



# Appropriate Use of Psychotropic Drugs in Children and Adolescents: A Clinical Monograph

Important Issues and Evidence-Based Treatments

*Presented by Magellan Healthcare & Magellan Rx Management,  
divisions of Magellan Health, Inc.*

*April 2017*

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*These guidelines are not intended to replace a practitioner’s clinical judgment. They are designed to provide information and to assist practitioners with decisions regarding care. The guidelines are not intended to define a standard of care or exclusive course of treatment. Healthcare practitioners using these guidelines are responsible for considering their patients’ particular situations in evaluating the appropriateness of these guidelines.*

# Introduction

The practice of evidence-based medicine requires health professionals and child welfare advocates to engage in a careful assessment of the risks and benefits of using psychopharmacological treatments in children and adolescents while addressing serious concerns of over-diagnosis and overtreatment in this vulnerable population. As attention to this problem grows, a strong undercurrent of anxiety and confusion exists about whether current use of psychotropic agents to remove undesirable impulses and behaviors of children may also affect neurological development, personality, character, and temperament. Similarly, suspicions exist that this trend may be driven by a supply-induced demand created by pharmaceutical companies and medical providers. This has been termed a type of clinical, cultural and “social iatrogenesis” whereby the increased use of unnecessary or dangerous treatments can lead to increased injury and higher healthcare costs (Morris and Stone, 2011, p. 300; Correll and Dratochvil, 2011, p.300).

Contributing factors to the sharp growth in the use of psychotropic drugs have been attributed to: “increased awareness of severe mental health problems in young children, development of medications considered safer than their older counterparts, and increased experience of practicing providers treating younger populations, as well as increased behavioral expectations of very young children in structured settings, such as childcare or preschool” (Fanton and Gleason, 2009, p. 754). While the field of psychiatric medicine has made tremendous strides in treating severe psychiatric disorders in very young, latency-age school children and adolescents, it may be “creating equally serious problems when relying on pharmacologic interventions alone” (Fanton and Gleason, 2009, p. 764). An evidence-informed and judicious approach to the use of psychotropic medications in the treatment of children and youth is urgently needed.

## Nature and Scope of the Problem

The Centers for Disease Control and Prevention’s 2012 *National Health and Nutrition Examination Survey* (NHANES) reported that approximately 13% of children ages 8 to 15 had a diagnosis of a mental disorder within the past year. Attention deficit hyperactivity disorder (ADHD) was the most common disorder, affecting 8.6% of this population, followed by mood disorders at 3.7%, and major depressive disorder, at 2.7% (National Institute of Mental Health, 2012). Results from the *National Comorbidity Study Adolescent Supplement* (NCS-A) reported lifetime prevalence of 46.3% for any mental disorder among those aged 13 to 18 years and a lifetime prevalence of 21.4% for severe disorder among this group (Merikangas et al., 2010). The NHANES also reported that 50.6% of children ages 8 to 15 years had received treatment for their disorder during the past year, with those children with ADHD disorders the most likely to receive treatment (47%) and children with anxiety disorders least likely to receive treatment (32.2%). In 2006, the American Psychological Association (APA) *Working Group on Psychotropic Medication for Children and Adolescents* summarized estimates for the morbidity associated with child and adolescent mental disorders showing prevalence rates for childhood disorders ranging from 17% to 22% and significant functional impairment in 15% of children and adolescents (APA, 2006). In addition, the APA expressed significant concern that “only one in five of these children receives services provided by appropriately trained professionals” (APA, 2006, p. 19). Estimates also showed that approximately 8 million of these youths were on one or more psychotropic medications (Morris and Stone, 2011). Increasing numbers and percentages of children treated with psychotropic drugs have been observed across populations—i.e., youth enrolled in Medicaid, foster care, preschoolers and adolescents (Fanton and Gleason, 2009; Pidano and Honigfeld, 2012).

The *2010 – 2012 Medical Expenditure Panel Surveys* identified trends in outpatient use of mental health services by children and adolescents 6 to 17 years of age from 1996 to 2012 (Olfson et al., 2015). Researchers observed a decline in the percentage of young people with more severe mental health impairment from 12.8% in 1996 through 1998 to 10.7% in 2010 through 2012. Data analysis showed a significant increase in mental health treatment and psychotropic medication use in children and adolescents in the United States between 1996 to

1998 and 2010 to 2012. From 1996 to 1998 to 2010 to 2012 the percentage of youths receiving any psychotropic medication increased from 5.5% in 1996 to 1998 to 8.9% in 2010 to 2012. Among youths with more severe impairment, the proportionate increase in the use of mental health services was from 26.2% to 43.9% whereas among youth with less severe or no impairment, the proportionate increase was from 6.7% to 9.6%. “However, the absolute increase in annual service use was larger among youths with less severe or no impairment (from 2.74 million to 4.19 million) than among those with more severe impairment (from 1.56 million to 2.28 million)” (Olfson et al., 2009). Increases occurred in the use of stimulants and related medications (from 4.0% to 6.6%), antidepressants (from 1.5% to 2.6%), and antipsychotic drugs (from 0.2 to 1.2%). Analysis showed “the increase in outpatient mental health treatment included approximately twice as many young people with less severe impairment as young people with more severe impairment, and roughly two thirds of new treatment episodes continued to involve youths without severe impairment” (Olfson et al., 2015, p. 3034). Authors suggested that pharmaceutical marketing as well as increasing public acceptance of psychotropic medications may have contributed to the increase in treatment of less severely impaired youths (Olfson et al., 2015).

A 2014 National Center for Health Statistics (NCHS) report presented key findings on the use of medication prescribed for emotional or behavioral difficulties among children aged 6 to 17 years from the *National Health Interview Survey*, 2011–2012 (Howie et al., 2014). Important findings included the following:

- 7.5% of children aged 6 to 17 years used medication for emotional or behavioral difficulties (greater use of prescription medications by males and non-Hispanic children than females and other racial/ethnic groups; health insurance status and poverty status affected percentages of children prescribed medications for emotional or behavioral difficulties);
- Compared with children with private insurance or who were uninsured, a higher percentage of children with Medicaid or CHIP coverage used prescribed medications; a lower percentage of uninsured children used prescribed medication than public or privately insured children;
- A higher percentage of children living at below 100% of the poverty level used prescribed medication for emotional or behavioral difficulties than children in families living at 100% to 200% of the poverty level;
- Parents reported that the medication helped the child “a lot” in more than 50% of the children prescribed medication for emotional or behavioral difficulties (Centers for Disease Control, 2014); and
- The report summarized that the use of medication to treat mental health problems has increased substantially over the past two decades among all school-aged children (Howie et al., 2014).

Additional data reported by the Medicaid and CHIP Payment and Access Commission (MACPAC) concerning children’s use of behavioral health services reported that older children were more likely to receive behavioral healthcare regardless of insurance type, mirroring higher prevalence of behavioral health conditions (MACPAC, 2016). The MACPAC report noted that children with special healthcare needs, i.e., increased risk for developing a chronic behavioral condition, use behavioral health services at higher rates than those without special healthcare needs. It noted that among this group, those enrolled in Medicaid or CHIP accessed mental health services at higher rates than those with private insurance (MACPAC, 2016).

In a published review of the clinical literature, Pidano and Honigfeld summarized recent findings from large epidemiologic studies:

- Two- to three-fold increase in the percentage of children and adolescents taking any psychotropic medication over a ten-year (1987 to 1996) period;
- Increase in psychopharmacological prescriptions from 3.4% in 1994 to 1995 to 8.3% in 2000 to 2001 resulting from adolescent office visits to physicians;
- Psychotropic drug use more pronounced for male patients;
- Drugs prescribed most often were various agents for treating attention deficit hyperactivity disorder, antidepressants, antipsychotics, mood stabilizers, and sedative-hypnotics (Pidano and Honigfeld, 2012).

Another large retrospective cohort study by Olfson et al. used data from the *National Ambulatory Medical Care Survey* from 1993 to 2002 to analyze office visits to physicians by children and adolescents. Findings revealed an approximate six-fold national increase in the absolute number of office-based visits that included prescription of antipsychotic medications in this population (Olfson et al, 2006). Cooper and colleagues found that new use of antipsychotics among children and adolescents nearly doubled in the six years after the introduction of the atypical psychotics for young persons (aged 2 to 18) enrolled in Tennessee’s managed Medicaid program (TennCare) from 1996 through 2001 (Cooper et al., 2004).

Data published by the Government Accountability Office (GAO) continue to verify these trends despite efforts by providers, children’s advocates and others to improve mental health treatment practices (GAO, 2012). The report, *Children’s Mental Health/Concerns Remain about Appropriate Services for Children in Medicaid and Foster Care*, analyzed nationwide data from the *Medical Expenditure Panel Survey* (MEPS) from 2007 through 2009 for children (ages 0 through 20) in Medicaid, State Children’s Health Insurance Programs (CHIP) and foster care comparing them against children who were privately insured. The GAO findings showed that on average, 6.2% of noninstitutionalized children in Medicaid nationwide and 4.8% of privately insured children took at least one psychotropic medication during a calendar year and noted that boys continue to have a utilization rate twice as high as girls (i.e., 8.4% versus 3.9%). In addition, compared with children privately insured, children in Medicaid were more than twice as likely to take an antipsychotic medication (i.e., 1.3% versus 0.5%). Based on their findings, the GAO recommended to Congress that both “federal and state initiatives to improve monitoring and oversight are appropriate, and that continued assessment of the prescribing of psychotropic medications to vulnerable populations and of the receipt of mental health services is important” (GAO, 2012, p. 38). Unfortunately, despite cumulative research evidence, children are treated with psychotropic medications too early in the treatment regimen rather than attempting to ameliorate the child’s psychiatric symptomatology with psychosocial, behavioral or family interventions as a first step or augmenting treatment (Correll and Dratochvil, 2011).

