse effects in youth,[41,42] as these inconsistencies in ascertaining and reporting data on medication safety in pediatric patients are a major current limitation. However, even regarding biological measures or organic side effects, the field has only slowly adopted the use of developmentally appropriate measures and thresholds. This is particularly pertinent for the assessment and tracking of age-inappropriate weight gain and abnormalities in cardiometabolic parameters, including effects on blood pressure, glucose, and lipids.[43]

The emergence of larger-scale conduct of psychopharmacology trials in children and adolescents can be attributed to the recognition that exposing a limited number of youngsters in controlled and well-supervised settings was more ethical than not conducting these studies, leading to the exposure of a much larger number of youngsters to largely untested medications in general clinical practice. Similarly, the field matured, accepting that a placebo control[44,45] in a limited number of patients was more ethical than using an active comparator of often similarly uncertain efficacy and safety or than remaining in doubt about the true efficacy and safety of a new compound or an agent that had been tested in detail only in adults. In this context, the initiative by the US Food

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and Drug Administration (FDA) to incentivize pharmaceutical companies to conduct pediatric studies in select drugs by granting a 6-month patent extension for adequate safety data in at least 100 youth followed for 6 months has contributed to the increase in an acute phase, placebo-controlled efficacy database as well as in 6- to 12-month open-label extension study–based safety and tolerability data. Additionally, new drugs with a likelihood of use in the pediatric population have recently been required to be tested in pediatric trials either prior to FDA approval or as a part of a postapproval commitment. In Europe, the European Medicines Agency has taken this a step further, requiring a pediatric investigational plan to be submitted with every submission of a medication for a new indication.

CONTROLLED EVIDENCE BASE FOR STIMULANTS, ANTIDEPRESSANTS, AND ANTIPSYCHOTICS IN YOUTH

Over the last decade, there has been a sharp increase in the number, size, and quality of psychopharmacologic studies in youth. Case series and open-label and crossover studies have been replaced by randomized controlled trials (RCTs) including many of the major medication classes, especially psychostimulants, antidepressants, and antipsychotics.

Psychostimulants

Given conservative estimates of ADHD prevalence rates of 3% to 7% in US children,[46] 60% to 85% continuation into adolescence, and up to 60% into adulthood,[47–49] and given the serious functional impairment associated with ADHD in youth as well as in adults,[50] effective management strategies for this early childhood–onset disorder are important.

Efficacy in ADHD. There is strong support for the efficacy of pharmacotherapy, especially of psychostimulants, as a first-line treatment for ADHD.[51] All stimulant medications currently approved for ADHD are either methylphenidate or amphetamine derivatives, both of which enhance the neurotransmission of dopamine and, to a lesser extent, of norepinephrine. Over the last decades, the pediatric database for the acute and long-term safety and efficacy of stimulants has continually grown, including more recently research in preschoolers and adolescents. In addition, data supporting the efficacy and safety of nonstimulant medications for ADHD have also increased significantly over the past decade.[51]

A meta-analysis of randomized, controlled pediatric studies of 2 FDA-approved treatments for ADHD, atomoxetine and stimulants, yielded a moderate effect size for atomoxetine of 0.63 and a large effect sizes of 0.99 and 0.95 for immediate- and extended-release stimulants, respectively.[52] These effect sizes translate into response rates of approximately 65% to 75% after the first stimulant trial (compared to 4%–30% with placebo) and 80% to 90% after 2 different, consecutive stimulant trials.[55] The calculated numbers needed to treat (NNTs) for study-defined response were 3 to 5 for stimulants and 4 for atomoxetine.[146] A third, more recently FDA-approved agent, the α_2 agonist guanfacine XR, had medium to large effect sizes of 0.43 to 0.86 in the 2 double-blind, placebo-controlled registration trials.[53,54] Moreover, recently, extended-release clonidine was also FDA-approved for monotherapy and as an adjunctive treatment in addition to stimulants.[51]

More recently, research has focused on improving the delivery mechanisms of stimulant medications to extend the duration of action. As a result, treatment can increasingly be individualized, having available multiple different formulations, including short-, intermediate-, and long-acting stimulants, as well as a variety of administration options, such as capsules, sprinkleable capsules, tablets, chewable tablets, oral solution, and transdermal patches.[51]

Three high-quality studies comparing stimulant treatment with psychosocial interventions have further advanced the field (Table 1). The Multimodal Treatment Study of Children With ADHD (MTA) was a seminal, longitudinal, 4-arm trial in 579 children aged 7 to 9.9 years with ADHD, combined type.[56] Patients were randomly assigned to manualized pharmacotherapy (consisting of immediate-release methylphenidate tid; final dose: 32.1 ± 15.4 mg/d), manualized behavioral intervention, combination of manualized pharmacotherapy (final dose: 28.9 ± 13.7 mg/d) plus behavioral intervention, or community treatment. Dose titration of methylphenidate was based on the patients' weight, on parent and teacher rating scale–reported efficacy, and on tolerability.[56] Alternative medications were allowed for patients with inadequate response to the initial methylphenidate trial. The behavioral treatment was structured and rigorous, including a 35-session parent training group; an 8-week, 5-days-per-week, 9-hours-per-day summer treatment program; and school-based treatment with 10 to 16 sessions of biweekly teacher consultation accompanied by 12 weeks of paraprofessionals directly working with the child.

Results indicated that all 4 treatment groups improved, but that the greatest improvement in ADHD symptoms occurred in the medication-only or the combined medication/psychosocial treatment groups. Combined treatment did not yield significantly greater benefits than medication management alone for core ADHD symptoms. Effect sizes for methylphenidate were moderate, ie, 0.52 for parent-reported efficacy and 0.75 for teacher-reported efficacy. In addition, modest advantages were found for specific non-ADHD symptoms and other functional outcomes. Rates of "excellent success" were 68% for combination treatment, 56% for medication treatment, 34% for psychosocial treatment, and 25% for community control treatment. This translates into NNTs of 3 for combination treatment, 4 for medication treatment, and 12 for psychosocial treatment, representing large effect sizes for combination treatment and medication treatment alone and very small effects of questionable clinical significance for behavioral treatment alone when compared with community control treatment that

Table 1. Randomized Studies Comparing Psychostimulants With a Psychosocial Intervention, a Combination of the Two, and a Control Condition

