

American Academy of Child and Adolescent Psychiatry

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PRACTICE PARAMETER FOR THE USE OF ATYPICAL ANTIPSYCHOTIC MEDICATIONS IN CHILDREN AND ADOLESCENTS

ABSTRACT

The need for effective therapeutic interventions for youths with a variety of neuropsychiatric conditions has led to the increasing prescription of atypical antipsychotics. This has occurred despite the fact that only recently have several atypical antipsychotics received indications by the U.S. Food and Drug Administration (FDA) for use in individuals less than 18 years of age. While there is a growing body of evidence that has evaluated the use of atypical antipsychotics in youths, there remains a compelling need for methodologically-rigorous trials assessing the efficacy and the acute and long-term safety of these drugs. This practice parameter reviews the current extant evidence regarding the efficacy and safety of these medications in children and adolescents and provides suggestions regarding their use. Recommendations for the administration and monitoring of side effects of these medications are also given. **Key Words:** atypical antipsychotic, medication, children, adolescents, safety, efficacy, practice parameter.

ATTRIBUTION

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AACAP practice parameters are developed by the AACAP Committee on Quality Issues (CQI) in accordance with American Medical Association policy. Parameter development is an iterative process between the primary author(s), the CQI, topic experts, and representatives from multiple constituent groups, including the AACAP membership, relevant AACAP Committees, the AACAP Assembly of Regional Organizations, and the AACAP Council. Details of the parameter development process can be accessed on the AACAP website. Responsibility for parameter content and review rests with the author(s), the CQI, the CQI Consensus Group, and the AACAP Council.

The AACAP develops both patient-oriented and clinician-oriented practice parameters. Patient-oriented parameters provide recommendations to guide clinicians toward best assessment and treatment practices. Recommendations are based on the critical appraisal of empirical evidence (when available) and clinical consensus (when not), and are graded according to the strength of the empirical and clinical support. Clinician-oriented parameters provide clinicians with the information (stated as principles) needed to develop practice-based skills. Although empirical evidence may be available to support certain principles, principles are primarily based on clinical consensus. This parameter is a patient-oriented parameter.

The primary intended audience for the AACAP practice parameters is child and adolescent psychiatrists; however, the information contained therein may also be useful for other mental health clinicians.

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INTRODUCTION

While there remains a public debate about the use of psychotropic medication in children and adolescents, the prescription of these drugs to young people continues to increase.¹⁻⁵ The atypical antipsychotic agents (AAAs), which are sometimes referred to as second generation antipsychotics (SGAs), are currently marketed in the United States for use in adults, adolescents and children for specific indications (see below), but are often prescribed “off-label” to treat other problems in children and adolescents. These AAAs include clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, and asenapine. These AAAs have established efficacy in the treatment of schizophrenia and bipolar mania in adults, and are utilized in the treatment of a variety of other illnesses as well. At present, risperidone and aripiprazole are labeled by the FDA for use in children or adolescents for irritability associated with autistic disorder (5-16 years for risperidone and 6-17 years for aripiprazole). In addition, risperidone, aripiprazole, olanzapine and quetiapine are FDA-approved for use in the treatment of adolescents with schizophrenia (ages 13-17) and youths between the ages of 10 and 17 years with bipolar I disorder suffering from mixed or manic episodes. Despite these limited FDA indications, the AAAs are still commonly prescribed for the treatment of numerous other conditions in pediatric patients.⁶⁻¹¹ As a result of both a general increase in the prescribing of antipsychotics and a decrease in the selection of typical antipsychotics, AAA use in young patients has been steadily increasing.^{3,4,12-14} These drugs are increasingly being prescribed to younger and younger children and disproportionately more frequently to males, to those in foster care and to those with Medicaid insurance.^{15,16,17} While the extant scientific evidence about the AAAs in youths is growing, much is still not known about the efficacy, tolerability, and long-term safety of these drugs in young people.^{18,19} Concerns about weight gain and metabolic

changes associated with the use of AAAs should prompt careful consideration and use of AAA for indications supported by the scientific evidence. The purpose of this parameter is to provide clinicians with a rational approach regarding the use of AAAs in children and adolescents.

For this parameter, the terms “child” or “children” will refer to patients ages 5 to 12 years. The term “adolescent(s)” will refer to those between the ages of 13-17 years (inclusive). “Youths” refers to patients between ages 5 and 18. While some research has evaluated the use of AAAs in preschool children,²⁰ and some studies have included children younger than 5, due to the paucity of published information in this age range, this practice parameter will be limited to recommendations for children ages 5 to 18. The diagnostic nosology that will be employed in this practice parameter will be the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).²¹

METHODOLOGY

Information and recommendations used in this parameter were obtained from literature searches using *Medline*, *PubMed*, *PsychINFO* and *Cochrane Library* databases and by iterative bibliographic exploration of articles and reviews beginning with more inclusive and sensitive searches employing the search term *atypical antipsychotics*, multiple free text and relevant medical subject headings (MeSH terms), and an initial time period from 1990 to 2010 current (2,420 citations). We narrowed our search by using delimiters and filters such as *age 0-18 years*, *English language only*, *human studies*, *published in the last 10 years*, and using the Boolean operator ‘AND’ *Clinical Trial*, ‘OR’ *Meta-Analysis*, *Practice Guideline*, *Randomized Controlled Trial*, *Review*, *Classical Article*, in addition to the terms treatment, safety, child, adolescent, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. Additional search terms included Tourette’s syndrome, autism, pervasive developmental disorder (PDD), childhood onset schizophrenia (COS), adolescent schizophrenia, obsessive compulsive disorder (OCD), eating disorders, anorexia nervosa, bulimia nervosa, attention-deficit/hyperactivity disorder (ADHD), conduct disorder (CD), and aggression to reduce citations to 238. For this practice parameter, we selected 147 publications for careful examination based on their weight in the hierarchy of evidence attending to the quality of individual studies, relevance to clinical practice and the strength of the entire body of evidence.