**Off-label administration of medications.** Another overarching issue to consider in pediatric psychopharmacologic practice is the fact that most medications used with preschool children are administered off-label. Children receive treatment with medications to treat symptoms/conditions for which approval by the Food and Drug Administration (FDA) has not been granted (Gleason et al., 2007). Fanton et al. alerted clinicians that “children have been described as ‘therapeutic orphans’ in the United States drug regulatory system,” noting that “preschool populations have been neglected more than school-aged peers” (Fanton et al., p. 755). In 2009, there “were only four medications approved for psychiatric indications in children younger than 6 years of age (i.e., haloperidol, chlorpromazine, d-amphetamine and risperidone)” (Fanton et al., p. 755). The FDA has approved only approximately 31% of psychotropic medications for use in children or adolescents. It is estimated that currently more than 75% of the prescriptions written for psychiatric illness in this population is off-label in usage (Solchany, 2011).

In a historical review of debates and developments in pediatric psychopharmacology, Correll and colleagues acknowledged research data which suggested that “psychiatric disorders are often more severe, chronic and unresponsive to therapies and associated with greater functional impairments and disease burdens if their onset occurs during childhood or adolescence compared to adulthood” (Correll and Dratochvil, 2011, p. 26). Authors further indicated that most major psychiatric disorders do have their onset in childhood or adolescence and stressed that the earlier the onset, the more malignant the course of the illness. While this may help us understand why severely ill youths should be prescribed psychoactive medications, it does not, however, address the issues of overtreatment or the concerns about inadequate efficacy data from pediatric randomized controlled trials (Correll and Dratochvil, 2011). At the present time, much of the published clinical trial findings applied to children and adolescents have been extrapolated from single-agent versus placebo drug trials using adult patients while measuring acute and short-term outcomes. More recent well-designed pediatric psychotropic drugs studies have pointed to a greater or different profile of susceptibility to adverse effects

in children compared to adults. Other dissimilarities include developmentally dependent variations in drug effectiveness, paradoxical drug reactions in susceptible youth and pharmacokinetic differences based on age and developmental anatomical/physiological maturity (Correll and Dratochvil, 2011; Gleason et al, 2007).

Current widespread use of psychotropic medication in children and youth must also be understood within the context of significant changes that have occurred in the mental health services system in the United States. The American Academy of Child and Adolescent Psychiatry (AACAP) reported the development of a manifest shortage of child and adolescent psychiatrists, more limited insurance coverage for inpatient and residential treatment, and few outpatient psychotherapy services provided by psychiatrists over the last 10 to 15 years (Walkup et al., 2009). The Bazelon Center for Mental Health Law reported that primary care providers furnish over one-half of the mental health treatment in this country and that about 25% of all primary care recipients have a diagnosable mental disorder. Moreover, the Bazelon Center and others have reported that as many as 50% of mental health problems go undiagnosed in the primary care setting (Pidano and Honigfeld, 2012; Bazelon Center). Studies have shown that primary care providers prescribe the majority of psychoactive medications used by children and adolescents. While most of the prescriptions are for attention deficit hyperactivity disorder (ADHD) and depression, data indicate that more than 75% of prescriptions for anxiolytics, antipsychotics and mood stabilizers for youths have also been ordered by primary care providers, not by psychiatrists (Pidano and Honigfeld, 2012).

## Integrated Care/Collaborative Care in the Treatment of Children with Behavioral and Emotional Problems

A recent study, using nationally representative data from the *Medical Expenditure Panel Survey*, compared mental healthcare that children and youth aged 2 to 21 receive from primary providers and other mental healthcare providers (Anderson et al., 2015). Analysis of data showed that 5.2% of children and adolescents in the United States had an office-based visit in the past year for a mental health condition. Among these children and adolescents, 34.8%, 26.3%, and 15.2% saw only a primary care physician (PCP), only a psychiatrist, or only a psychologist or social worker, respectively. Comanagement by PCPs and psychiatrists was involved in 6.7% of the conditions. Children who visited a PCP were more likely to receive medications for ADHD than those who visited a psychiatrist, and PCPs prescribed medications to a higher percentage of children than did psychiatrists. Authors noted that this study found PCPs, not psychiatrists, were the most common providers for pediatric mental healthcare. Finding that comanagement with other mental health specialists appeared uncommon, authors emphasized the use of “collaborative care models with psychotherapy and programs that provide point-of-care to PCPs from mental health experts” (Anderson et al., p. e1184). A report from the Substance Abuse and Mental Health Services Administration (SAMHSA) and the Health Resources and Services Administration (HRSA) discussed the need for “an approach to delivering care that comprehensively addresses the primary care, specialty care, behavioral health, and social support needs of children and youth in a continuous and family-centered manner” (SAMHSA, 2013).

A recent study analyzed data from the Philadelphia Neurodevelopment Cohort to examine patterns of associations between mental and physical conditions in youth (n= 9014) ages 8 to 21 (Merikangas et al., 2015). Measures included both electronic records and interview data. Findings included:

- Approximately 20% of youth experienced a neurologic/central nervous system or developmental condition;
- Younger age groups (<18 years) were more likely to have developmental conditions whereas older youth (>18) had higher rates of immunologic, gastroenterologic, or oncologic disorders;
- The most frequent mental disorders among youth were ADHD (18.2%), mood disorders (12.4%), and anxiety disorders (11.7%);

- Approximately one in five youth screened positive for subclinical psychosis spectrum; and
- The prevalence of ADHD decreased with age while mood disorders increased with age.

In the above study, authors found a “direct association between the severity of the physical condition and most classes of mental disorders, as well as with functional impairment,” e.g., a link between severe central nervous system conditions and ADHD and mood disorders; and a link between developmental conditions and ADHD, behavioral disorders and psychosis spectrum symptoms (Merikangas et al., p. e927). Mood disorders were less likely to be associated with developmental disorders. Authors emphasized that these patterns of comorbidity confirm the importance of “cross-specialty” integration; they indicated that this “hidden morbidity” needs to be addressed via better integration of mental health and medical specialty care in children. Authors highlighted that “prospective tracking of cross-disorder morbidity will be important to infer causal mechanisms and to establish more effective mechanisms for prevention and intervention (Merikangas et al., p. e935).

**Core principles of the collaborative care model for integrating physical and mental healthcare include:**

- Patient-centered team care;
- Population-based care;
- Evidence-based care, accountable care; and
- Measurement-based care/scale-based care (AIMS Center, 2017).

Measurement-based care, sometimes called scale-based care or stepped care, affects clinical care as it relies on data collected throughout treatment, and it is a core component of evidence-based practices (Scott and Lewis, 2015). It “provides insight into treatment progress, highlights ongoing treatment targets, reduces symptom deterioration, and improves client outcomes” (Scott and Lewis, 2015, p. 49). Clinical outcomes are measured by evidence-based tools, e.g. the PHQ-9 depression scale used to monitor the severity of depression as well as the response to treatment, and the GAD-7 to measure anxiety levels and track clinical change and patient progress. The scales track a patient’s progress and guide treatment plans (Eghaneyan et al., 2014). Based on whether or not the child or adolescent is showing improvement as a result of a treatment, the treatment may be changed until goals are achieved. Eghaneyan pointed to the care manager’s role in the development of a patient progress report to provide feedback to providers using graphs of PHQ-9 and GAD-7 scores. Measurement is then used to influence treatment plans (Eghaneyan et al., 2014). Guo et al. have acknowledged how measurement-based care allows psychiatrists to individualize treatment decisions for each patient (Guo et al., 2015).

## Children in Foster Care

State government public sector health systems face a trend where children in foster care have become increasingly more vulnerable to inappropriate and excessive medication use. These children have many needs related to emotional and psychological stress because they have typically experienced abuse in neglectful, serial or chaotic caretaking environments and often present with past traumatic and reactive attachments that can mimic or complicate mental disorders (Texas Department of Family and Protective Services and the University of Texas, 2010). Studies have shown that in addition to being in foster or state care, other factors that increase the risk of improper use of psychotropic drugs in children and youth include: being poor, living in group care, being hospitalized in psychiatric inpatient units, and being incarcerated (Solchany, 2011). An analysis from the Centers for Medicare and Medicaid Services (CMS) of Medicaid data (2002 to 2007) for children in foster care (n=686,000) for 47 states and the District of Columbia showed that while there was wide variation, the range of rates for polypharmacy use was 1% to 14% and 3% to 22% for antipsychotic drug usage (Policy Lab, 2012).

Children in foster care receiving any type of medication must have the consent of a caregiver. However, states differ in medication consent authority since some require biological parent permission, whereas others

require a state board/panel, foster parent, the court or other designated authorities (e.g., physicians or staff in residential settings). Unfortunately, states still report many cases where children in foster care were given psychotropic drugs without the required legal consent. Child advocates and clinicians see this as an area that needs to be rectified given the importance of the decision to use psychotropic agents in children. It is critical that the caregiver with consent authority be familiar with the specific child's needs, the therapeutic agents being prescribed and the intended impact/clinical outcomes for the specific agents. Professional second opinions are uniformly recommended in cases that may be complex (e.g., children under 6 years, pregnant teens, multiple medications), involve atypical antipsychotic medications or demonstrate treatment-resistance (Solchany, 2011).

In a retrospective analysis of data on usage of mental health services and psychotropic medications among children (n= 1491) age six and younger in foster care during the period 2009 through 2011, authors investigated the prevalence of psychotropic drug use with a special emphasis on changes in prevalence for each year increase in age (dosReis et al., 2014). Psychiatric disorders of children included:

- Disruptive behavior disorder - 14%;
- Internalizing disorder (depression, anxiety, or posttraumatic stress disorder) - 7%; and
- Mood disorder - 3%.