Study	Sample Size	Age Range (y)	% Males	Diagnosis	Treatment	Study Duration	Conclusion
Multimodal Treatment Study of Children With ADHD (MTA)[56–58]	579	7–9.9	80	ADHD	Subjects were randomly assigned to a manualized medication management program, an intensive psychosocial treatment, a combination of the two, or community treatment	14 mo	Combined treatment did not yield significantly greater benefits than medication management alone for core ADHD symptoms. Rates of "excellent success" were 68% for combination treatment, 56% for medication treatment, 34% for psychosocial treatment, and 25% for community control treatment
New York Montreal Study of Long-Term Methylphenidate and Multimodal Psychosocial Treatment in Children with ADHD[59,60]	133	7–9	93	ADHD	Study of children who responded to short-term methylphenidate, then were randomly assigned to methylphenidate alone, methylphenidate plus psychosocial treatment (parent training and counseling, social skills training, psychotherapy, and educational assistance), or methylphenidate with a psychosocial attention control treatment	2 y	Combined treatment did not lead to superior functioning compared to methylphenidate alone, and all treatment groups demonstrated significant improvement that continued over 2 y. Investigators concluded there was no support for routinely adding psychosocial interventions to stimulants for ADHD
Preschool ADHD Treatment Study (PATS)[61–63]	303	3–5.5	76	ADHD	Fewer than 10% of the children responded to an initial course of parent training, and ultimately 165 were initiated on pharmacotherapy. Mean optimal dose of immediate-release methylphenidate, dosed tid, was 14.2 mg/d	70 wk	While methylphenidate was effective, the effect size was smaller than that found in school-aged children in the study, perhaps due at least in part to the conservative dosing. Moderate to severe adverse effects occurred in 30% of preschoolers, including emotional outbursts, initial insomnia, repetitive behaviors/thoughts, decreased appetite, and irritability. A total of 11% discontinued methylphenidate due to intolerable adverse effects, compared to < 1% of school-aged children in MTA

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

could consist of medication and/or behavioral treatment.[149] In subsequent analyses at 3 years[57] and 8 years,[58] there were no differences in outcome on the basis of initial treatment assignment anymore, but rather baseline functioning was the most consistent predictor. However, treatment had not been controlled beyond the 14 months of the active study, indicating that outcomes seem to differ only when effective and evidence based treatments are maintained according to at least somewhat controlled protocols or guidelines.

A second study that investigated medication, psychosocial, and combination treatment for ADHD was the New York Montreal Study of Long-Term Methylphenidate and Multimodal Psychosocial Treatment in Children with ADHD (Table 1).[59] In this 2-year study, 133 children aged 7 to 9 years with ADHD who had responded to short-term methylphenidate treatment were randomly assigned to treatment with methylphenidate, methylphenidate plus psychosocial treatment (parent training and counseling, social skills training, psychotherapy, and educational assistance), or methylphenidate plus a psychosocial attention control treatment. Consistent with the MTA results, combination treatment was not superior to methylphenidate alone, and all treatment groups demonstrated significant improvement that was generally maintained over 2 years, although after 1 year, all patients were single-blindedly assigned to pill placebo, with reinitiation of methylphenidate as needed.[60]

A third seminal, National Institute of Mental Health (NIMH)–funded stimulant study in ADHD was the Preschool ADHD Treatment Study (PATS), which enrolled 303 moderately to severely impaired preschoolers aged 3–5.5 years with ADHD (Table 1).[61,62] Fewer than 10% of the children responded to an initial course of parent training, and ultimately 165 were randomly assigned to 14 months of either placebo or immediate-release methylphenidate (1.25 mg, 2.5 mg, 5 mg, or 7.5 mg tid), using a titration schedule modeled after MTA. This study was needed, as stimulants were used clinically for children below the age of 6 years, and only a few, small randomized studies had been conducted in preschoolers that used immediate-release methylphenidate at relatively low doses (< 0.6 mg/kg compared to 0.3–1.0 mg/kg used in studies of older children), and at potentially too infrequent intervals (ie, qd or bid dosing, rather than tid dosing that might be necessary in younger children who have a faster drug metabolism). PATS subjects received 1 week of treatment with each dose during an initial, double-blind, crossover titration phase, and 22% of subjects responded

best to 7.5 mg tid (final most efficacious dose: 14.22 ± 8.1 mg/d, or 0.7 ± 0.4 mg/kg/d).[61,62]

Comparing PATS with MTA results revealed age group differences. Compared to school-aged children, preschoolers responded to lower weight-adjusted optimal doses of immediate-release methylphenidate (0.7 mg/kg/d compared to 1.0 mg/kg/d) and had slower clearance of a single dose of methylphenidate,[30] more emotional adverse events (eg, proneness to crying, irritability, and crabbiness), more study withdrawal due to adverse effects (11% vs < 1%), and smaller effect sizes for response (ie, 0.35 and 0.43 based on parent ratings for parent- and teacher-reported efficacy, respectively, compared to 0.52 for parents and 0.75 for teachers in the MTA study). Thus, results from this study suggested that in preschoolers with ADHD, clinicians should utilize slower titration and smaller doses of stimulants and monitor adverse effects more closely.[63]

Efficacy in disruptive behavior disorders. A meta-analysis of pharmacologic treatments for maladaptive aggression in youth (mean age: 9.1 years, 84.2% male) identified 18 RCTs with stimulants (16 with methylphenidate, 1 combination study of methylphenidate and mixed amphetamine salts, and 1 combination of methylphenidate, dextroamphetamine, and pemoline).[64] The primary diagnoses included ADHD (13 studies), disruptive behavior disorders (3 studies), autism (2 studies), and mental retardation (1 study), and all but 6 studies allowed for comorbid diagnoses of conduct disorder, oppositional defiant disorder, or ADHD. The average trial duration was 27.2 days, and the weighted average dose of methylphenidate was 0.93 mg/kg/d. Consistent with a prior meta-analysis on this topic, in which stimulants had an effect size of 0.84,[65] stimulants had a pooled mean effect size for pediatric aggression of 0.78, a medium to large effect size.[64] However, crossover studies were included in these calculations that are less methodologically sound, and, to date, no head-to-head comparison between stimulants and antipsychotics, the other medication class with a large effect size for aggression, exists. In a recently completed systematic review of placebo-controlled efficacy of stimulants for rating scale–based aggression, stimulants (6 studies, 907 patients) had a pooled effect size of 0.6 and an NNT for response of 4.[147]

Stimulant tolerability. All stimulant formulations have roughly similar adverse event profiles, including a potential for delayed onset of sleep, appetite suppression, weight loss, headache, abdominal pain, stomach upset, growth delays, and increases in pulse as well as blood pressure.[34,51,61] Less common adverse effects that might require management include tics and emotional lability/irritability. Emotional outbursts and irritability might be more frequent in younger children and those with developmental delays.[30] Concerns about the cardiovascular safety of psychostimulants have prompted specific recommendations to obtain historical and physical information to identify at-risk children with structural cardiac abnormalities and premedication cardiovascular symptomatology. However, potentially medication-related changes in pulse and blood pressure have also been observed in children with ADHD without preexisting cardiac abnormalities. For example, in a 10-year Florida Medicaid claims study, stimulant-treated patients with ADHD had 20% more emergency room visits and 21% more office visits for cardiac symptoms than patients not receiving stimulants.[28] However, cardiac mortality was not increased in patients currently receiving stimulants or those with a history of stimulant use. Likewise, Gould et al[27] reported similar rates of sudden death in pediatric patients taking psychostimulants compared to children in the general population, with 11 sudden deaths reported between 1992 and 2005. However, in a matched case-control study comparing data for 564 reports of sudden death in 7- to 19-year-olds with the deaths of 564 same-aged children who died in a motor vehicle accident, a significant association of stimulant use with sudden death emerged (odds ratio = 7.4; 95% CI, 1.4–74.9).[27] Nevertheless, absence of autopsy data in most cases and the possibility of non–medication-related effects complicate the interpretation of these results.