OVERVIEW OF ATYPICAL ANTIPSYCHOTICS

Eight AAAs are available for use in the United States. Their “atypicality” stems largely from their lower propensity to cause extrapyramidal side effects (EPS) when compared to the older “typical” antipsychotics.

The AAAs were developed and initially studied as treatments for psychotic illnesses in adults. In youths, however, AAAs have principally been used for non-psychotic conditions including aggressive and dysfunctional behavior in the context of autism and PDD, aggressive behavior in patients with disruptive behavioral disorders (DBDs), manic and mixed episodes in bipolar disorder, resistant ADHD, Tourette’s syndrome and other tic disorders, OCD, eating disorders, depression, sleep problems,²² and difficulties with impulse control associated with personality disorders. In fact, it appears that aggression, and not psychosis, is the most common target symptom for which AAAs are prescribed to youths.^{7,11,18,23-25}

DIFFERENCES AMONG THE AAAs

Although the AAAs have similar FDA approved indications in adults, the available evidence suggests that they have different safety profiles and may have different degrees of both efficacy and tolerability in individual patients. Distinctions between the AAAs are likely conferred by the significant differences in receptor binding affinity between these agents.^{19,24,26} Each agent blocks, to varying degrees, dopamine D2 receptors (the putative mechanism of their antipsychotic activity). However, each agent has additional distinct receptor binding profiles in the central nervous system (CNS). As a result of these differences, it is important to remember that what is true about the safety, tolerability, or efficacy of a given compound may not be true for another AAA and these medications are clearly not interchangeable.

EVIDENCE BASE FOR PRACTICE PARAMETERS

In this parameter, recommendations for best assessment and treatment practices are stated in accordance with the strength of the underlying empirical and/or clinical support, as follows:

- Clinical Standard [CS] is applied to recommendations that are based on rigorous empirical evidence (e.g., meta-analyses, systematic reviews, individual randomized controlled trials) and/or overwhelming clinical consensus.
- Clinical Guideline [CG] is applied to recommendations that are based on strong empirical evidence (e.g., non-randomized controlled trials, cohort studies, case-control studies) and/or strong clinical consensus.
- Option [OP] is applied to recommendations that are based on emerging empirical evidence (e.g., uncontrolled trials or case series/reports) or clinical opinion, but lack strong empirical evidence and/or strong clinical consensus.
- Not Endorsed [NE] is applied to practices that are known to be ineffective or contraindicated.

The strength of the empirical evidence is rated in descending order as follows:

- (rct) Randomized, controlled trial is applied to studies in which subjects are randomly assigned to two or more treatment conditions
- (ct) Controlled trial is applied to studies in which subjects are non-randomly assigned to two or more treatment conditions
- (ut) Uncontrolled trial is applied to studies in which subjects are assigned to one treatment condition
- (cs) Case series/report is applied to a case series or a case report

CURRENT STATE OF RESEARCH WITH AAAs IN YOUTHS:

When possible, clinicians should try to follow evidence-based practices and the existing empirical data on the efficacy and safety of AAAs. As the field is rapidly changing, this requires continual re-evaluation of the literature database. What follows is a brief description of what is currently known regarding the six AAAs that have been marketed in the United States and have pediatric data, presented in order of marketing release. Two more recently approved AAAs, paliperidone and asenapine, have no data available pertaining to their use in young people and will not be considered in this parameter.

Clozapine: In the adult population, clozapine is indicated for the use of treatment refractory schizophrenia; however, due to the associated risk of agranulocytosis, it is not considered a “first-line” medication. In children and adolescents, the strongest empirical

evidence supports the use of clozapine for patients suffering from treatment refractory schizophrenia and for those youths who require antipsychotic treatment but who have experienced severe EPS with other agents.²⁷

A double-blind study comparing the efficacy of clozapine to haloperidol in 21 treatment resistant youths with schizophrenia found greater benefit for both positive and negative symptoms with clozapine when compared to haloperidol.^{28(rct)} There is also evidence that clozapine is superior to olanzapine in treatment resistant patients with schizophrenia.^{29(ut),30(rct)}

In addition, there are several open-label studies that provide evidence to support the use of clozapine for treatment resistant schizophrenia in children and adolescents.^{26(ut),27(ut),31(ut)} Open-label studies/case reports have noted that clozapine may also be effective for aggressive behavior in treatment refractory youths with psychotic illnesses or bipolar disorder.^{32(cs),33(ut),34(cs)} A case series examining the use of clozapine in treatment resistant adolescents with posttraumatic stress disorder (PTSD) reported possible salutary effects from this drug.^{35(cs)} Case reports have also described the use of clozapine in the treatment of youths with treatment-resistant autistic disorder.^{36(cs)}

Risperidone: Of the AAAs, risperidone has the most substantive amount of methodologically stringent evidence about its use in children and adolescents.