Treatment with at least one psychotropic medication occurred in 12% of the children (128 children), while only 7% had at least one psychotherapy visit during the three-year study period. Of those receiving a psychotropic medication and who had spent 365 days or more in foster care, 63% were male, 83% were black, and 55% were age 5 or 6. In 2010, 6% of the children overall received a psychiatric medication, with prevalence increasing with each year increase in age. Days of use of antipsychotics and ADHD medication significantly increased with each year of age. Authors summarized findings of this study:

- Use of psychotropic medication began among preschool-age children, becoming more prevalent by age six;
- Among children as young as age four, three or more psychotropic classes began;
- Likelihood of using antipsychotic, antidepressant, and ADHD medications for three or more weeks per month increased with each increase in year of age; and
- Few children in the study (7%) received psychotherapy.

Authors noted that these results suggest a trend toward chronic use of psychotropic medication in children, and emphasized the importance of ensuring an adequate trial of psychosocial treatment prior to treatment with psychotropic medications. They expressed concerns about possible adverse effects of antipsychotic exposure affecting brain size, neuronal circuitry, and brain volume, and metabolic adverse events in young children, while stressing the importance of routine metabolic monitoring to reduce antipsychotic use and minimize adverse events. In concluding, authors stated, "Long-term studies are needed to evaluate the effect of chronic exposure on children's health and well-being" (dosReis et al., 2014, p. 1457).

**Antipsychotic use by foster care youths.** A study investigated the relationship between foster care and rates of antipsychotic use by foster care youths by analyzing Medicaid claims data for youths in foster care (n=301,894) and those not in foster care (n= 5,092,574) (Vanderwerker et al., 2014). Authors discussed how questions have been raised in recent years concerning an increased use of antipsychotics medications by children and adolescents who do not have psychotic, developmental, or major mood disorders. The drugs are increasingly used to treat ADHD, disruptive behavior disorder, and conduct disorders. Data from this study found the following:

- Youths in foster care were more likely to be older, male, African American, and non-Hispanic than youths not in foster care;
- Youths in foster care had higher rates of ADHD, disruptive behavior disorder, conduct disorder, and stress-related disorders, and a significantly higher rate (7.4%) of antipsychotic use than youth not in foster care (1.4%);



- Analysis found that “prevalence of antipsychotic use and clinically diagnosed mental disorders was substantially higher among foster care youths than among youths enrolled in Medicaid who were not in foster care” and that demographic characteristics explained only a small portion of the difference. (Vanderwerker et al., p. 4)

Vanderwerker et al. suggested some reasons that foster care youths are more likely to receive antipsychotics including:

- More challenging behaviors in a foster care setting;
- Less resources, time, and training of case workers; and
- Limited number of psychiatrists and PCPs pressured by teachers and foster care parents to intervene medically to treat foster care youths.

Authors were unable to access psychotherapeutic interventions due to lack of records in the claims data. They noted that other studies have reported that foster children beginning treatment with an antipsychotic were significantly less likely to receive psychotherapeutic interventions. Authors suggested further studies are needed to assess how implementation of psychotropic monitoring systems and integration of trauma-informed care into behavioral health treatment may lead to improvements in clinical outcomes for youths in foster care (Vanderwerker et al., 2014).

**Antipsychotic use in children aged 4 years and younger.** A recent study examined the use of psychotropic medication among children aged 4 years and younger in Medicaid programs from 36 states (Garfield et al., 2015). Authors noted that most prescribing of psychotropic medications in young children is off-label, with lack of routine testing of the medications and lack of FDA approval for use in treating young children. Authors examined the use of psychotropic drugs for treating ADHD, depression or anxiety, and psychotic illness or bipolar disorder. Findings included:

- 1.19% of children received a prescription for a psychotropic medicine between 2000 and 2003;
- Antidepressants (sertraline hydrochloride), tranquilizers/antipsychotics (risperidone) and stimulants (amphetamines) were the most common medications; and
- 17% and 0.34% of infants aged younger than 1 year and children aged between 1 and 2 years, respectively, were prescribed psychotropic drugs.

As the children aged, the analysis showed that depression or anxiety predominated in 1- and 2-year olds while prescriptions for ADHD and psychotic disorders increased in the 3- and 4-year old children. Authors expressed worry that the findings indicate use of psychotropic drugs among very young children. Further, they acknowledged that lack of chart data prevented determination of the specific indication or behavioral symptom associated with the prescribed drug. They stated, “These findings cannot be interpreted as evidence of the prevalence of psychiatric disorders among these children, nor of the appropriateness of the prescribing of psychotropic drugs for such conditions” (Garfield et al., 2015, p. 528). In conclusion, authors indicated that **“preschoolers are receiving psychotropic medications despite limited evidence supporting safety or efficacy” and that “future research should focus on implementing medication use practice parameters in infant and toddler clinics, and expanding psychosocial interventions for young children with behavioral problems”** (Garfield et al., p. 524). Sharma et al. discussed how off-label prescribing of psychotropic medication to children and adolescents “does not imply an improper, illegal, contraindicated or investigational use. “Therapeutic decision making must always rely on the best available evidence and balance this against the risks and benefits for the individual patient” (Sharma et al., 2016, p. 420; Frattarelli et al., 2014).

**Medicaid prior authorization policies.** From 1993-1998 to 2005-2009, antipsychotic prescribing to youth increased from 0.16% to 1.07% in office-based physician visits (Schmid et al., 2015). Authors reported that in Medicaid-insured youth, antipsychotic use is five times greater than in privately insured youth, and indications

are mostly for clinician-reported externalizing behavior disorders rather than the FDA-approved indications, e.g., psychotic disorders, bipolar disorder, and autism-related irritability. Government reports have called for improving pediatric psychotropic medication oversight in state Medicaid agencies, and utilizing age-restricted prior authorization policies to monitor psychotropic use. In their review of antipsychotic-related Medicaid prior authorization policies for youth between June 2013 and August 2014, authors found the following:

- 31 states have implemented prior authorization policies within the past five years;
- Most of the states have applied policies to children younger than 5, 6, or 7 years of age;
- About half of the states have incorporated a peer review process involving a psychiatrist or other physician specialty. (Schmid et al., 2015)

Authors referred to a recent study by Stein et al. (2014) showing minimal effect of such a policy in one mid-Atlantic state in reducing antipsychotic use in children. They cautioned about potential unintended consequences of these policies, e.g., inadequate treatment and substitution of potentially inappropriate, off-label psychotropic medication classes. Authors discussed the need for Medicaid oversight programs to ensure appropriate cardiometabolic monitoring practices and evidence-based nonpharmacological treatments are implemented (Schmid et al., 2015).

The above referenced study by Stein et al. examined Medicaid data from two large mid-Atlantic states, from November 2007 through June 2011, one of which required prior authorization for antipsychotics for children less than 13 years of age and another, which required no prior authorization (Stein et al., 2014). Authors examined the effect of the prior authorization policy on antipsychotic prescription rates filed for Medicaid-enrolled children finding the following:

- In states with prior authorization for antipsychotics for children 6 to 12 years of age: average monthly rate of antipsychotics used decreased from 9.8% to 9.5% (0.3% decrease) after start of the prior authorization period (August 2009); average monthly rate increased by 0.32% to 2.1% for children 0-5 years; and
- In states with no prior authorization for antipsychotics for children 6 to 12 years of age: average monthly rate of antipsychotics used slightly decreased to 5.9% (0.08% decrease) since August 2009; average monthly rate decreased to 0.65% (0.009% decrease) for children 6 to 12 years of age.

Authors found “that new prior authorization policies for antipsychotic medication resulted in a modest but statistically significant decrease in their use among 6 to 12 year olds, but did not have a significant effect on antipsychotic use among 0 to 5 year olds” (Stein et al., 2014, p. 374). Authors indicated the need for further research to understand the effects, both utilization and clinical, of prior authorization policies.

A national telephone-administered survey of state Medicaid psychotropic-monitoring programs targeting youths assessed the implementation strategies of state Medicaid psychotropic-monitoring programs using data collected from August 2011 through December 2012 (dosReis et al., 2016). Authors noted variability within types of state Medicaid psychotropic-monitoring programs, with prior authorization the most common model. Authors noted that programs focused exclusively on antipsychotics in many states, and that youths in foster care have higher rates of antipsychotic use than other Medicaid-insured youths. They also advised that monitoring other psychotropic medications is also important. Study findings included:

- A 64% decrease in polypharmacy over a six-year period;
- Only 50% of antipsychotic prescribing conformed to best practices defined by the AACAP parameters; and
- Lack of metabolic monitoring was the main reason for not meeting best practices.

**Authors emphasized the “tremendous opportunity for educating the medical community on practice guidelines and available resources to assist providers in managing the care of youths”** (dosReis et al., p. 1148). They suggested the need for future studies to evaluate whether prior authorization or consultation models, specific psychotropic classes targeted, or other program components may have the largest impact on outcomes, quality of care, and best practices.

A study, conducted to detect and measure racial/ethnic differences in antipsychotic drug use among children enrolled in Medicaid, analyzed data from the population of children (n = 5.8 million) enrolled in Medicaid, ages 2 to 20, from eight states for 2005 to 2009 (Cataife and Weinberg, 2015). Findings included:

- Physician services were most common, followed by psychiatric services;
- There was evidence of racial/ethnic differences in the prescribing of antipsychotic medications;
- The likelihood of having an antipsychotic prescription fill was lower for African Americans, American Indians, Asians, and Hispanics by 1.8%, 1.5%, 2.0%, and 1.8%, respectively, than for white children.

Authors indicated that these are large effects “considering that the probability of an antipsychotic prescription fill across child-years was 2.4%” (Cataife and Weinberg, p. 950). They also noted that the differences could not be explained by differences in mental health needs or differences in levels of aversion to pharmacological treatment.