Antidepressants

As shown by the fact that approximately 2% of children and adolescents in the United States receive a prescription for a selective serotonin reuptake inhibitor (SSRI), clinicians consider antidepressants acceptable treatments for children and adolescents with mood, anxiety, and obsessive-compulsive disorders.[31] Randomized placebo-controlled trials are generally thought to indicate that SSRIs and selective serotonin and noradrenergic reuptake inhibitors (SNRIs) are effective in youth with mood, anxiety, and obsessive-compulsive disorders.[31] As family physicians and, to a lesser extent, pediatricians have become more comfortable using these medications in the pediatric population, prescribing rates continue to increase despite concerns about adverse events.

Efficacy in major depressive disorder, obsessive-compulsive disorders, and anxiety disorders. In a review of 27 published and unpublished studies, Bridge and colleagues[31] examined the relative risks and benefits of antidepressant medications (SSRIs, nefazodone, venlafaxine, and mirtazapine) in youth with major depressive disorder (MDD) (N = 15), obsessive-compulsive disorder (OCD) (N = 6), and non-OCD anxiety disorders (N = 6). The NNT for MDD was 10 (95% CI, 7–15), for OCD was 6 (95% CI, 4–8), and for non-OCD anxiety was 3 (95% CI, 2–5), corresponding to a small, a medium, and a large effect size, respectively. For OCD and non-OCD anxiety disorders, younger and older subjects responded equally well. Conversely, for children younger than 12 years with MDD, only fluoxetine showed benefit over placebo. In most studies, the within-group response rate for medication hovered around 60% across trials independent of age, gender, or diagnosis. Interestingly, what distinguished a positive from a negative MDD trial was the size of the placebo response rate: the larger the placebo response, the greater the likelihood of a negative study. Given that an increased number of sites

Table 2. Randomized Studies Comparing Antidepressants With a Psychosocial Intervention, a Combination of the Two, and a Control Condition

Study	Sample Size	Age Range (y)	% Males	Diagnosis	Treatment	Study Duration	Conclusion
Pediatric OCD Treatment Study (POTS)[69]	112	7–17	50	OCD	Randomly assigned to CBT alone, medical management with sertraline alone, the combination of the two, or pill placebo	12 wk	All 3 active treatments superior to placebo in reducing OCD symptoms, although the remission rate for combined treatment was 53.6%; for CBT alone, 39.3%; for sertraline alone, 21.4%; and for placebo, 3.6%
Child/Adolescent Anxiety Multimodal Study (CAMS)[71,72]	488	7–17	50	Separation anxiety disorder, social phobia, or generalized anxiety disorder	Randomly assigned to sertraline, CBT, their combination, or pill placebo	12 wk	All 3 active treatments were significantly superior to placebo. Response rate for combination treatment was 81%, followed by both CBT alone (60%) and sertraline alone (55%), compared to only 24% with placebo
Treatment for Adolescents With Depression Study (TADS)[67,73–81]	439	12–17	46	MDD	Randomly assigned to fluoxetine with medical management, weekly CBT, their combination, or pill placebo	12 wk (acute phase)	Adolescents who received fluoxetine or combination therapy had significant improvements at 12 wk, while those receiving CBT alone did not separate from placebo. Response rates at 12 wk were 71.0% for combination treatment, 60.6% for fluoxetine, 43.2% for CBT, and 34.4% for placebo. By the end of 9 mo of treatment, response rates for combination (81.3%), fluoxetine (71.6%), and CBT (68.5%) were virtually identical
Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)[82–85]	334	12–18	30	MDD (had not responded to a 2-mo trial with an SSRI)	Randomly assigned to a second, different SSRI (paroxetine, citalopram, or fluoxetine); a different SSRI plus CBT; venlafaxine; or venlafaxine plus CBT	12 wk	The 2 arms with CBT plus medication demonstrated a higher response rate (54.8%) than a medication switch alone (40.5%), with no difference in response rate between venlafaxine and a second SSRI

Abbreviations: CBT = cognitive-behavioral therapy, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, SSRI = selective serotonin reuptake inhibitor.

predicted a poor response, it is likely that method variance—perhaps reflecting baseline inflation, rater unreliability, and early dropout—rather than lack of efficacy accounts for the large number of failed trials in pediatric major depression. Consistent with this interpretation, all 3 fluoxetine MDD trials—2 of which were funded by the NIMH[66,67] and 1 of which, funded by Eli Lilly, was conducted using academic sites[68]—were strongly positive, with placebo response rates around 35%, which is at the low end of a range that in negative trials approached 60%.

It is heuristically valuable in this regard to examine 4 very high quality, NIMH-funded studies in OCD, anxiety disorders, and adolescent MDD that compared specific antidepressants with cognitive-behavioral therapy (CBT), their combination, and placebo (Table 2).

The NIMH-funded Pediatric OCD Treatment Study (POTS) randomly assigned 112 patients with OCD aged 7 to 17 years to treatment with CBT, medical management with sertraline, the combination of the two, or pill placebo (Table 2).[69] All 3 active treatments were superior to placebo in reducing OCD symptoms, although clinical remission rates were 53.6% for combined treatment, 39.3% for CBT alone, and 21.4% for sertraline alone, compared to only 3.6% for placebo only. This translated into NNTs of 2 for the combination treatment and 3 for CBT (both representing large effect sizes), as well as 6 for sertraline, which was identical to the results in the aforementioned meta-analysis,[31] representing a moderate effect size. Thus, the POTS findings support an initial treatment approach for youth with OCD to consist of either CBT or sertraline as monotherapy or a combination of the two.

In a study by the Research Unit on Pediatric Psychopharmacology (RUPP) Anxiety Study Group,[70] 128 youth aged 6 to 17 years with social phobia, separation anxiety disorder, or generalized anxiety disorder (GAD) were enrolled who had failed to improve with 3 weeks of a psychosocial intervention. Patients were then randomly assigned to 8 weeks of fluvoxamine dosed up to 300 mg/d or placebo. In this trial, fluvoxamine was significantly superior to placebo on both the Pediatric Anxiety Rating Scale and the Clinical Global Impressions-Improvement scale. Response rates were 76% with fluvoxamine versus 29% with placebo, resulting in a large effect sized NNT of only 2, being slightly more effective compared to the NNT of 3 in the previously cited meta-analysis.[31]

One of the most relevant studies in pediatric anxiety disorders was the recently completed Child/Adolescent Anxiety Multimodal Study (CAMS).[71,72] In CAMS, 488 patients aged

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7 to 17 years with separation anxiety disorder, social phobia, or GAD were randomly assigned to sertraline, CBT, their combination, or pill placebo.[71] All 3 active treatments were significantly superior to placebo. The highest response rate, based on a rating of much or very much improved on the Clinical Global Impressions-Severity of Illness scale, was observed in the combination treatment (81%), followed by both CBT alone (60%) and sertraline alone (55%), compared to a response rate of only 24% with placebo.[72] These results translate into an NNT of 2 for the combination treatment and 3 for CBT alone, representing large effect sizes, and 4 for sertraline alone, representing a moderate effect size.