In one of the largest methodologically rigorous studies involving the use of AAAs in children, risperidone was examined as a treatment for serious behavioral problems in children with autism ages 5-17. In this multi-site trial, a total of 101 children with autism participated in a double-blind trial of risperidone, 0.5mg to 3.5mg per day versus placebo. The results from the initial study, a six month continuation trial, and the blinded discontinuation trial found that risperidone treatment resulted in significant improvement in behavioral problems that persisted at six months and relapsed with medication discontinuation.^{37(rct),38(rct),39(rct)}

A substantive amount of research has been done regarding the use of risperidone in the treatment of youths with disruptive behavior disorders.⁴⁰ Recently, a study examined the impact of long-term risperidone treatment in children ages 5-17 with disruptive behavior disorders who had initially responded to a 12 week trial of medication. Youths were randomized to placebo or continued risperidone treatment for six months. There were significant differences in relapse rates indicating that prolonged treatment with risperidone was beneficial for these children.^{41(rct)}

Prospective studies, including one double-blind, placebo controlled trial, have reported the effectiveness of risperidone in the treatment of youths with schizophrenia,^{42(ut),43(ut),44(rct),45(rct),46(ut)} disruptive behaviors in autism and other PDDs,^{37(rct),38(rct),39(rct),47(ut)} disruptive behaviors in children with sub-average intelligence,^{48(rct),49(rct)} and impulsive aggression in conduct disorder/disruptive behavior disorders.^{50(rct)} The use of risperidone in the reduction of tics in Tourette's syndrome is supported by one double-blind placebo controlled trial in adolescents and several other less rigorous studies.^{51(rct),52(rct),53(rct),54(rct)}

Open trials, retrospective chart reviews, and a double-blind, placebo controlled study of risperidone have noted clinical benefit for patients with bipolar illness.^{20(ut),55(cs),56(ut),57(rct)} A post-hoc analysis of 155 children with comorbid ADHD, sub-average IQs and disruptive behavior found risperidone to be safe and effective with and without psychostimulant use.^{58(ct)} The recent update from the Texas Children's Medication Algorithm project recommends the addition of an AAA for the treatment of comorbid ADHD and aggression not responsive to behavioral intervention and psychostimulants.⁵⁹ In adults, there are case reports of adjunctive use of risperidone in refractory patients with OCD. However in the child and adolescent literature,

reports of worsening or new onset OCD symptoms in youths treated with risperidone have been published.^{11(cs),37(rct),60(cs),61(cs),62(cs),63(cs)} A case report found improvement in the symptoms of two adolescents with anorexia nervosa.^{64(cs)} Studies have reported the long-term safety and potential benefits of long-term risperidone therapy in youths with several different neuropsychiatric conditions.^{39(rct),65(ut),66(ut),67(ut)}

Olanzapine: Of the AAAs, olanzapine's receptor binding profile most closely matches that of clozapine. There is one double-blind, placebo-controlled study that has reported the short-term efficacy of olanzapine in the treatment of adolescents with schizophrenia.^{68(rct)} There is another double-blind, placebo-controlled study reporting the short-term efficacy of olanzapine in the treatment of adolescents with bipolar illness suffering from a manic or mixed episode.^{69(rct)} Another double-blind study, of 50 total patients, comparing olanzapine, risperidone and haloperidol in psychotic youths found olanzapine's effectiveness to be comparable to both haloperidol and risperidone.^{44(rct)} In addition, an acute, randomized, double-blind study of olanzapine, risperidone, and molindone has noted that both AAAs did not have superiority to molindone in treating early onset schizophrenia spectrum disorders.^{45(rct)} However, in that study, olanzapine showed the greatest amount of weight gain.

Olanzapine may also provide benefit to patients suffering from PDDs, based on the results of open-label trials and 1 small RCT.^{70(ut),71(ut),72(ut),73(rct)} There are also reports suggesting that olanzapine might be an effective intervention for patients with anorexia and other eating disorders.^{74(cs),75(cs),76(cs),77(cs)} Case reports and small open-label trials indicate that olanzapine may be effective in reducing tic severity in youths with Tourette's syndrome.^{78(cs),79(cs),80(ut)} Although olanzapine is also available as an intramuscular preparation, limited data exists about its use in youths.

In short, while there are recent double-blind studies to provide data about the short-term efficacy and tolerability of olanzapine in the treatment of youths with mania or schizophrenia, there is a paucity of published long-term safety data. This is particularly important based on the propensity of olanzapine to cause weight gain of a substantive magnitude.