Another study examined the relationship between measures of the severity of child maltreatment and Medicaid expenditures for psychotropic medications (Raghavan et al., 2016). Authors linked child participants (n = 4453) in the first *National Survey of Child and Adolescent Well-Being* (NSCAW) to their Medicaid claims from 36 states. They discussed how Medicaid bears most of the costs of mental health services for the principal consumers of these services: children subject to abuse or neglect who come into contact with child protection agencies for suspected maltreatment. Measures of severity of child maltreatment included:

- Assessment by child’s welfare worker of physical abuse, sexual abuse, neglect, and abandonment;
- Number of different types of abuse experienced by the child; and
- Child welfare worker’s assessment of level of harm caused by the abuse. (Raghavan et al., 2016)

The outcome measure was the sum of psychotropic expenditures incurred per child per year of the study. Of the sample of children, 52%, 53%, 32%, and 9% were male, white, African American, and below age 2, respectively. Authors found that “severity of maltreatment had no additional significant effect on drug expenditures after the analyses controlled for externalizing and internalizing child behaviors” and that “Clinicians use medications in an attempt to alleviate the emotional, cognitive, and behavioral effects of abuse and neglect, grouped into disorders” (Raghavan et al., p. 917). Magnitude of maltreatment affected the odds of psychotropic medication use; children who were physically abused had higher odds of psychotropic drug use when compared with those without physical abuse history. Discussing limitations of the study, authors stated the underreporting of maltreatment while noting that some forms of maltreatment were not captured in the study.

**Programs created by states to recognize challenges in providing optimal care to children with mental health and/or behavioral health issues.** The Centers for Medicare and Medicaid Services (CMS), the Administration for Children and Families (ACF), and the Substance Abuse and Mental Health Services Administration (SAMHSA) have worked together for the strengthening of systems of prescribing and monitoring use of psychotropic medication among children in foster care. They indicated how various state programs have organized their programs around practices, e.g., high dose, young age, polypharmacy (CMS, 2012). CMS posted examples of states that created programs to ensure that patients receive appropriate combination of psychosocial and medical care.

State Medicaid Approaches on Child Antipsychotic Monitoring Programs are available in the named states below with notations about some parts of the program (Medicaid, 2017):

- **Arkansas**—requires prescriber to fax a signed and dated informed consent when starting a new antipsychotic agent; must state the targeted symptoms being treated and adverse effects; must be signed by prescriber and parent/guardian; has had dramatic effect in reducing the number of children in all age groups receiving an antipsychotic agent;
- **California**—supported education outreach to providers to improve metabolic monitoring rates among children and adolescents prescribed antipsychotic medication; intervention letters sent to all prescribers of antipsychotic medications to children and adolescents;
- **Illinois**—began checking client eligibility on every request for a psychotropic medication in children less than 18 years of age; consent for all psychotropic medications through the Department of Children and Family Services;
- **Indiana**—comprehensive initiative providing oversight, monitoring, education and consultation to youth in state care who are prescribed psychotropic medications; established “red flag” indicators based on AACAP practice parameters and Texas Psychotropic Medication Utilization Parameters for Foster Children; youth meeting indicators automatically referred to psychiatry consultation team for case review and follow-up;
- **Louisiana**—review of current best practice guidelines and clinically experienced consults to ensure safe and effective utilization of psychotropic medications;
- **Maryland**—established peer review program to address concerns that increasing number of children are prescribed antipsychotics with lack of laboratory monitoring of those children; established a prior authorization process; established a Preferred Drug List;
- **Minnesota**—a collaborative psychiatric consultation must be completed before atypical antipsychotic and attention deficit disorder and attention deficit hyperactivity disorder medication unless patient already stabilized on medication or prescriber indicates child is in crisis;
- **Mississippi**—emerging consensus is that significant improvements may require prior authorization review by experts in child/adolescent psychiatry; completing updated white paper on mental health diagnosis and treatment of foster and non-foster children; developing new strategies for assuring appropriate utilization of antipsychotic medications;
- **Montana**—state study revealed that foster children were prescribed antipsychotics nine times the rate of other Medicaid recipients; evaluating use of psychotropic medications in Montana Medicaid children, with focus on foster care children, using a clinical pharmacist to evaluate and improve prescribing and monitoring of psychotropic medication; educational and clinical interventions; increased metabolic syndrome monitoring;
- **North Dakota**—state law prohibits prior authorization on antipsychotics, anticonvulsants, antidepressants and stimulants for ADHD; utilizes quantity limits, duplicate therapy edits, and first fill edits;
- **Oklahoma**—joined five other states in collaborative effort to improve quality of care for children experiencing mental health difficulties; MEDNET support by AHRQ grant; Pharmacy Management Consultants – SoonerPsych Program; rotating interventions for adherence, metabolic monitoring, polypharmacy, and diagnosis; and
- **Texas**—includes charts of usual recommended doses of common psychotropic medications; charts reflect usual doses and information as resource for clinicians, not as a substitute for sound clinical judgement in individual patients; may be need for higher doses in specific patients; careful monitoring and documentation or response to treatment must be performed. (Medicaid, 2017).

# Controversies in Clinical Management

**Long-term prospective validity of psychiatric diagnoses in very young children.** Areas of pediatric psychopharmacological treatment in the forefront of debate have been highlighted by experts as issues of special concern to prescribers. As discussed previously, the use of psychotropic medication in children of preschool age is a practice that is severely limited by the lack of evidence targeted to this age group (Gleason et al., 2007). This phenomenon is compounded by serious questions concerning the long-term prospective validity of psychiatric diagnoses in very young children. Fanton et al. stressed that although ADHD and post-traumatic stress disorder (PTSD) “appear to demonstrate ‘homotypic continuity,’ meaning that the disorder continues to be present at follow up,” other studies show that “the vast majority of children with mental health problems as toddlers and preschoolers will continue to have a psychiatric diagnosis in their school-age years, though not necessarily the same condition, suggesting that heterotypic continuity has valid implications”—i.e., prescribing agents used for school age manifestations of a disorder in a pre-school child (Fanton and Gleason, p. 755). In addition to considering the long-term prospective validity of a diagnosis when selecting a medication, it is important to understand that psychiatric medications (except methylphenidate) are not dosed by weight as are other pediatric medications. Thus, the need for prescribers to “start low and go slow” is essential for safe medication administration in children and adolescents (Fanton and Gleason, p. 755).

**Public health advisory alerting healthcare professions to increased suicidality (ideation and attempts) in clinical trials of antidepressants in the pediatric population.** Another controversy in pediatric psychopharmacology transpired over the last decade. The treatment of depression in children and adolescents was significantly altered when in October 2003 the FDA released a public health advisory alerting healthcare professions to increased suicidality (ideation and attempts) in clinical trials of antidepressants in the pediatric population. A year later, in 2004, a black box warning was issued for all antidepressants for patients under 18 years of age prompting a precipitous drop of 25% in rates of both diagnosis and treatment of depression by pediatric and non-pediatric primary care physicians (Birmaher and Brent, 2007). An FDA committee later conducted a meta-analysis of 24 clinical trials of nine antidepressants (n=4,400) in the pediatric population which showed a very small increase (0.7%) in risk of suicidal thinking/behavior, but no increase in actual completed suicides. Further data revealed that trepidation in using antidepressants for this population actually created a barrier to treatment and resulted in a corresponding 25% increase in the completed suicide rate in children and adults (Correll and Dratochvil, 2011; Walkup et al, 2009; Birmaher et al., 2007). At the present time, the AACAP Parents Medical Guide Workgroup recommends to parents and caregivers that “through careful monitoring, the development of a safety plan, and the combination of medication with psychotherapy, the risks for increased suicidal thoughts can be managed. For moderate to severe depression, there is benefit in the use of medication because of a higher rate of relief, and more complete relief, from depressive symptoms than not using any medication” (Brent et al., 2007, p. 11).

A recent study examined the risk of suicide attempt and self-inflicted injury in depressed children ages 5 to 17 based on whether they were treated with antidepressants (Gibbons et al., 2015). Authors analyzed two different large scale medical claims databases including youth (n=221,028) with new episodes of depression from 2004 through 2009. The “simple unadjusted and unweighted analysis showed significantly increased risk of suicide attempt and self-inflicted injury when patients were receiving antidepressant treatment” (Gibbon et al., p. 213). Adjusting for dynamic treatment selection using marginal structural models (MSM), “a non-significant relationship between antidepressant treatment and suicide attempt and self-inflicted injury” was found (Gibbons et al., p. 213). Authors concluded that the use of MSM shows that “treatment selection effects” influenced both suicide attempts and self-inflicted injuries, and that “if there is a direct effect of antidepressant treatment on suicide attempt and self-inflicted injury rates in youth, it is much smaller in magnitude than has been previously suggested” (Gibbons et al., p. 213).

**Apprehension on the use of stimulants in the treatment of ADHD.** While stimulant medication has strong evidence and clinical history of efficacy in treating core ADHD symptoms, apprehension continues on the use of stimulants in the treatment of ADHD due to concerns about cardiovascular side effects and stunted growth rates in children (Texas Department of Family and Protective Services et al., 2010; American Academy of Pediatrics, 2011). In 2008, a joint advisory statement of the American Academy of Pediatrics (AAP) and the American Hospital Association (AHA) responded to a very small increase in sudden death from adverse cardiac events in children taking methylphenidate and amphetamine. The advisory recommended a physical exam and expanded patient/family health history focusing on cardiovascular disease risk factors (i.e., specific cardiac symptoms, Wolf-Parkinson-White syndrome, sudden death in the family, hypertrophic cardiomyopathy and long QT syndrome) and an electrocardiogram (EKG) at the physician's discretion for children being prescribed stimulants. The professional medical communities issuing this advisory recommended reasonable screening measures which would not result in a reduction in access to stimulant treatment (American Academy of Pediatrics, 2011; Magellan Health, Inc., 2014).