In the Treatment for Adolescents With Depression Study (TADS), 439 adolescents aged 12–17 years with moderate to severe depression were randomly assigned to one of 4 treatments: fluoxetine with medical management, weekly CBT, their combination, and pill placebo (Table 2).[67,73] Adolescents who received fluoxetine or combination therapy had significant improvements in depression ratings at 12 weeks, whereas those receiving CBT alone did not separate from placebo. Response rates at 12 weeks were 71.0% for combination treatment, 60.6% for fluoxetine, 43.2% for CBT, and 34.4% for placebo. The corresponding NNTs for response with combination of CBT plus fluoxetine and with fluoxetine monotherapy were 3 (95% CI, 2–4) and 4 (95% CI, 3–8), respectively,[67] large effect sizes that were much more favorable than the NNT of 10 in the aforementioned meta-analysis.[31] Younger and less severely/chronically ill youth who were less suicidal and less hopeless and who had less melancholic features or other comorbidities benefited more.[74] Notably, the mean duration of the current depressive episode prior to randomization was as long as 70 weeks, indicating little likelihood of spontaneous remission in these moderately to severely ill teens with MDD.[75] While this study demonstrated the key role of pharmacotherapy in the treatment of adolescent MDD, the combination treatment was most successful acutely for a number of secondary outcomes, including the treatment of patients with comorbid ADHD[76] and the reduction of suicidal events.[77,78] Of note, by the end of 9 months[79,80] and 1 year[81] of treatment, combination, fluoxetine, and CBT responses were virtually identical, and patients staying in the study generally retained their benefits.

A second trial comparing pharmacotherapy and psychotherapeutic intervention in pediatric depression was the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) study,[82,83] which focused on more chronically depressed and treatment-resistant youth than TADS. This 12-week study randomly assigned 334 adolescents aged 12 to 18 years with MDD and lack of response to a 2-month initial trial with an SSRI to switch to one of 4 conditions: a different SSRI (citalopram, fluoxetine, or paroxetine); a different SSRI plus CBT; an antidepressant of a different class (venlafaxine); or venlafaxine plus CBT (Table 2).[82] The 2 arms with CBT plus medication demonstrated a higher response rate (54.8%) than a medication switch alone (40.5%), with no difference in response rate between switch to a second SSRI or venlafaxine.[82] This difference in response rates translates into an NNT of 7 in favor of the combination treatment over antidepressants alone in chronically depressed adolescents. TORDIA demonstrated that for adolescents with depression who do not respond to an initial SSRI, a switch to another antidepressant, combined with CBT, should be considered. Even if CBT is not feasible, simply changing medications yielded a 40.5% improvement, and within- and outside-class switches were equally effective. However, venlafaxine was associated with greater increases in pulse and diastolic blood pressure and more frequent skin problems than other SSRIs.[82] At 24-week follow-up, 38.9% of the 334 adolescents enrolled in the study achieved remission without differences based on initial treatment assignment.[84] Response at week 12, as well as lower baseline depression, hopelessness, and self-reported anxiety, suicidal ideation, and family conflict, mediated remission status at week 24.[84] Of patients who responded by week 12, 19.6% had a relapse of depression by week 24. At 72-week follow-up, an estimated 61.1% of the randomized youths had reached remission, but of the 130 remitted youth at week 24, 25.4% relapsed in the subsequent year.[85] Randomly assigned treatment during the first 12 weeks did not influence remission rate or time to remission, but patients assigned to SSRIs had a significantly more rapid decline in self-reported depressive symptoms and suicidal ideation than those assigned to venlafaxine.[85] Moreover, more severe depression, greater dysfunction, and alcohol or drug use at baseline mediated lack of remission. Of note, the depressive symptom trajectory in remitters had already separated from that of nonremitters by the first 6 weeks of treatment.[85]

Antidepressant tolerability. Adverse effects in youth treated with SSRIs and SNRIs include 3 main categories: nonpsychiatric, psychiatric, and suicidal events. Nonpsychiatric adverse events, such as nausea or headache, are typically transient and easily managed by slowing titration or dose reduction.[51] Psychiatric adverse events, such as switch into mania or "behavioral activation" (an ill-defined mixture of agitation, restlessness, insomnia, and affective instability) are less frequent, but of potentially greater importance for the child's functioning. Fortunately, conversion to mania is rare, and behavioral activation symptoms, which are also uncommon, typically respond to dose reduction.[51]

Suicidal events (classified as worsening ideation, an interrupted attempt, or an actual attempt) have become an adverse effect focus in antidepressant-treated youth.[83,86–88] In September 2004, an FDA Advisory Committee reviewed results of a meta-analysis of 24 controlled clinical trials of 9 antidepressants, which included approximately 4,400 pediatric patients.[89] While there were no completed suicides, the cumulative risk for suicidality (suicidal thinking or behavior), collected as spontaneous adverse event reports, was approximately 4% with antidepressants versus approximately 2% with placebo. In this respect, the Bridge et al[31] meta-analysis extended the earlier report,[89] identifying a small, but nontrivial, increase in risk of 0.7% (95% CI,

0.1%–1.3%), corresponding to a number needed to harm (NNH) of 143, which is larger, indicating lower risk, than the NNH of 50 identified in the earlier FDA analysis and the NNH of 43 in TADS. This very small and clinically undetectable effect is nonetheless of public health importance because of the large number of nonfatal suicidal events—approximately 2 million—occurring in youth in the United States each year. Importantly, however, completed suicides are fortunately very rare, and there were no completed suicides in the FDA sample of 4,400 patients, the TADS sample, or the Bridge et al[31] meta-analyzed studies, and epidemiologic evidence suggests that youth with depression receiving antidepressants are at lower risk for death by suicide than untreated youth.[73]

In the TADS, suicidality information was systematically collected, both at baseline and during follow-up, and about 30% of youth endorsed recent thoughts or behaviors related to self-harm before randomization, with combined treatment showing a statistically significant excess at baseline.[67] During the study, all 4 treatment groups (CBT, fluoxetine, their combination, and pill placebo) led to a systematically assessed decrease in suicidality, although fluoxetine demonstrated the smallest reduction.[67] To our knowledge, this is the only high-quality examination of ideation as contrasted to events, which shows that the impact of medication is not only on behavior. With respect to suicidal events, data from the TADS indicate that adding depression-specific CBT to fluoxetine eliminates the fluoxetine-associated risk for suicidal events specifically and psychiatric adverse events more generally.[73] In both instances, the risk from fluoxetine alone was double that for combined treatment, which was equivalent to those for CBT and placebo.[67,73] Of note, the NNH for suicidal events in the POTS, RUPP Anxiety, and CAMS trials was at infinity; that is, there were no suicidal events in these studies, indicating that the risk is largely confined to MDD trials. An examination of those trials (buttressed by the CAMS finding) that used sertraline as the active treatment found the same result.[87] In addition, the risk for a suicidal event in female subjects was about twice that for males, and adolescents were at higher risk than children, suggesting that depressed female adolescents represent the highest risk group.