Quetiapine: One double-blind study found that in adolescents with mania, treatment with quetiapine plus divalproex sodium was associated with greater symptom reduction than treatment with quetiapine plus placebo.^{81(rct)} In an acute, double-blind, placebo-controlled study, efficacy of quetiapine has been reported in children and adolescents with bipolar mania.^{82(rct)} Another placebo-controlled study has found that quetiapine has efficacy in adolescent schizophrenia.^{83(rct)} Open-label trials have noted potential benefit for aggression in conduct disorder, psychosis, mania, and tic disorders.^{84(ut),85(ut),86(ut),87(ut),88(ut),89(ut)} Two reports in patients with PDD suggested sub-optimal effectiveness but another report suggested more positive findings in this patient population.^{85(ut),90(cs),91(cs)} A case report of improvement of OCD symptoms with quetiapine has been reported.^{92(cs)} Long-term studies of quetiapine in youths found that it was reasonably safe and associated with satisfactory clinical outcomes.^{93(ut),94(ut)}

Ziprasidone: A double-blind, placebo-controlled trial reported that low doses (20-40mg per day) of ziprasidone was superior to placebo in the treatment of 28 patients ages 7-17 years with Tourette's syndrome.^{95(rct)} Another double-blind, placebo-controlled study reported efficacy for ziprasidone in the treatment of manic or mixed episodes in youths suffering from bipolar I disorder.^{96(rct)} However, an industry-sponsored trial of ziprasidone for early-onset schizophrenia

was stopped due to concerns over lack of efficacy.^{97(rct)} Case series have reported improvement associated with ziprasidone therapy for youths with a variety of neuropsychiatric conditions, including schizophrenia, autism/PDD, major depression with psychosis, bipolar disorder, and psychosis.^{98(cs),99(cs),100(cs),101(cs),102(cs)} Case reports of a small number of youths treated with intramuscular ziprasidone have also described positive clinical outcomes without significant side effects.^{103(cs),104(cs)}

Aripiprazole: Preliminary studies suggest that patients with mania, conduct disorder with aggression, and PDD/autism might benefit from treatment with aripiprazole.^{105(cs),106(ut),107(ut),108(ut),109(ut),110(ut)} Data from double-blind, placebo-controlled studies have described efficacy for aripiprazole in both youths ages 10-17 suffering from manic or mixed states,^{111(rct)} adolescents ages 13-17 suffering from schizophrenia,^{112(rct)} and children with irritability associated with autistic disorder.^{113(rct)}

Comparison with Older Antipsychotic agents and other Issues

Recent data from adult and child/adolescent studies as well as meta-analyses and reviews suggest that AAAs are not necessarily more effective than older antipsychotic agents.^{45(rct),114,115} Recently, a FDA advisory panel, while supporting the use of some AAAs as adjunct treatment for refractory major depressive disorder (MDD), opposed approval as stand-alone treatment for MDD and generalized anxiety disorders in adults due to cardiac, metabolic and other safety risks. While many AAAs can be sedative, there is an almost total absence of data supporting their use as hypnotics alone. No data is available for children or adolescents on asenapine, the newest AAA approved for use in adults with acute or ongoing schizophrenia or acute mania alone or with lithium.

In summary, there exists a paucity of methodologically rigorous studies evaluating the use of AAAs in children and adolescents. Evidence is strongest in supporting use of AAAs for children and adolescents with schizophrenia and bipolar I disorder, while evidence for use with disruptive behavior disorders is much less robust except in youth with autism. Currently, only one study supports the use of AAAs in long-term treatment for disruptive behavior.^{41(rct)} While there is increasing evidence of the effectiveness of these agents in specific clinical situations their long-term safety profile has yet to be effectively evaluated and characterized.

SAFETY ISSUES AND CONCERNS

The AAAs are associated with several significant risks and the rates and severity of particular side effects differ among the AAAs. These side effects can occur with treatment initiation but some may also develop after sustained use. When evaluating side effects, a clinician should consider not only the objective severity of the side effects, but also the subjective distress in the individual patient, as both these factors are important contributors to non-compliance and treatment failure. When choosing an AAA for a patient, it is essential to evaluate the potential benefit to the patient in light of the associated risk of the use of the medication.

Weight changes, diabetes, and hyperlipidemia: Significant weight gain may occur with the use of the AAAs. This weight gain appears to be largest with clozapine and olanzapine, although clinically significant weight gain occurs during treatment with risperidone and quetiapine. Based primarily on data from adults, aripiprazole and ziprasidone appear to have the

lowest propensity for weight gain.^{116,117} Studies examining the impact of antipsychotics on weight gain in youths suggest that AAA-associated weight gain may be greater in young people when compared to adults.^{118,119} Studies evaluating the impact of AAAs on triglycerides and cholesterol have noted an association between alterations in triglyceride levels with weight gain. Although limited short-term data failed to find large significant changes in cholesterol and triglyceride levels in youths, no long-term studies have examined these parameters and therefore the long-term implications are unknown.¹²⁰ All AAAs have a black-box warning regarding the possibility of developing diabetes mellitus during pharmacotherapy with these agents. Case reports of diabetes in youths being treated with a variety of the AAAs exist.¹²¹⁻¹²⁴ Additionally, there is evidence to suggest that the risk of diabetes may be weight independent and differs between the AAAs.¹²⁵

Cardiovascular: The impact of the AAAs on the cardiovascular (CV) system has been of increasing interest. CV changes that have been observed in youths treated with the AAAs include prolongation of the QTc interval, orthostatic hypotension, tachycardia, and pericarditis. There are limited short-term data, and even less long-term data concerning the clinical relevance of these changes. However, the limited data available indicate there may be a greater propensity for CV changes in youths as compared to adults.^{26,131,132}

A prolonged QTc is associated with an increased risk of Torsades de Pointes and lethal ventricular arrhythmias. Although concern about the impact of the AAAs on the QTc interval has focused mainly on ziprasidone, the cardiovascular safety profile of other agents has yet to be definitively characterized due to the limited amount of data.¹³¹ While no documented cases of sudden death due to cardiac arrhythmias have been reported with the use of AAAs, there is sufficient evidence to support the conclusion that AAAs do impact the QTc and this should be addressed when using these agents.¹³³

In addition to concerns about the QTc interval, there are other cardiovascular events, including tachycardia, orthostatic hypotension, and coronary artery disease associated with weight gain, that should also be considered.¹³⁴ In adults, clozapine appears to have the highest associated incidence of tachycardia and orthostatic hypotension, while other agents appear to have less impact on blood pressure and pulse.