Another area of apprehension involves one of the most common stimulant adverse effects—i.e., appetite loss. The *Multimodal Therapy of ADHD (MTA) Study* three-year follow-up analysis conducted in 2007, revealed the persistent effect of stimulant agents on decreasing growth velocity, especially when children are on higher doses. The AAP publication, *ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention Deficit Hyperactivity Disorder in Children and Adolescents*, indicated these outcomes demonstrated a small reduction in growth (i.e., ranging from 1 to 3 cm), affected mainly weight and diminished after the third year of treatment as a temporary drug effect. Currently, the AACAP Parents Medical Guide Workgroup recommends that parents focus on the timing of their child's stimulant dosing so as not to interfere with appetite and maintenance of adequate caloric intake (Brent et al., 2012; Magellan Health, Inc., 2014).

**Treatment in primary care settings.** As discussed previously, the majority of treatment for behavioral health conditions occurs in pediatric primary care settings. Their substantial role in prescribing psychotropic medications is an issue of significant concern as argued by Pidano et al. because “there have been studies suggesting too much may be expected of these providers when they do not have the benefit of extensive training in behavioral health or the support of mental health specialists in their practice” (Pidano and Honigfeld, 2012, p. 931). Pidano's critique noted research findings signifying pediatric primary care providers “do not always identify the disorders presented by their patients and have reported substantial variations in their comfort level with diagnosing various psychiatric disorders” (Pidano and Honigfeld, p. 931). Authors also indicated that while primary care physicians are most comfortable in prescribing stimulant drugs, many do prescribe atypical antipsychotics and other combinations. This same critique also indicated that although studies have shown similarities in medications and dosing when comparing primary care and psychiatric practices, the patient retention rate beyond the first visit was much higher for psychiatrists (Pidano and Honigfeld, 2012).

Given the significant national shortage of child psychiatrists, there remains a realistic need to rely on primary care clinicians to perform screenings of children for mental disorders and treat uncomplicated ADHD, anxiety or depression. However, the problem of follow-up care and ongoing monitoring of mental health problems in pediatric primary care is a matter that must be addressed (Texas Department of Family and Protective Services, 2010).

# Principles for Optimal Psychopharmacotherapy Practice

In 2009, the AACAP published the *Practice Parameter on the Use of Psychotropic Medication in Children and Adolescents*, to promote the appropriate and safe use of psychotropic medications in children and adolescents with psychiatric disorders by emphasizing the best practice principles that underlie medication prescribing (Walkup et al., 2009). The AACAP developed these guidelines to accommodate the wide range of appropriate psychopharmacological practice by prescribers from different clinical specialties operating in today's varied practice settings. The AACAP practice parameter underscores the importance of the prescriber to establish routine procedures for **consistent** approaches to assessment and treatment along with active family participation and their understanding of the illness and challenges facing the patient. In addition, this parameter emphasizes that the practice of pediatric psychopharmacotherapy requires the integration of information from the scientific evidence base, while also employing state-of-the-art clinical skills in accordance to a family's needs and values (Walkup et al., 2009).

The best practices guiding treatment of children and adolescents with psychotropic drugs involve multiple steps and overarching professional principles specified by the AACAP parameter as follows (Walkup et al., 2009).

- Principle 1:** Before initiating pharmacotherapy, a psychiatric evaluation is complete.
- Principle 2:** Before initiating pharmacotherapy, a medical history is obtained, and a medical evaluation is considered when appropriate.
- Principle 3:** The prescriber is advised to communicate with other professionals involved with the child to obtain collateral history and set the stage for monitoring outcomes and side effects during the medication trial.
- Principle 4:** The prescriber develops a psychosocial and psychopharmacological treatment plan based on the best available evidence.
- Principle 5:** The prescriber develops a plan to monitor the patient, short and long term.
- Principle 6:** Prescribers should be cautious when implementing a treatment plan that cannot be appropriately monitored.
- Principle 7:** The prescriber provides feedback about the diagnosis and educates the patient and family regarding the child's disorder and the treatment and monitoring plan.
- Principle 8:** Complete and document the assent of the child and consent of the parents before initiating medication treatment and at important points during treatment.
- Principle 9:** The assent and consent discussion focuses on the risks and benefits of the proposed and alternative treatments.
- Principle 10:** Implement medication trials using an adequate dose and for an adequate duration of treatment.
- Principle 11:** The prescriber reassesses the patient if the child does not respond to the initial medication trial as expected.
- Principle 12:** The prescriber needs a clear rationale for using medication combinations.
- Principle 13:** Discontinuing medication in children requires a specific plan.

The AACAP practice parameter also specifies that this approach is necessary for safe, effective and proactive treatment and should help decrease the stigma that some children and their parents may experience from participating in psychiatric care. This consistent and rigorous method for assessment and treatment should also safeguard against: (1) the introduction of unacceptable variability into the pharmacological treatment of children; (2) the underuse of established psychosocial and pharmacological treatment approaches; and (3) the prescription of ineffective/outdated treatment approaches, inappropriate medications or medication combinations. It is also important that these recommended practices are implemented in an effort to eliminate demoralization experienced by patients and families receiving substandard treatment, “dropping out” of care or not seeking necessary treatment in the future (Walkup et al., 2009).

## Research Evidence for Treatment Efficacy of Psychotherapeutic Agents

The AACAP practice parameter verifies a current evidence base in pediatric psychopharmacology that now includes data from randomized controlled trials on both pharmacokinetics (what the body does to the medication) and pharmacodynamics (what the medication does to the body) (Walkup et al., 2009). To that end, this parameter specifies that efficacy and safety data are available for single pharmacological agents in the short-term treatment of a number of childhood psychiatric disorders—i.e., major depressive disorder (MDD), ADHD, obsessive-compulsive disorder (OCD), other anxiety disorders including separation anxiety disorder (SAD), social phobia and generalized anxiety disorder (GAD), mania, tic disorders, and aggression/impulse control as evidenced in autism and disruptive behavior disorders. However, the AACAP parameter indicates that extensive clinical practice and data from adult studies currently guide medication choices for schizophrenia since the clinical presentations are similar for patients across all age groups. Additionally, this parameter recognizes the smaller evidence base supporting psychotropic medication combinations which may be justifiably used in complex comorbid presentations, enhancement of outcome for treatment-refractory or partially responsive patients or to manage side-effects (Walkup et al., 2009).

Key findings from clinical research literature using analysis from published clinical systematic reviews by recognized experts and professional consensus guidelines are summarized in the sections below outlining the best pharmaceutical treatment options available for children and adolescents. Information is presented from the *2016–2017 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents*. The Florida Medicaid Drug Therapy Management Program updates the guidelines every two years by a group of stakeholders; i.e., the Florida Expert Panel made up of nationally recognized experts, academicians, child and adolescent psychiatrist, pediatricians, pharmacists, primary care providers, and medical directors of Medicaid health plans and community mental health centers. Findings from a thorough literature review are presented to the expert panel which reaches a consensus on adopting particular recommendations. Emphasis is on the evidence from randomized controlled trials and systematic review. The guidelines recommend the use of clinical rating scales, which collect patient data throughout treatment and provide insight into treatment progress. The guidelines are ordered by “level” of treatment with the beginning of treatment at Level 1. The guidelines allow for starting at a higher level during certain conditions, e.g., severe symptoms. Clinicians are expected to make decisions based on clinical judgement, best evidence, and guideline recommendations. The needs of individual patients are considered in relation to both symptoms/needs and family preferences for treatment (AHCA, 2017).

### Mood Disorders

**Bipolar Disorder:** Children and adolescents seem to have more modest benefits from traditional mood stabilizers (i.e., lithium and antiepileptics) than adults where study findings support greater benefits (i.e., reduction in mania) with second-generation antipsychotics (SGAs)—i.e., aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone. However, SGAs caused more weight gain and somnolence than mood stabilizers in



youth and adults, and SGAs caused greater weight gain in youth than adults. Researchers noted that more direct head-to-head comparator trials are still needed. Also, the relative efficacy of combining two mood stabilizers compared with one antipsychotic agent at the present time is not known (Correll and Dratochvil, 2011; Correll et al., 2010; Liu et al., 2011). Currently, the Preschool Psychopharmacology Working Group (PPWG) of the AACAP recommends a trial of risperidone after the failure of psychotherapeutic efforts to treat mania since this drug is the option with the most available data on effectiveness and tolerability in this age group (Gleason et al, 2007). To date, the FDA has indicated risperidone, quetiapine, aripiprazole and asenapine for use in children aged 10 or older, and olanzapine for children aged 13 and older with bipolar disorder (i.e., mania and mixed mania); lithium for adolescents aged 12 and older; and aripiprazole and lithium as treatments to prevent the recurrence of bipolar symptoms in children and adolescents (Correll et al., 2010; American Academy of Child Adolescent Psychiatry, 2012). There is currently insufficient evidence on treatment of bipolar depression in children and adolescents. Therefore, the AACAP *Practice Parameter for the Assessment and Treatment of Depression in Children and Adolescents* suggests avoiding the use of antidepressants based on research findings of their ineffectiveness on bipolar depression and danger of triggering manic episodes in the adult population (Birmaher et al., 2007).

The *2016–2017 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents* recommend monotherapy with aripiprazole, risperidone, quetiapine or asenapine in children between the ages of 10 to 17 (Agency for Health Care Administration [AHCA], 2017). For children and adolescent ages 10 to 17 who have had only partial response to a single atypical antipsychotic, the guidelines recommend augmentation with a mood stabilizer (lithium, VPA/divalproex). The next level of treatment is monotherapy with a different antipsychotic (except clozapine) or a combination with mood stabilizers, e.g., olanzapine and fluoxetine. At the last level, the diagnosis is reassessed and either clozapine or ECT in adolescents is considered. The combination of two antipsychotics is not recommended at any level of treatment. In order to minimize side effects when switching psychotropic medication, the guidelines recommend avoiding abruptly stopping, starting, and or switching to reduce withdrawal phenomena and risk of rebound. Slow switching using cross-titration is recommended. The first medication should not be reduced by more than 25 to 50% per 5 half-lives (AHCA, 2017).