Taken together, these studies identify a positive benefit-to-risk ratio for short-term treatment with SSRI or SNRI medication in adolescents and, perhaps, children with MDD and in patients of all ages with anxiety and OCD. Despite a large number of negative industry-sponsored trials, it is highly likely that the positive risk-benefit ratio is a class effect for both benefits and adverse events in patients treated with SSRIs and SNRIs. Adding CBT to medication management substantially enhances benefits and minimizes adverse events of most types. While supporting data are not definitive, the reduction in suicidal events in depressed teens obtained by adding CBT to medication is quite striking. Withholding medication is clearly not a reasonable solution. The 25% reduction in prescriptions or antidepressants that accompanied the black box warning was associated with a 25% increase in completed suicide rate,[90] presumably because these medications effectively treat depression and consequently reduce depression-associated mortality from suicide.[91]

Antipsychotics

On the basis of the broadened use of second-generation antipsychotics (SGAs), in particular, antipsychotic prescribing has increased substantially in youth.[10,11] This fact has increased the importance of scrutinizing the efficacy and safety of antipsychotics in youth across different indications. The debate about antipsychotic prescribing in children and adolescents has been fueled by the fact that antipsychotics are being used largely for nonpsychotic disorders and off-label indications[9,10,13]; by disagreement about the validity of psychiatric diagnoses during childhood, particularly bipolar disorder[6,92]; by concerns about a possible lack of psychosocial interventions and their replacement by antipsychotics, especially for the treatment of disruptive and aggressive spectrum disorder[93,94]; and by reports about more frequent and more severe antipsychotic adverse effects that can have long-term psychological and physical health implications when occurring during critical phases of development.[95,96]

However, as concerns about antipsychotic prescribing in youth have increased, so has the controlled database for antipsychotics in youth with schizophrenia, bipolar mania, and autistic disorder.[97] These studies, mostly completed in the last 5 years, have been the basis for the FDA approval of the 4 most prescribed SGAs in youth. As of April 2011, aripiprazole, olanzapine, quetiapine, and risperidone have FDA-approved pediatric indications for bipolar mania (age 10–17 years; olanzapine: 13–17 years) and for schizophrenia (age 13–17 years). Moreover, paliperidone was also just approved by the FDA for adolescents with schizophrenia aged 13 to 17 years. In addition, aripiprazole and risperidone have an indication for irritability/aggression associated with autistic disorder (age 6–17 years), and controlled trial data exist for disruptive behavior disorders (mostly with risperidone) and tic disorders.[98]

Efficacy in pediatric schizophrenia/psychosis. More recently, after the sole availability of a few older, small, and underpowered active-controlled trials with first-generation antipsychotics, one of which included a placebo arm with 8 to 15 patients in each treatment arm,[3] 7 randomized, placebo-controlled antipsychotic trials have been completed in patients with pediatric schizophrenia.[99,102,136,139,140]

In one 6-week, international, multisite, placebo-controlled trial each (N = 107 to 302 per study), aripiprazole (10 mg or 30 mg),[139] olanzapine (2.5–20 mg),[136] quetiapine (400 mg or 800 mg),[99] paliperidone (1.5 mg, 3 mg or 6 mg [dependent on weight] and 6 mg or 12 mg [dependent on weight]),[102] and risperidone (1–3 mg or 4–6 mg)[140] were all superior to placebo in adolescents (aged 13–17 years) regarding the primary outcome, the change in the PANSS total score (Figure 1). In an additional trial, risperidone

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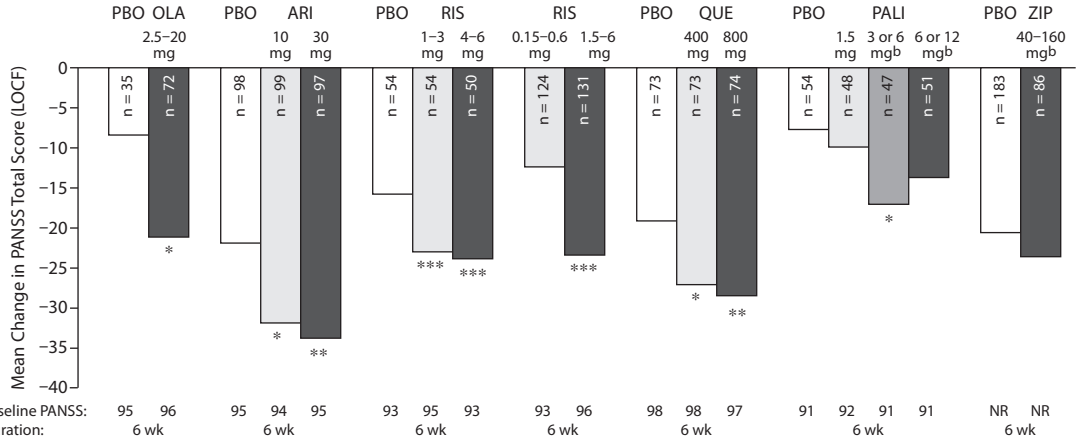
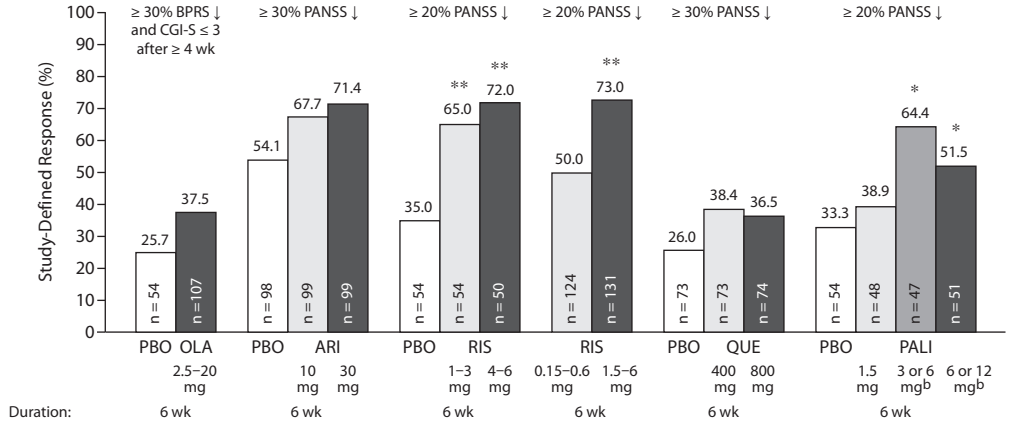
Figure 1. Improvement in PANSS Total Score From 7 Randomized, Placebo-Controlled Trials in Pediatric Patients With Schizophrenia (aged 13–17 y)[a]



[a]Doses expressed as daily doses.
[b]Dependent on weight.
*$P < .05$ vs placebo.
**$P < .01$ vs placebo.
***$P < .001$ vs placebo.
Abbreviations: ARI = aripiprazole, LOCF = last observation carried forward, NR = not reported, OLA = olanzapine, PALI = paliperidone, PANSS = Positive and Negative Syndrome Scale, PBO = placebo, QUE = quetiapine, RIS = risperidone, ZIP = ziprasidone.