Agranulocytosis and neutropenia: Clozapine may be associated with neutropenia and potentially fatal agranulocytosis. It is possible that the risk for these events is greater in children when compared to adults.^{12,28,135,136} However, there are also case reports in adults of neutropenia associated with risperidone, olanzapine and quetiapine.¹³⁷⁻¹³⁹ The relationship between neutropenia and agranulocytosis remains unclear and careful consideration of treatment options should follow the development of neutropenia in any youth being treated with an AAA.¹³⁶

Hepatic dysfunction: Case reports of hepatic dysfunction in youths possibly related to rapid weight gain and steatohepatitis, have been published.^{28,140-142} Though there are case reports in adults and children of AAA associated hepatotoxicity this appears to be a rare occurrence. The possibility of a relationship between rapid weight gain and incidence of hepatic injury does exist and ought to be useful in guiding recommendations for monitoring.

Prolactin: Elevation of prolactin levels is associated with several of the AAAs. In adults and youths, risperidone appears to have the largest propensity for prolactin elevation.^{62,143-146}

Olanzapine and ziprasidone appear to have less propensity for increasing prolactin levels, while clozapine, quetiapine, and aripiprazole do not appear to elevate prolactin levels in adults.¹⁴⁷⁻¹⁵⁰ Prolactin elevations may lead to symptoms such as amenorrhea, galactorrhea, and gynecomastia. A recent retrospective study did not find any evidence for delays in growth or puberty in children treated with risperidone for one year.¹⁵¹ However, the long-term significance of asymptomatic prolactin elevations remains uncertain.

Seizures: Electroencephalogram (EEG) abnormalities have been reported with the use of AAAs.¹⁵² While the greatest risk for seizures associated with the AAAs appears to be with clozapine, there is a lack of data regarding the EEG changes associated with the prescription of other AAAs to youths.

EPS, tardive dyskinesia and withdrawal dyskinesias: Although the incidence of EPS and tardive dyskinesia is significantly lower when using AAAs as compared to the traditional neuroleptics, there still exists the potential for the development of EPS and movement disorders with these agents. The currently available data suggests that there is a higher risk of movement disorders in youths as compared to adults.¹²

Neuroleptic malignant syndrome (NMS): While a very rare complication of treatment with antipsychotics, NMS, a combination of autonomic instability, elevated temperature, rigidity and elevated levels of creatine phosphokinase (CPK), can be fatal. Case reports exist of NMS with all of the AAAs. This severe, though rare complication, is of concern when using these medications in any age patient.¹⁵³

Cataracts: Over the years, several ophthalmological side effects have been reported in patients treated with psychotropic medications. Animal research reported quetiapine to be associated with the development of cataracts in beagle puppies. For this reason, the manufacturer of quetiapine recommends that an examination of the lens be performed on or around the initiation of treatment and at six month intervals thereafter during chronic therapy, and that a method that is sensitive to detect cataract formation (such as a slit lamp evaluation) be employed. At the present time, there are neither reports of cataracts occurring in youths nor any published studies specifically examining this adverse event in youths.¹⁵⁴

SCREENING AND ASSESSMENT

Recommendation 1. *Prior to the initiation of and during treatment with an AAA, the general guidelines that pertain to the prescription of psychotropic medications should be followed [CS].*

While there are certain considerations that apply specifically to the use of AAAs in youths, the AACAP Practice Parameter on the Use of Psychotropic Medication in Children and Adolescents presents a series of principles to guide the clinician when using psychotropic medications in children and adolescents.¹⁵⁵ These principles include a careful diagnostic assessment, attention to comorbid medical conditions, a review of other drugs the patient is being prescribed, the creation of a multi-disciplinary plan, including education and psychotherapeutic interventions for the treatment and monitoring of improvement, and a thorough discussion of the risks and benefits of psychotropic treatment with both the youth and their guardians.

Recommendation 2. *When selecting any AAA for use in a child or adolescent, the clinician should follow the most current available evidence in the scientific literature [CS].*

Concerns have been raised that AAAs are being over-prescribed to youths. For some conditions, AAAs serve as a primary treatment (e.g., schizophrenia). In other circumstances, AAAs are generally only used after other interventions, both psychosocial and pharmacological, have failed (e.g., disruptive behavior disorders). Thus, when considering prescribing an AAA to a child or adolescent, the clinician should not only perform a meticulous diagnostic assessment, but should also clearly identify the target symptoms for which the medication is being utilized. Once a clinician determines that a patient might benefit from treatment with an AAA, the selection of the particular drug, the dosing regime instituted, and the scheduling of safety monitoring should be guided by the existing scientific literature. The evidence for each AAA varies and continual updates in the literature are found (See Section on Current State of Research). Clinicians are advised to regularly check the current literature in order to have access to the most recent data. Table 1 provides a summary of the literature supporting the use of AAAs in specific clinical populations as well as current FDA-approved indications, which currently include only schizophrenia, bipolar disorder, and specific symptoms of autistic disorder. In the absence of specific FDA indications or substantial empirical support for the use of AAAs for other specific problems (e.g., disruptive behavior disorders) in populations of children and adolescents, clinicians should consider other pharmacological or psychosocial treatment modalities with more established efficacy and safety profiles prior to the onset of AAA use.