**Major Depressive Disorder (MDD):** The AACAP parameter on depression noted above indicated that depressed patients treated with selective serotonin re-uptake inhibitors (SSRIs) have a relatively good response rate (40 to 70%) but, with the exception of fluoxetine, the placebo response rate is also high (30 to 60%) (Birmaher et al., 2007). Fluoxetine and escitalopram (SSRIs), along with doxepin (tricyclic), are the only antidepressants approved by the FDA for the treatment of child and adolescent depression. For children younger than 12 years of age, only fluoxetine showed significant benefit over placebo in clinical trials (Correll and Dratochvil, 2011; Magellan Health, 2014; GAO; Gentile, 2010). As well, the PPWG of the AACAP recommends fluoxetine as the first-line treatment for depression in preschoolers (Gleason et al., 2007). Other clinical trials have demonstrated the effectiveness of sertraline or citalopram against placebo for the treatment of MDD in youth (Sakolsky and Birmaher, 2012; Cincinnati Children’s Hospital Medical Center, 2010). The *Treatment for Adolescents with Depression Study* (TADS) compared treatments for moderate to severely depressed youth and found that 70% of those who received fluoxetine combined with weekly cognitive-behavioral therapy (CBT) had response rates showing significant improvement at 12 weeks followed by 60.6% for those treated with fluoxetine alone, 43.2% treated with CBT alone and 34.4% for placebo (Correll and Dratochvil, 2011). Another important trial, the *Treatment of Resistant Depression in Adolescent (TORDIA) Study* demonstrated that for adolescents with depression who do not respond to an initial SSRI (i.e., fluoxetine, citalopram or paroxetine), a switch to another antidepressant (i.e. another SSRI or the selective serotonin and norepinephrine reuptake inhibitor [SNRI]-venlafaxine) combined with CBT should be considered for a better clinical response (Correll and Dratochvil, 2011; Sakolsky and Birmaher, 2012).

The *2016–2017 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents* recommend the use of medication with psychosocial treatment for children under age 6 with depression (AHCA, 2017). If after levels 1 and 2 psychotherapeutic interventions there is poor response to the treatment alone

or if depression is severe, the guidelines recommend treatment with fluoxetine combined with psychosocial treatment. Monitoring for behavioral disinhibition, i.e., impulsive, sensation-seeking behaviors, lack of self-regulation, and suicidality, is required during this treatment. Tricyclic antidepressants or paroxetine are NOT recommended for children under age 6. For children and adolescents ages 6 to 17 years, level 1 treatment includes active support during a six-week trial (mild symptoms) including psychosocial interventions and psychoeducation. Recommendations for level 2 treatment include fluoxetine alone or in combination with cognitive behavioral therapy (CBT) or interpersonal psychotherapy (IPT). For age 12 and older, escitalopram may be considered. If after level 2 there is no adequate response to therapy, a switch to another medication, e.g., fluoxetine, is recommended. If poor or no response to level 3 interventions, the guideline recommends referral to a mental health specialist, and increased psychosocial intervention and medication dose if tolerated. At level 5 treatment, previously used SSRIs may be switched to sertraline, citalopram, bupropion or venlafaxine; augmentation of an SSRI with bupropion, thyroxine, lithium, buspirone, mirtazapine, aripiprazole, quetiapine, or risperidone may be considered. In case of severe depression or psychotic symptoms, ECT may be considered for adolescents (AHCA, 2017).

In a review of literature focused on psychopharmacology treatment in children and adults, authors indicated that “the evidence base for fluoxetine is the strongest and supported by pediatric registrations trials, and buttressed by data from the *Treatment of Adolescent Depression Study (TADS)* and the *Treatment of SSRI-Resistant Depression Study (TORDIA)* and by relapse-prevention data that suggest durability of treatment effect” (Strawn et al., 2016, p. 3). Authors noted that results of a recent meta-analysis showed that improvement occurs over the first four weeks of treatment with the plateauing of improvements in symptoms afterwards. The TORDIA study found that frequent assessment, is paramount in assessing treatment response (Strawn et al., 2016, p. 3).

### **Obsessive-Compulsive Disorder (OCD)**

The AACAP Workgroup on Quality Issues that developed the *Practice Parameter for the Assessment and Treatment of Children and Adolescents with Obsessive-Compulsive Disorder* lauded rapid advances seen in the previous decade in the knowledge of the pharmacotherapy of OCD affecting children and adolescents. However, this parameter continues to recommend cognitive-behavioral therapy (CBT) as the first line of treatment for mild to moderate cases of OCD because CBT “presents a logically consistent and compelling relationship between the disorder, the treatment and the specified outcome.” The AACAP parameter further specifies that for youth with moderate to severe OCD, medication is indicated in addition to CBT (Geller et al., 2012, p. 104). The combination of CBT and an SSRI may be more effective than CBT in these patients with severe OCD (Strawn et al., 2016). Strawn et al. reported studies suggesting that although SSRIs may be beneficial, the effect sizes of SSRIs are smaller compared with the effect sizes of SSRIs for patient pediatric anxiety disorders other than OCD. At the present time, there are four medications that have FDA approval for use in OCD in children and adolescents: the tricyclic antidepressant, clomipramine, for children aged 10 and over, and the SSRIs: sertraline (6 and older), fluoxetine (7 and older) and fluvoxamine (8 and older) (Kodish et al., 2011). A meta-analysis of all published randomized controlled medication trials in children and adolescents with OCD showed their moderate effect size and statistically significant difference against placebo with differences in absolute response rates ranging from 16% (sertraline and fluvoxamine) to 24% for fluoxetine. Additionally, clomipramine was superior to each of the SSRIs, where they were comparably effective. However, professional consensus supports the use of newer SSRIs over clomipramine because of tolerability and safety in children and adolescents (Geller et al., 2012). The PPWG of the AACAP recommends the newer SSRIs for use in preschoolers only when in accordance with professional consensus and FDA recommendations (Gleason et al., 2007). The *Pediatric OCD Treatment Study (POTS I)* demonstrated that combined treatment was superior to either CBT or sertraline alone, but that all were superior to placebo (Correll and Dratochvil, 2011; Geller et al., 2012; Kodish et al., 2011; Franklin et al., 2011). Further, the *POTS II Study* revealed that especially for children with a family history of OCD, CBT with exposure/response prevention should be augmented with SSRI treatment for maximum effect (Garcia et al., 2010). One proposed medication algorithm for pediatric anxiety proposed by Kodish et al. indicated that after two failed

SSRI adequate trials, clomipramine should be considered for OCD. In cases of no response or familial preference, buspirone or mirtazapine alone or as an augmentation may be tried. Lastly, the use of benzodiazepines for acute relief of severe symptoms or after no response to multiple trials may be in order (Kodish et al., 2011).

## Anxiety Disorders

Although non-OCD disorders (i.e., General Anxiety Disorder, Social Anxiety Disorder, and Specific Phobias) are more prevalent than OCD in childhood, clinical studies on efficacy of treatments are far more limited. Researchers have also acknowledged that the non-OCD anxiety disorder subtypes are often mixed in study treatment arms making it very difficult to compare treatment responses with precision (Kodish et al., 2011). One of the most important studies of pediatric anxiety cited by experts was the recent *Child/Adolescent Anxiety Multimodal Study (CAMS)* where patients (n=488; ages 7 to 17 yrs.) with non-OCD anxiety disorders showed the most improvement in combination CBT/sertraline (81%), followed by CBT alone (60%), and sertraline alone (53%) compared with 24% response rate to pill placebo (Correll and Dratochvil, 2011; Kodish et al., 2011). An earlier clinical trial, the *Research Unit on Pediatric Psychopharmacology (RUPP) Study* of children (n=128; 6 to 17 yrs.) with non-OCD disorders were treated with fluvoxamine or placebo after they failed to improve with psychosocial treatment. The response rates were very favorable for fluvoxamine at 76% versus 29% for placebo (Correll and Dratochvil, 2011; Gleason et al., 2007; Kodish et al., 2011; Connelly et al., 2007). The AACAP *Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders* also confirmed the efficacy of fluoxetine compared to placebo in treating non-OCD disorders but cautioned this treatment response was markedly less dramatic for social phobia (Kodish et al., 2011; Connelly et al., 2007). The PPWG of the AACAP recommended paroxetine only as the first-choice medication for preschoolers in the non-OCD cases because it has been used most extensively in older children and adolescents and has the strongest safety profile (Gleason et al., 2007). In the treatment of GAD specifically, the SNRI, venlafaxine extended-release (XR) demonstrated significant superiority to placebo in two randomized controlled studies. Overall, SSRIs and SNRIs have shown clear benefit in the treatment of GAD in children and adolescents, with an overall response rate almost double that of placebo, with SSRIs slightly more beneficial than venlafaxine XR (Kodish et al., 2011; Connelly et al., 2007). In addition, the aforementioned medication algorithm for pediatric anxiety proposed by Kodish et al. indicated that after two failed SSRI adequate trials, venlafaxine XR should be considered for non-OCD in children and adolescents. As recommended for OCD, and in cases of no response or familial preference, buspirone or mirtazapine alone or as an augmentation may be tried. In addition, prescribers may consider use of benzodiazepines for acute relief of severe symptoms or if no response is evident after multiple medication trials (Kodish et al., 2011).