Figure 2. Study-Defined Response Rates in Pediatric Patients With Schizophrenia[a]



[a]Doses expressed as daily doses.
[b]Dependent on weight.
*$P < .05$ vs placebo.
**$P < .001$ vs placebo.
Abbreviations: ARI = aripiprazole, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, OLA = olanzapine, PALI = paliperidone, PANSS = Positive and Negative Syndrome Scale, PBO = placebo, QUE = quetiapine, RIS = risperidone.

(1.5–6 mg) was superior to a pseudoplacebo of risperidone (0.15–0.6 mg).[101] By contrast, paliperidone (1.5 mg and 6 mg or 12 mg [dependent on weight]) did not separate from placebo, but response rates were significantly superior in both the medium- and high-dose arms.[102] Moreover, according to data available to date, one trial comparing ziprasidone with placebo (40–80 mg/d target dose in patients weighing < 45 kg and 80–160 mg in the others; see Figure 1) was discontinued by the sponsor due to lack of efficacy as determined in an interim analysis that revealed significant regional differences with higher placebo response rates in South America and Asia than in the United States and Europe.[100,138] Of note, the only studies/dose arms that failed in pediatric schizophrenia had a weight-based dosing schedule. Pooled NNTs based on the response rates for each of these SGAs ranged from 4 with risperidone to 10 with quetiapine, translating into moderate to small effect sizes, which were statistically significant except for olanzapine, which included the fewest participants (Figure 2).

In all, 7 head-to-head trials compared antipsychotics in youth with schizophrenia or psychosis.[3,103–105] Across these active-controlled studies with modest sample sizes per treatment group (ranging from 11–42) and short durations (4–8 weeks), no differences in efficacy were observed

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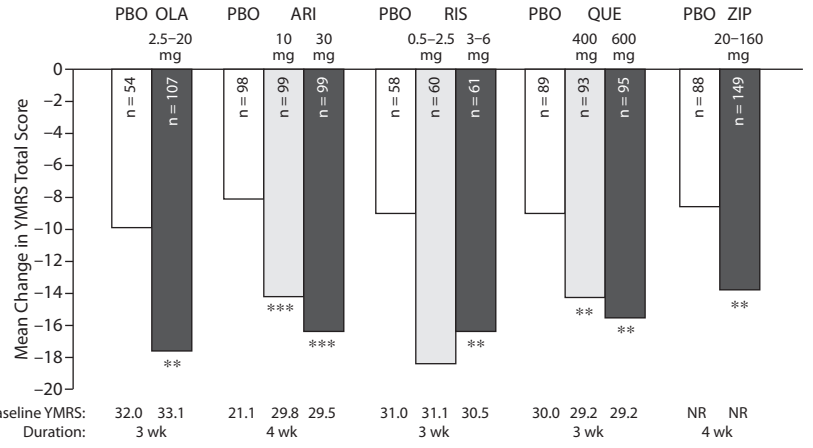
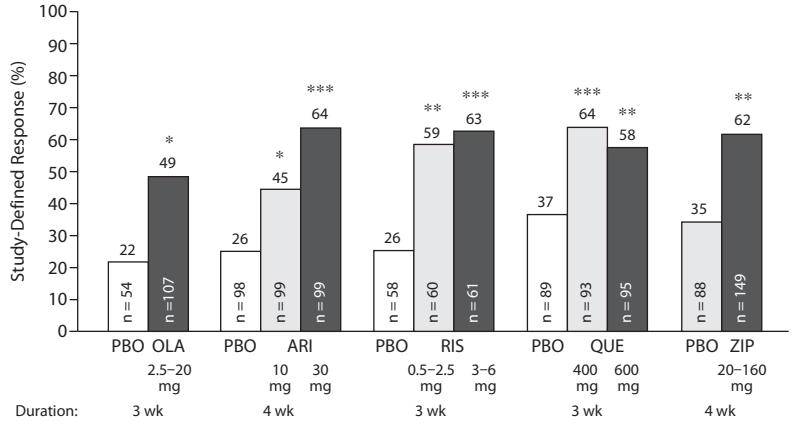
Figure 3. Improvement in YMRS Total Score From 5 Randomized, Placebo-Controlled Trials in Pediatric Patients With Bipolar I Disorder (aged 10–17 y)[a]



[a]Doses expressed as daily doses.
**$P < .01$ vs placebo.
***$P < .001$ vs placebo.
Abbreviations: ARI = aripiprazole, NR = not reported, OLA = olanzapine, PBO = placebo, QUE = quetiapine, RIS = risperidone, YMRS = Young Mania Rating Scale, ZIP = ziprasidone.

Figure 4. Response Rates (≥50% reduction in YMRS total score) in Pediatric Patients With Bipolar I Disorder Mania[a]



[a]Doses expressed as daily doses.
*$P < .05$ vs placebo.
**$P < .01$ vs placebo.
***$P < .001$ vs placebo.
Abbreviations: ARI = aripiprazole, OLA = olanzapine, PBO = placebo, QUE = quetiapine, RIS = risperidone, YMRS = Young Mania Rating Scale, ZIP = ziprasidone.

Efficacy in pediatric bipolar I disorder with manic or mixed episode. Eight, mostly recent, RCTs demonstrated efficacy of SGAs in pediatric patients with bipolar I mania. Five RCTs in youths (aged 10–17 years) showed superior efficacy of antipsychotic monotherapy compared to placebo regarding reduction in the Young Mania Rating Scale (YMRS) score.[26] In 1 international, multisite, placebo-controlled trial each, lasting either 3 weeks (olanzapine, risperidone, quetiapine) or 4 weeks (aripiprazole, ziprasidone), aripiprazole (10 mg or 30 mg),[141] olanzapine (2.5–20 mg),[142] quetiapine (400 mg or 600 mg),[143] risperidone (0.5–2.5 mg or 3–6 mg),[144] and ziprasidone (20–160 mg)[145] were all superior to placebo in children and adolescents (age 10–17 years; 13–17 years for olanzapine) regarding the primary outcome, the change in the YMRS total score (Figure 3).[26] In pediatric bipolar I disorder mania, NNTs of the pooled dose arms for "response" (defined as at least a 50% reduction in the YMRS total score) compared to placebo (Figure 4) ranged from 3 to 4, corresponding to large to moderate effect sizes.