There are almost no data about the use of AAAs in pre-school aged children. As this group is one that may be particularly vulnerable, a marked amount of caution is advised before prescribing an AAA to a preschooler.

Recommendation 3. *Due to the specific risks associated with the use of AAAs, additional factors to address, prior to the initiation of treatment with the AAAs, include obtaining a personal and family history of diabetes and hyperlipidemia, seizures and cardiac abnormalities, as well as any family history of previous response or adverse events associated with AAAs [CS].*

As there exists limited short and long-term safety data for the AAAs in youths, careful attention to family history (when available), and personal history of underlying medical conditions that may be adversely impacted by the AAAs should be thoroughly examined.

The establishment of the current state of the youth's health and careful attention to baseline measures of vital signs, weight/BMI, and a blood glucose (preferably fasting) evaluation should be included in this assessment. While a family history of diabetes or cardiac problems may not preclude the use of these agents when the scientific evidence supports their use, a positive family history may guide the clinician in choosing between the AAAs and ought to influence the frequency of monitoring of these physiologic parameters. When prescribing AAAs for children in foster care, community or residential placements the local child welfare and/or juvenile justice agency should be contacted in an effort to obtain additional personal and family history of diabetes and hyperlipidemia, seizures and cardiac abnormalities as well as previous response to AAAs. Although recent data suggests an increased risk for sudden death for adults having taken AAAs,¹⁵⁶ there is no evidence of heightened risk for children and adolescents. Nevertheless, clinicians should look to identify young patients at potentially high risk for cardiac events. In patients with a history, either personal or family, of cardiac abnormalities, including syncope, sudden unexplained death, or arrhythmias, a baseline electrocardiogram (EKG) and

subsequent monitoring should be carefully considered. Pediatric cardiology consultation might also be considered. Routine magnetic resonance imaging (MRI) or computerized tomography (CT) imaging of the brain is not required prior to initiating treatment with an AAA and should only be performed when indicated by the clinical history.

Recommendation 4. *Dosing of the AAAs should follow the “start low and go slow” approach and seek to find the lowest effective dose, recognizing that dosing may differ based on the targeted symptoms and patient diagnosis [CG].*

The dosing strategy and target dose should be guided by the current state of evidence in the literature. However, there are still gaps in what is known about dosing regimens of the AAAs in youths. When evidence-based dosing strategies are available, they should be employed. In patients for whom little is known about empirically-derived dosing, beginning with low doses with slow progression is recommended. The goal of treatment should be to use the lowest effective dose in order to minimize the risk of side effects. Based on currently available evidence, the upper limit of dosage for an AAA should not exceed the maximum recommended dose described for adults.

Recommendation 5. *Target dosing should be supported by the current literature and will vary depending on the condition being treated [CG].*

Evidence from the literature suggests that different doses are required for different conditions and target symptoms. In addition, differences in dosing between individuals may also occur as a result of allelic variations, many of which are not yet fully understood. For example the target dose for psychosis or mania may be significantly higher than the target dose for treating aggression in children with PDDs. Additionally the evidence suggests that lower doses are effective for the treatment of tic disorders.^{157(RET),158(ct),159(cs)} Dosing of the AAAs may not be the same for adults and youths. Care should also be used when examining studies as the safety of established low doses in children and adolescents may not translate into safety in higher adult doses. Determination of an appropriate target dose should follow both the current scientific literature and the clinical response of the patient, while also monitoring the patient for side effects and tolerability.

Recommendation 6. *If side effects do occur, a trial at a lower dose should be considered; however, certain side effects may preclude further treatment with the specific AAA [CG].*

If an AAA is clinically effective, but there is concern about side effects, slowly lowering the dose and examining the response is suggested. If the side effects are alleviated, an attempt to gradually increase the dose again can be considered. In children it appears that there is an increased propensity for the development of movement disorders with AAA use at any dose. Although there are cases of successful re-challenge with an AAA after NMS in adult patients, there is little information about this in youths. Extreme caution is urged when restarting an AAA in a child who has previously had symptoms consistent with NMS. The safety of the agent in the particular patient must be carefully evaluated before continuing with the medication once a side effect has been noted.

Recommendation 7. *The use of multiple psychotropic medications in refractory patients may, at times, be necessary but has not been studied rigorously and clinicians should proceed with caution [OP].*

Reasons that more than one medication, each from a different class of agents, might be prescribed include patients with complex comorbid conditions or those with partially-responsive or treatment resistant cases.^{58,160} In clinical practice it is not unusual to have a patient on multiple psychotropic medications from different classes of drugs. It appears that a substantial number of hospitalized children and adolescents receive more than one psychotropic medication. Unfortunately, there are limited data regarding the long-term use of combinations of medications in youths. For this reason, careful consideration is needed prior to employing AAAs as part of a polypharmacy regimen, and should be avoided if possible. Specifically, for patients who are being prescribed a psychotropic of uncertain efficacy, it is generally recommended that the AAA be seen as a substitute treatment, rather than as an adjunct for the currently-prescribed drug.