The *2016–2017 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents* recommend that treatment for anxiety disorders in children under age 6 begin with psychotherapy for at least 12 weeks, including the parents and exposure-based cognitive behavioral therapy adapted to young children. If poor/partial response to psychotherapy, the guidelines recommend treatment with fluoxetine and concurrent psychotherapy for children ages 4 to 5 years. The guidelines advise review of black box warning with parents while monitoring for suicide ideation. Fluoxetine, starting at 1 to 2 mg/day, is recommended for eight to 10 weeks with maximum dosing of 5 to 10 mg/day. After six to nine months of medications, a gradual downward titration is recommended. Sertraline combined with psychotherapy may be considered where fluoxetine is unsuccessful. For youth 6 to 17 years of age, the guidelines recommend psychoeducation and exposure-based CBT for mild to moderate anxiety disorder. Evidence-based psychosocial interventions are recommended if CBT is not available. For moderate to severe anxiety disorder or lack of response to CBT, treatment may be initiated with fluoxetine or sertraline alone or combined with CBT, and if one of these medications is not effective or there are treatment-limiting side effects, a switch to the other medication is recommended. Where the treatments above are not successful, duloxetine alone or combined with CBT or fluvoxamine alone or in combination with CBT is recommended. If these are not successful, consideration of escitalopram, citalopram, or venlafaxine in combination with CBT are recommended. The guidelines do not recommend treatment with paroxetine or benzodiazepines as first or second-line treatment.

A recent study performed a systematic review of five randomized, double-blind, placebo-controlled trials that assessed the effects of sertraline, fluoxetine, venlafaxine ER, and duloxetine in pediatric patients (n = 1186) with generalized anxiety disorder to examine the efficacy, safety, and tolerability of psychopharmacologic interventions in youth with GAD (Dobson and Strawn, 2016). Authors concluded that results of this review suggested that the “SSRIs and SNRIs are generally efficacious and well tolerated, with their benefits well outweighing their risks in youth with GAD” (Dobson and Strawn, p. 52). However, they also indicated that the “potential association between treatment with an SSRI/SNRI and suicidality in youth with GAD remains unclear” (Dobson and Strawn, p. 52).

## **Post-Traumatic Stress Disorder (PTSD)**

The diagnostic entity, PTSD, is generally disaggregated from other anxiety disorders research studies because of the uniqueness of its etiology and treatment. It is widely acknowledged that there is scant evidence to guide the pharmacological treatment of PTSD in children and adolescents (Cohen et al., 2010); Strawn et al., 2010). The AACAP *Practice Parameter for the Assessment and Treatment of Children and Adolescents with Posttraumatic Stress Disorder* recommends the use of trauma-focused cognitive-behavioral therapy (TF-CBT) alone as the first line treatment for PTSD in school-aged children and adolescents with the addition of an SSRI only if the child’s symptom severity or lack of response suggested a need for additional interventions (Cohen et al., 2010). Two randomized trials have been conducted on sertraline in this population. These findings were equivocal because the effectiveness of sertraline comparable to placebo or CBT alone or combined with sertraline resulted in similar improvements (Strawn et al., 2010). The AACAP practice parameter does stress that school-aged children and adolescents suffering from PTSD who have comorbid depressive disorder, GAD, OCD or other disorders known to respond to SSRIs should be treated with these agents earlier in treatment (Cohen et al., 2010). In contrast, the PPWG of the AACAP asserted that they “cannot recommend the use of psychopharmacological interventions for PTSD in preschoolers” in their medication algorithms since the only randomized drug trials for this disorder have been performed on adults and the “clinical evidence supporting psychotherapeutic interventions for PTSD is quite strong” (Gleason et al., 2007, p. 1558). More recent open-label studies of  $\alpha$ - and  $\alpha$ -adrenergic blocking agents (i.e., clonidine, propranolol) have shown promise in decreasing PTSD symptoms such as basal heart rate, anxiety, impulsivity and hyperarousal in children and youth (Cohen et al., 2010; Strawn et al., 2010).

The *2016–2017 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents* indicates a **lack of empirical evidence supporting the use of psychotropic medication in children 6 years old or younger for the treatment of PTSD**. For children older than 6 years whose PTSD symptoms include impaired sleep, psychotherapy augmentation with prazosin may be considered, and for persistent intrusive symptoms or increased arousal/reactivity, psychotherapy augmentation with clonidine or guanfacine may be considered. The guidelines do not recommend the use of SSRIs, benzodiazepines, or second-generation antipsychotics for the treatment of PTSD in children and adolescents. The use of two or more medications that reduce sympathetic arousal concurrently, e.g., prazosin, guanfacine, clonidine, is not recommended (AHCA, 2017).

## **Disruptive Behavioral Disorders/Aggression**

Maladaptive aggression has been defined as a nonspecific, serious symptom accompanying many childhood disorders—i.e., oppositional defiant disorder (ODD), conduct disorder, ADHD and bipolar disorder. Severe problems with aggression have significant consequences in both social and academic functioning. Experts have termed maladaptive aggression the “fever” of child psychiatry because it is common, nonspecific, and as a phenomenon described it as “the language of the inarticulate” involving behavior that is unplanned, unprofitable and poorly controlled. It is differentiated from predatory aggression that is planned, sometimes profitable and highly controlled (AACAP, 2010). The consensus development initiative, *Treatment of Maladaptive Aggression in Youth (T-MAY)*, sponsored by Rutgers Center for Education and Research on Mental Health Therapeutics (CERT), provides recommendations for a standardized approach in dealing with maladaptive

aggression seen in outpatient settings. CERT Guidelines indicate antipsychotics are the most studied class of drugs and have demonstrated the largest efficacy for disruptive/aggressive conditions, particularly risperidone versus placebo. In addition, the first-generation antipsychotic, haloperidol, demonstrated effectiveness in the treatment of aggression in hospitalized patients (Rosato et al., 2012). In a clinical review of studies, Correll et al. also noted that thioridazine was found to be an effective first-generation antipsychotic agent for aggressive behavior in conduct-disordered youth (Correll and Dratochvil, 2011). Other results from controlled clinical trials using conduct disorder as the principal diagnosis for inclusion, showed promise for mood stabilizers (e.g., divalproex, lithium), antipsychotics and stimulants (Gleason et al., 2007; Steiner et al., 2007; Blader et al., 2009). Both the CERT Guidelines and the AACAP *Practice Parameter for the Assessment and Treatment of Child and Adolescents with Oppositional Defiant Disorder* recommend considering psychosocial interventions (i.e., evidenced-based parent and child skills training) as the first-line treatments since medications are to be considered “adjunctive, palliative and noncurative” (Steiner et al., 2007, p. 137). These guidelines also underscore the need for prescribers to target initial psychopharmacological treatment to the underlying primary psychiatric or comorbid diagnosis(es) as this may ameliorate impulsive aggressive behavior (Rosato et al., 2012). In addition, the AACAP practice parameter indicates that many children who have an early onset of ODD, later progress to develop conduct disorder or antisocial personality disorders. The PPWG of the AACAP recommends a trial of risperidone for preschoolers with disruptive behavior disorders with severe aggression but without co-occurring ADHD. Although the PPWG notes the effectiveness and tolerability of risperidone in this age group, they recommend it should be discontinued after six months in order to reassess underlying symptoms and further validate diagnosis (Gleason et al., 2007).

The *2016–2017 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents* recommend psychosocial interventions, e.g., parent management training or parent-child interaction therapy, multisystemic therapy, or applied behavioral analysis, as initial treatment targeting the underlying disorder first in children under 6 years (AHCA, 2017). If psychosocial treatment is not effective or in cases of severe impairment or severe aggression, the guidelines recommend monotherapy with methylphenidate formulation, then amphetamine formulation or low dose alpha-2 agonists, then atomoxetine. The guidelines also recommend consideration of combination therapy of stimulant with alpha-2 agonists. If there is insufficient response to the above, low dose risperidone or aripiprazole is considered. For children ages 6 to 17 years, parent management training, parent-child interaction therapy, behavioral therapies, multimodal interventions, CBT, and family therapy are recommended as initial treatments. If the above treatments are not successful, the guidelines recommend first treating the primary disorder, e.g., ADHD, anxiety disorder, mood disorders, before treating aggression with other pharmacologic agents. Monotherapy with methylphenidate formulation, then amphetamine formulation or alpha-2 agonists, then atomoxetine are considered after treatment of the underlying disorder. A combination therapy of stimulant with an alpha-2 agonist is another consideration. The guidelines indicate that “for affective aggression if benefits outweigh risks, consider starting with low-dose risperidone or aripiprazole (most robust evidence for use at the time of publication) (AHCA, p.26). If the above interventions are not successful, the guidelines recommend considering switching to an antipsychotic medication or adding an antipsychotic medication to the ongoing psychosocial and/or pharmacological treatment. The guidelines caution that risperidone or aripiprazole are recommended at low doses and that titration to appropriate dose to target symptoms is important. After these treatments and if failure to respond to treatment occurs, the guidelines recommend switching to a different antipsychotic (either risperidone or aripiprazole). If there is a failure to respond to the different antipsychotic, other antipsychotics for which less evidence exists may be considered.

A recent article examined the role of medication in the treatment of aggression in youth with pathological aggression (Gurnani et al., 2016). Authors noted that a significant number of prescriptions for aggressive behavior are provided by primary care clinicians due to the small number of child and adolescent psychiatrists. Although limited research supports the use of medication treatment when no underlying disorder is identified, authors noted that atypical antipsychotics are increasingly prescribed, including by primary care providers. They also indicated that impulsive aggression is the subtype of aggression thought to be most effectively treated by

pharmacotherapy. **Authors advised that medications for aggression “should be used judiciously and with close patient monitoring, given potential safety concerns”** (Gurnani et al., p. 69). Authors stated that the treatment of aggression in children and adolescents is of high priority because delinquency, substance abuse, continuing aggression, and adult antisocial behavior may result from lack of treatment. They concluded that pharmacotherapy generally be targeted to the primary disorder, and in cases of nonresponse to the treatment, switching or combining medications may be beneficial. Authors referred to current guidelines, i.e., TRAAAY and T-MAY, to guide implementation of appropriate therapeutic interventions (Gurnani et al., 2016).