Few head-to-head studies between antipsychotics and conventional mood stabilizers have been conducted. In 1 placebo-controlled trial, quetiapine (mean dose: 450 mg) added to valproic acid was superior in adolescents with bipolar I mania to valproic acid monotherapy.[109] In 1 active-controlled trial, quetiapine and valproate were equally effective regarding the YMRS change, but quetiapine was superior regarding a 50% reduction in the YMRS score, and speed of response was faster with quetiapine.[110] In an additional, recent study comparing risperidone with valproic acid, risperidone was also superior to the mood stabilizer.[111] This superiority of SGAs compared to mood stabilizers for pediatric mania was recently confirmed in a systematic review and indirect comparison of placebo-controlled trials with either SGAs or lithium/antiepileptics.[26] However, more direct head-to-head comparator trials are needed, as well as those including additional nonpharmacologic strategies. Moreover, the relative efficacy of 2 mood stabilizers compared with 1 antipsychotic is unknown. Furthermore, the efficacy of SGAs for bipolar depression in youth is currently unclear.[148]

among nonclozapine antipsychotics.[3,103–105] This includes investigator-initiated and federally funded, active-controlled trials, all showing that symptom response was not significantly different between olanzapine and risperidone,[103,104] between olanzapine or risperidone and haloperidol[103] or molindone,[104] or between olanzapine and quetiapine.[105] By contrast, in small-scale studies with only 10 to 21 patients per treatment group, lasting between 6 and 12 weeks, clozapine was superior to haloperidol,[106] standard dosing of olanzapine,[107] or "high-dose" (up to 30 mg) olanzapine,[108] with an NNT of 3 for response in the latter study, representing a large effect size.

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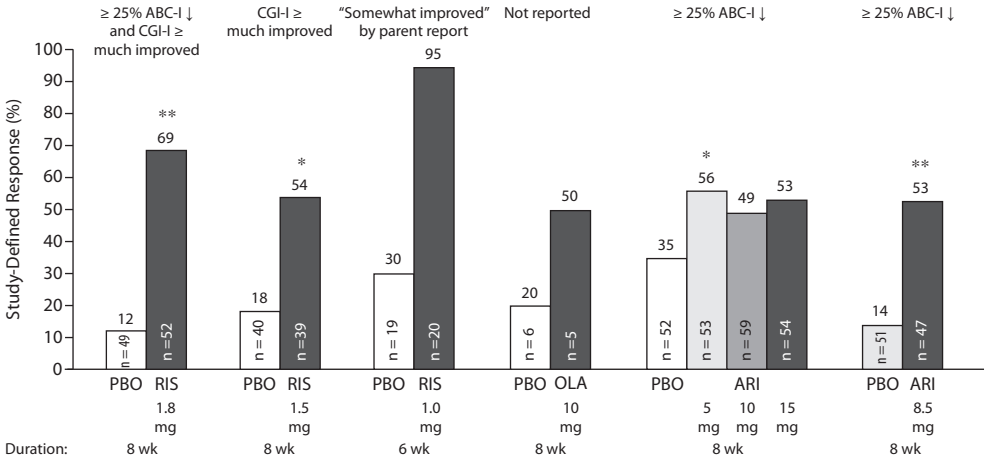
Figure 5. Study-Defined Response Rates in 5 Randomized, Placebo-Controlled Trials of Pediatric Patients With Autism[a]



[a]Doses expressed as daily doses.
*$P < .05$ vs placebo.
**$P < .001$ vs placebo.
Abbreviations: ABC-I = Aberrant Behavior Checklist-Irritability subscale, ARI = aripiprazole, CGI-I = Clinical Global Impressions-Improvment scale, OLA = olanzapine, PBO = placebo, RIS = risperidone.

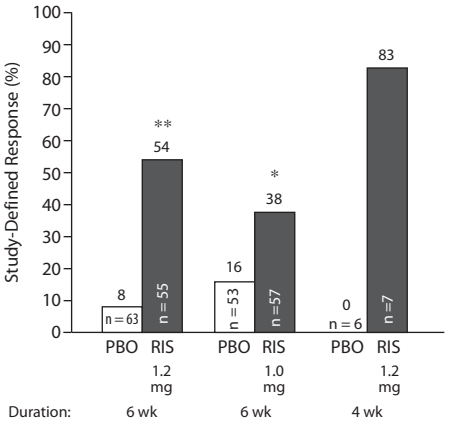
Efficacy in autistic disorder. Eight RCTs in pediatric patients with autism spectrum disorders have been completed.[112–117] In 5 adequately powered (> 30 patients), randomized, placebo-controlled trials, risperidone[113–115] and aripiprazole (5–15 mg[116] or 5 mg, 10 mg, and 15 mg[117]) showed superior efficacy compared to placebo regarding the primary outcome, the irritability subscale score of the Aberrant Behavior Checklist (ABC), in pediatric patients with autistic disorder. While stereotypic behaviors improved also, the core deficits of verbal and nonverbal communication were not altered by antipsychotic treatment. The pooled effect sizes against placebo were moderate to large, ie, 0.7 to 0.8 for risperidone[113–115] and 0.5 to 0.8 with aripiprazole.[116,117] NNTs for study-defined "response" in autism spectrum disorders ranged from 2 to 4 for risperidone,[113–115] 4 in a small study of 11 patients treated with olanzapine,[118] and 4 to 7 in 2 studies[116,117] with aripiprazole, with greater efficacy in the higher dose arms in the flexible-dose study[117] (Figure 5). In addition to the acute phase trials, in 2 placebo-controlled relapse prevention studies, risperidone was significantly superior to placebo in maintaining efficacy in the ABC irritability subscore.[119,120]

To date, only 1 randomized study,[121] by the RUPP Autism Network, has examined the effects of parent training added to risperidone versus risperidone monotherapy for maladaptive and irritable behavior. The study was conducted in 124 children (aged 4–13 years) with pervasive developmental disorders plus frequent tantrums, self-injury, and aggression. In this 24-week study, risperidone plus parent training resulted in a greater reduction of maladaptive behaviors than medication treatment alone. Moreover, risperidone dose requirements were lower in the combination treatment group.[121] While these results were encouraging, Clinical Global Impressions scale scores did not differ, and head-to-head studies of pharmacologic and nonpharmacologic treatments, alone and in combination, for aggressive behaviors associated with autism-spectrum disorders are sorely needed.

Efficacy in disruptive behavior disorders. Across 8 placebo-controlled studies in youth with aggressive behaviors associated with conduct disorder, disruptive behavior disorders, ADHD, and/or mental retardation/subaverage IQ superiority, all involving risperidone, the antipsychotic was superior to placebo regarding the study-defined response measure.[57,122–126] Because the scales used in these studies differed, only study-defined response rates are displayed (Figure 6),[122,124,125] translating into NNTs of 2–5, representing moderate to large effect sizes. In 1 additional, active-controlled trial, molindone was found to be as effective as thioridazine for conduct disordered youth.[127] Finally, risperidone also showed superior efficacy for relapse prevention compared to placebo in 1 large, 6-month placebo-substitution trial.[128] Although a number of RCTs found psychosocial and behavioral interventions to be successful for reducing aggressive and externalizing behaviors in youth,[129,130] studies comparing antipsychotics with behavioral intervention, combination, and placebo are lacking. The same is true of studies that investigate the best sequencing approach between psychotropic and behavioral interventions.

Efficacy in Tourette's disorder. Superiority of risperidone compared to placebo was shown in 2 randomized, placebo-controlled trials of youths with Tourette's disorder (N = 54), with either risperidone[131] or ziprasidone,[132] with an NNT of 4 for risperidone. Although a recent RCT found a behavioral intervention to be successful for reducing tics in Tourette's disorder,[133] studies comparing antipsychotics with

Figure 6. Study-Defined Response Rates (CGI-I ≥ much improved) in 3 Randomized, Placebo-Controlled Trials of Pediatric Patients With Disruptive Behavior Disorders[a]



[a]Doses expressed as daily doses.
*$P < .05$ vs placebo.
**$P < .001$ vs placebo.
Abbreviations: CGI-I = Clinical Global Impressions-Improvment scale, PBO = placebo, RIS = risperidone.

behavioral intervention, the combination of the two, and placebo are lacking.