Recommendation 8. *The simultaneous use of multiple AAAs has not been studied rigorously and generally should be avoided [NE].*

There is no clear evidence to support the use of more than one AAA in either adults or youths. Due to the possibility of significant risks associated with these agents, the use of more than one agent is not recommended and is not supported in the scientific literature. Failure to respond to an inadequate dose of a single AAA agent or after only one to two weeks at a target dose should not be considered a reason to add an additional AAA. Consideration of medication combinations should only begin after patients are refractory to medication trials of each AAA and, perhaps older antipsychotic agents or other evidence-supported agents (such as mood stabilizers) at the appropriate target dose(s) and adequate length of treatment.

Recommendation 9. *After the failure of one AAA the selection of an alternative medication may include consideration of another AAA and/or a medication from a different class of drugs [OP].*

While these medications fall within the same general class, it is clear they are not interchangeable. Significant differences in side effect profiles and mechanism of action exist and switching among these agents should be done with clear and precise reasoning reflective of current empirical data. If a patient fails to have an adequate response after reaching the target dose for an adequate trial length (generally four to six weeks), the need to switch to an alternative AAA is not always indicated. Re-evaluation of the initial diagnosis, assessment for comorbid conditions, and the redefining of targeted symptoms may lead to try a trial of a different class of medication in these patients.

Recommendation 10. *The acute and long-term safety of these medications in children and adolescents has not been fully evaluated and therefore careful and frequent monitoring of side effects should be performed [CG].*

There is limited short-term safety and even less long-term safety data in youths treated with AAAs. Increased vigilance in the monitoring of the potential side effects is therefore needed, recognizing practical limitations. Ideally, monitoring of BMI, blood pressure, fasting blood glucose and fasting lipid profiles should follow, whenever feasible, the recommendations found in the consensus statement put forth by the American Diabetes Association and the American Psychiatric Association.¹¹⁶ (see Table 2) Although clinicians should recognize that

some patients may have difficulties with transportation or time constraints given school and parental work schedules, regular monitoring is still important in the follow up of children and adolescents taking AAAs.

Recommendation 11. *BMI should be obtained at baseline and monitored at regular intervals throughout treatment with an AAA [CS].*

Obesity is associated with an increased risk of cardiovascular disease, diabetes, knee and joint injury, hyperlipidemia and hypertension. For these reasons, weight should be monitored closely. This may be particularly important if the AAA is co-administered with an agent (from another drug class) that is associated with weight gain. Prior to the initiation of treatment with AAAs, parents and patients should be advised about potential weight gain and recommendations for proper nutrition and exercise plans provided.^{18,116} At baseline and regular intervals, BMI should be plotted on age specific diagrams. Developmentally normed growth charts can be found at the Center for Disease Control web site (www.cdc.gov/growthcharts). Consideration of weight management interventions and increased regularity of blood glucose and lipid levels should be implemented if AAA induced weight gain exceeds 90th percentile BMI for age, or a change of five BMI units in those youths who were obese at the beginning of treatment.¹⁹

Recommendation 12. *Careful attention should be given to the increased risk of developing diabetes with the use of AAA, and blood glucose levels and other parameters should be obtained at baseline and monitored at regular intervals [CS].*

Adult studies have found an association between the development of diabetes/abnormal glucose regulation and the use of AAAs.^{116,117} There is also evidence to suggest that the development of diabetes is not only directly related to weight gain.¹²⁵ Therefore, careful monitoring for diabetes, through close attention to the clinical signs and symptoms of diabetes, and regular monitoring of blood glucose levels and, as needed, hemoglobin A1C is warranted.^{121,161,162}

Recommendation 13. *In those patients with significant weight changes and/or a family history indicating high risk, lipid profiles should be obtained at baseline and monitored at regular intervals [CG].*

The AAAs are associated with changes in lipid profiles, hyperlipidemia, and hypercholesterolemia. There are limited safety data regarding the impact of the AAAs in youths. Studies have shown that elevated lipid levels, even early in life, may have a role in the development of cardiovascular disease throughout the lifespan.¹³⁴ Therefore, when using AAAs careful attention should be given to these concerns, especially in those youths with significant weight gain and a positive family history. For patients whose family history is not available, particularly careful consideration regarding medication choice and monitoring is recommended. In youths who have significant weight changes, further evaluation or intervention should also be considered.

Recommendation 14. *Measurements of movement disorders utilizing structured measures, such as the Abnormal Involuntary Movement Scale, should be done at baseline and at regular intervals during treatment and during tapering of the AAA [CS].*

As some of the most concerning short and long-term associated side effects with these agents are movement disorders, careful attention to their development is warranted. Standardized

rating scales and measurements such as the Abnormal Involuntary Movement Scale (AIMS) and the Neurological Rating Scale (NRS) should be obtained at baseline and regularly throughout treatment.^{163,164}

Recommendation 15. *Due to limited data surrounding the impact of AAAs on the cardiovascular system, regular monitoring of heart rate, blood pressure and EKG changes should be performed [CG].*

As there are limited data specifically addressing the cardiovascular impacts of AAAs in children, clinicians should consider following the guidelines of the American Heart Association. These guidelines include taking a careful family history of sudden or unexplained deaths, a careful history of the patient concerning syncope episodes or palpitations, and consideration of alternative therapy if the sustained resting heart rate is >130 beats per minute, the PR interval is >200 milliseconds, the QRS is >120 milliseconds, or the QTc is >460 milliseconds.¹⁶⁵ While routine EKGs may not be needed for all patients, in those with a family history of cardiac abnormalities or sudden death, or a personal history of syncope, palpitations, or cardiovascular abnormalities, a baseline EKG and subsequent monitoring should be carefully considered.