Antipsychotic tolerability. Studies comparing antipsychotic adverse effect rates in children and adolescents with those in similar studies of adults indicated that youth were at higher risk for developing a number of antipsychotic-induced side effects.[19,96,134–136] These included higher rates of sedation, extrapyramidal side effects (except for akathisia), withdrawal dyskinesia, prolactin elevation, weight gain, and at least some metabolic abnormalities.

By contrast, tardive dyskinesia[137] and diabetes[19,135] were less likely to occur in youth compared to adults. However, this finding is likely due to the short follow-up periods in youth and presence of an accumulated risk and added lag time in adults, raising concerns about a potential shortening of the time until these long-term complications occur when antipsychotic treatment is initiated during childhood.

In the era of first-generation antipsychotic use, extrapyramidal side effects and tardive dyskinesia were the predominant adverse effect concerns with first-generation antipsychotics.[137] Since the introduction of SGAs (ie, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, and lurasidone [in order of introduction into the US market]), concerns about neuromotor side effects have largely been replaced by worries about cardiometabolic side effects, such as weight gain and dysregulation of the lipid and glucose homeostasis.[19,25,96] Recent studies suggest that youth are more prone to rapid and significant weight gain with antipsychotics, and that this weight gain extends to antipsychotics that in adults are generally considered weight neutral, yet that the metabolic effects vary across antipsychotics despite ubiquitous elevation in all body composition parameters with all studied SGAs.[96] Although more research is needed, this suggests that weight-independent, direct metabolic effects seem to exist that vary across individual antipsychotics. Long-term studies of general antipsychotic tolerability and, especially, cardiovascular and metabolic outcomes are needed. Finally, efforts are required at increasing appropriate monitoring and management of adverse antipsychotic effects in youth.

Table 3. Areas of Pediatric Psychopharmacology Research Requiring Further Attention

Studies including large and generalizable samples
Long-term, longitudinal studies that track therapeutic and adverse effects over time and relate outcomes to different stages of development
Strategies overcoming the limitations created by high dropout rates in long-term studies
Well-powered placebo-controlled studies
Well-powered active-controlled pharmacologic monotherapy and, especially, combination treatment studies
Well-powered comparative pharmacologic and nonpharmacologic studies, in monotherapy and in combination
Linkage of efficacy and effectiveness outcomes
Identification of meaningful and simple effectiveness measures
Identification of clinical and, especially, biological response predictors that would allow for an individualization or, at least, stratification of treatment based on baseline or early intratreatment variables
Broader-based utilization of novel technologies, eg, electronic medical record and centralized video rating in remote, diverse, nonacademic settings
Utilization of increasingly sophisticated biological assessments, including "omics" platforms
Increasing use of adaptive designs, smart trials, research networks, and large registries
Dissemination and application of research findings into measurement-based, evidence- and guideline-driven assessment and treatment delivery in clinical practice settings
Increasing linkage of basic, clinical, and services research initiatives, involving a number of translational steps that will ultimately help to improve the diagnosis, treatment, and outcomes of youth with severe psychiatric conditions

FUTURE DIRECTIONS AND CONCLUSIONS

Although considerable progress has been made, especially relative to the previous abundant absence of randomized controlled trial data, pediatric psychopharmacology still remains a stepchild of adult pharmacology, and more, larger, and longer studies need to be funded and conducted in youth.

Areas that require further work and innovation span a number of priority areas summarized in Table 3. Moreover, the field needs stakeholders—academia, industry, the NIMH, the FDA, and consumer groups—to support practical clinical trials and, where those are not possible, observational studies, conducted in generalizable treatment settings and patients to generate precise benefit and risk estimates of treatments in clinically important patient subgroups.[39] Moreover, practical clinical trials can provide a robust platform to study moderators and mediators and biomarkers and biosignatures of treatment outcome, as well as to test the multistage treatment strategies utilizing dynamic treatment regimens that are required to achieve the goal of increasingly personalized treatment of psychiatrically ill youth.

In conclusion, while especially the last decade has seen a large increase in our knowledge about the safety and efficacy of psychopharmacologic treatments in youth, a number of challenges remain to be addressed, and more work is clearly needed. It is hoped that in 10 years, the field will have been able to acquire and utilize the necessary resources to propel the area of pediatric clinical psychopharmacology to new levels of insight by linking it with, but not replacing it by, pharmacoepidemiologic or biological approaches and advances.

Drug names: aripiprazole (Abilify), asenapine (Saphris), atomoxetine (Strattera), citalopram (Celexa and others), clonidine (Catapres, Duraclon, and others), clozapine (Clozaril, FazaClo, and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), guanfacine (Intuniv, Tenex, and others), haloperidol (Haldol and others), iloperidone (Fanapt), lithium (Lithobid and others), lurasidone (Latuda), methylphenidate (Focalin, Daytrana, and others), mirtazapine (Remeron and others), molindone (Moban), olanzapine (Zyprexa), paliperidone (Invega), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), valproic acid (Depakene, Stavzor, and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

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Potential conflicts of interest: **Dr Correll** has been a consultant and/or advisor to or has received honoraria from Actelion, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon, Eli Lilly, IntraCellular Therapies, Ortho-McNeil/Janssen/Johnson & Johnson, Merck, Otsuka, Pfizer, and Sepracor/Sunovion and has received grant support from the Feinstein Institute for Medical Research, the National Institute of Mental Health (NIMH), the National Alliance for Research in Schizophrenia and Depression (NARSAD), and Ortho-McNeil/Janssen/Johnson & Johnson. **Dr Kratochvil** has received grant support from Eli Lilly and Shire; has been a consultant for Eli Lilly, Neuroscience Education Institute, Theravance, Seaside, Quintiles, and Pfizer; is Editor of the *Brown University Child & Adolescent Psychopharmacology Update*; received study drug for an NIMH-funded study from Eli Lilly and Abbott; and received royalties from Oxford Press. **Dr March** has served as a consultant or scientific advisor to Pfizer, Eli Lilly, GlaxoSmithKline, Bristol-Myers Squibb, Johnson & Johnson, Psymetrix, Attention Therapeutics, Avenir, Alkermes, Vivus, Scion, and MedAvante; has received research support from Eli Lilly and Pfizer; has received study drug for an NIMH-funded study from Eli Lilly and from Pfizer; is an equity holder in MedAvante; receives royalties from Guilford Press, Oxford University Press, and MultiHealth Systems; and receives research support from NARSAD, NIMH, and National Institute on Drug Abuse. Dr March has not engaged in promotional work, eg, speakers bureau or training, for over 15 years. Dr March's conflict of interest is fully reported to Duke University and is viewable at http://www.dcri.duke.edu/research/coi.jsp, and a conflict of interest management plan has been established.

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