Recommendation 16. *Although there is a relationship between AAA use and elevations of prolactin, the current state of evidence does not support the need for routine monitoring of prolactin levels in asymptomatic youths [OP].*

As the relationship between prolactin levels and clinical outcome has yet to be more precisely defined, prolactin measurement during antipsychotic pharmacotherapy does not appear to be warranted in the absence of possible prolactin-related side effects. When symptoms of elevated prolactin do develop, treatment considerations should include: decrease dosing of the AAA, switching to a different AAA, or medication discontinuation.

Recommendation 17. *Due to drug-specific risks, additional monitoring should be considered for specific AAAs [CG].*

Clozapine: Labeling for clozapine provides guidelines regarding the monitoring of hematological parameters for patients being treated with this agent. Although not developed for use in youths, per se, these monitoring parameters should be employed in children and adolescents treated with clozapine. Due to clozapine's propensity to lower the seizure threshold, a pre-treatment EEG and a comparison EEG when optimal drug levels have been achieved should also be considered. Additionally, an EEG should be part of the evaluation of a patient on clozapine who is experiencing acute behavioral changes.^{9,24,32} For those patients who gain a substantive amount of weight, monitoring of liver enzymes should also be considered.

Quetiapine: There are data from animals-based studies to suggest the possibility that quetiapine is associated with a risk of cataract formation. For this reason, a baseline ophthalmologic examination with periodic re-assessment is recommended by the manufacturer.

Ziprasidone: Due to the increased risk of QTc changes in patients treated with this drug, and in the absence of definitive data about the safety of this agent in the young, obtaining an EKG at baseline and once a stable dose is achieved is recommended.

Recommendation 18. *The limited long-term safety and efficacy data warrants careful consideration, before the initiation of medication, of the planned duration of the medication trial [CG].*

Careful consideration of treatment duration is needed. In clinical practice, medications are often continued for years, and while this may be appropriate in specific cases, the indefinite use of the AAA should not be assumed. Regular assessments of the continued need for the AAA should be done. The determination of treatment duration should be based on multiple factors including the severity of symptoms, the psychosocial settings, and the natural course of the illness being treated.

Recommendation 19. *Abrupt discontinuation of a medication is not recommended [CS].*

Risks are associated with the abrupt discontinuation of these agents, including withdrawal dyskinesia. The abrupt withdrawal of a medication that has been ameliorating symptoms may also clinically destabilize a patient as a result of symptom exacerbations. Ideally, the discontinuation of an AAA should be carefully planned, and meticulous monitoring by the clinician is required. Except in cases where a severe and/or dangerous side effect has developed, these agents should not be abruptly discontinued.

PARAMETER LIMITATIONS

AACAP practice parameters are developed to assist clinicians in psychiatric decision-making. These parameters are not intended to define the sole standard of care. As such, the parameters should not be deemed inclusive of all proper methods of care nor exclusive of other methods of care directed at obtaining the desired results. The ultimate judgment regarding the care of a particular patient must be made by the clinician in light of all of the circumstances presented by the patient and his or her family, the diagnostic and treatment options available, and available resources.

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Table 1
Evidence for the Use of Atypical Antipsychotics

	Clozapine	Risperidone*/**/***	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole*/**/***
Schizophrenia/psychosis	+++	+++	++++	++++	+	++++
Bipolar Disorder	++	+++	+++	++++	+++	+++
Disruptive Behavior Disorders (DBDs)/Aggression	++	+++	+++	++	+	+
Autism/PDD irritability,	+	++++	+++	+	+	++++
Tourettes/tics		++++	+		+++	
Eating Disorders			+			
Posttraumatic Stress Disorder (PTSD)	+					
Long term Safety Studies		+		+		

4
5 +++++ multiple RCTs

6 +++++ one RCT

7 ++ uncontrolled trial(s)

8 + Case studies

9

10 * FDA Indication for Schizophrenia 13-17 years

11 ** FDA Indication for Treatment of manic or mixed episodes associated with Bipolar I Disorder as monotherapy or adjunctive to

12 lithium or valproate in adults and pediatric patients aged 10 to 17 years (Aripiprazole only)

13 ***FDA Indication for Treatment of irritability associated with autistic disorder in children and adolescents aged 5/6-16 years

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Table 2

ADA Screening Guidelines for Patients on Second-Generation Antipsychotics

	Baseline	4 weeks	8 weeks	12 weeks	Annually
Personal & family history	X				X
Weight (BMI)	X	X	X	X	
Waist circumference	X				X
Blood pressure	X			X	X
Fasting plasma glucose	X			X	X
Fasting lipid profile (HDL, LDL, TG, total cholesterol)	X			X	

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