## **Attention Deficit Hyperactivity Disorder (ADHD)**

The amphetamines and methylphenidate are stimulant drugs that remain first-line treatments for ADHD with strong demonstrated efficacy in treating the core symptoms of hyperactivity, impulsivity, inattentiveness and associated aggressiveness. Higher stimulant doses generally are associated with better reduction in symptoms where it is estimated that at least 70% of school-aged children respond favorably to stimulant medication (Magellan Health, 2014). The non-stimulant SNRI drug, atomoxetine, was approved by the FDA to treat ADHD and since it is not a controlled substance, it is more convenient for patients and physicians while reducing abuse potential. Atomoxetine does not offer the option for a drug holiday unlike stimulants and should be taken daily (Magellan Health, 2014). Meta-analytic findings of clinical trials for atomoxetine and stimulants yielded a moderate effective size for atomoxetine of 0.63 and large effect sizes of 0.99 and 0.95 for immediate and extended-release stimulants, respectively (Correll and Dratochvil, 2011). More recently, the extended-release formulation of  $\alpha$ -adrenergic agonists, clonidine and guanfacine, were granted FDA-approval for the treatment of ADHD as adjunctive agents along with stimulant medications. None of these medications have FDA approval for use in preschool-aged children. Nevertheless, current clinical guidelines now stipulate that children as young as 4 years of age may be diagnosed and treated for ADHD when academic/behavioral problems and core symptoms suggest the disorder and since ADHD does show diagnostic homotypic continuity throughout childhood and adolescence (Magellan Health, 2014). The PPWG of the AACAP recommends methylphenidate as the first-line psychopharmacological treatment for preschool ADHD and if ineffective, a switch to an amphetamine formulation. The PPWG algorithm further allows clinicians to use individual clinical factors to choose between atomoxetine and  $\alpha$ -agonists at this juncture, since the existing evidence does not support the superiority of agents to the other (Gleason et al., 2007). After a six-month trial of medication, the PPWG of the AACAP recommends discontinuing the agent for a period of observation in order to confirm an ADHD diagnosis in the preschool child before resuming a psychopharmacological regimen (Gleason et al., 2007). Additionally, the off-label use of SGA drug, risperidone, has shown promise in study results of children with aggressive behavior in ADHD. These findings need to be corroborated with supporting evidence from future clinical studies comparing antipsychotics with behavioral intervention, combination treatments and placebo (Correll and Dratochvil, 2011; Magellan Health, 2014).

The American Academy of Pediatrics (AAP) *Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention Deficit Hyperactivity Disorder in Children and Adolescents* makes distinctions by the age cohort of children with ADHD regarding the recommended order in which drug treatments should be instituted. Specifically, the AAP recommends: (1) evidence-based parent- or teacher-administered behavioral treatment should be instituted before a medication trial in preschoolers where drug therapy should be introduced only if there is no improvement; (2) combined behavioral and pharmacological interventions should be considered first-line approaches for school-aged children; and (3) medications should initially be prescribed for adolescents and behavioral treatments are optional, although preferable (AAP, 2011; Magellan Health; 2014).

The *2016–2017 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents* under age 6 recommend that the initial treatment of children with ADHD is parent management skills training or other behavioral intervention at home and/or school for at least 12 weeks, followed by the initiation of monotherapy with methylphenidate formulation (AHCA, 2017). The next level of treatment, if methylphenidate is not successful, considers monotherapy with atomoxetine; warning: the child must have ability to swallow the

medicine whole. The next level of treatment considers amphetamine formulation (FDA indications for ages 3 to 5 years old) although there is a limited clinical trial evidence base. Alpha-2 agonists may also be considered although no published data exists. The guidelines indicate that after a period of six months of sustained improvement on any effective medication treatment, the medication must be tapered to determine its lowest effective dose and possibility of discontinuation. For the treatment of children and adolescents ages 6 to 17 years old, the guidelines recommend psychostimulant monotherapy as initial treatment (methylphenidate class or amphetamine class, either short or long acting), and if the first choice is not effective, guidelines recommend monotherapy with another stimulant. An alternative choice is extended-release alpha-2 agonist monotherapy. The next level of treatment recommended is a combination of extended-release alpha-3 agonists with psychostimulant or atomoxetine. The next level of treatment recommended is an immediate-release alpha-2 agonist as monotherapy or combined with other ADHD medication classes. Only after treatments at the above levels and if none of the treatments result in satisfactory response, the guidelines recommend bupropion or tricyclic antidepressants. The guidelines recommend that the following are not recommended in the treatment of ADHD in children and adolescents 6 to 17 years old: antipsychotic medication to treat core symptoms of ADHD; concurrent use of two or more alpha-2 agonists; concurrent use of two different stimulant classes; and desipramine (AHCA, 2017).

Strawn et al. reviewed literature related to medications for the treatment of ADHD in children and adolescents (Strawn et al., 2016). They noted that ADHD is the most prevalent mental disorder in children and adolescents, negatively affecting academic, social, and family functioning. They reported that the FDA has approved almost two dozen stimulant medications, considered first-line psychopharmacologic interventions to treat this disorder in children and adolescents. Authors referred to guidelines that “recommend long-acting preparations as first-line stimulant pharmacotherapies in youth with ADHD ages 6 years or above” (Strawn et al., 2016, p. 7). Highlights from this study include the following: smaller effect sizes and more side effects from stimulants when used in children under age 6 years than in older children; response to stimulants affected by psychiatric comorbidities (3 or more comorbidities in preschoolers with ADHD predictive of no response to the therapy); greater benefit from behavioral therapy in school-age children with comorbid anxiety and ADHD than those with ADHD alone; co-occurring substance use disorder associated with poorer response to stimulant treatment; considerable debate about management of cardiovascular side effects of stimulant medication resulting in conflicting recommendations; non-stimulants considered second-line treatments for patient unable to tolerate stimulants, although may be considered first-line due to concern for abuse or diversion of stimulant medications; and FDA boxed warning carried by atomoxetine for the small risk of suicidal thinking (Strawn et al., 2016).

### **Autism Spectrum Disorders (ASDs)**

There is currently no pharmacologic agent that is effective in treating the core behavioral manifestations of autism (Brasic and Pataki, 2012; Carrasco et al, 2012). Nevertheless, certain drugs may be effective in treating the associated maladaptive behavior problems and comorbid psychiatric disorders—e.g., OCD, depressive disorders, GAD and ADHD (Brasic and Pataki; Meyers et al., 2007). DSM-5 notes that approximately 70% of individuals with ASD have one comorbid psychiatric disorder and 40% may have two or more comorbid mental disorders (DSM-5, 2013). In cases where a DSM-5 comorbid disorder has been made, the patient can be treated with medications that are used in treating these conditions in typically developing children. In the absence of a clear comorbid psychiatric diagnosis, and in cases where behavioral interventions and environmental modifications have proven suboptimal, the AAP guideline recommends a “target-symptom cluster approach” with the use of an appropriate psychotropic agent as follows: (Meyers et al., 2007; Plauche et al., 2007, pp. 1169, 1170).

- Repetitive behavior, rigidity, obsessive-compulsive symptoms—selective serotonin reuptake inhibitors (SSRIs) i.e., fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine, sertraline
- Hyperactivity, impulsivity, inattention symptoms—atypical antipsychotic agents (i.e., risperidone, aripiprazole, olanzapine, quetiapine, ziprasidone), valproic acid, stimulants (i.e., methylphenidate, dextroamphetamine, mixed amphetamine salts) and alpha agonists (i.e., clonidine, guanfacine)

- Aggression, explosive outburst, self-injury—atomoxetine, atypical antipsychotic agents (i.e., risperidone, aripiprazole, olanzapine, quetiapine, ziprasidone), alpha agonists (i.e., clonidine, guanfacine), anticonvulsant mood stabilizers (i.e., levetiracetam, topiramate, valproic acid), SSRIs (i.e., fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine, sertraline), beta-blockers (i.e., propranolol, nadolol, metoprolol, pindolol)
- Sleep dysfunction—melatonin, ramelteon, alpha agonists (i.e., clonidine, guanfacine) and antihistamines (i.e., diphenhydramine, hydroxyzine)
- Anxiety—mirtazapine, SSRIs (i.e., fluvoxamine, citalopram, escitalopram, paroxetine, sertraline), buspirone
- Depressive phenotype—SSRIs (i.e., fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine, sertraline), mirtazapine
- Bipolar phenotype—anticonvulsant mood stabilizers (i.e., carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate, valproic acid), atypical antipsychotic agents (i.e., risperidone, aripiprazole, olanzapine, quetiapine, ziprasidone) and lithium

While SSRIs are commonly prescribed in the treatment of autism, their usage has been largely extrapolated from research on adults. In addition, results of more recent large studies of their usage in children and autism have been disappointing (Williams et al., 2010; Vega and Anderson, 2012). Meta-analytic findings on the efficacy of SSRIs for repetitive behaviors in ASDs showed that current published literature overstates SSRI effectiveness when also examining their treatment effects as demonstrated in unpublished literature. Similarly, other meta-analytic findings on the use of SSRIs for core symptoms of autism (i.e., communication, social interaction and behavior problems) showed lack of efficacy in the treatment of autism. These findings have led to a diminution in their usage because of drug side effects and the possible emergence of suicide-related behaviors (Williams et al., 2010; Vega and Anderson, 2012). Atypical antipsychotics, risperidone and aripiprazole, are the two best-studied medications to treat the challenging or repetitive behaviors manifested in ASD. Since strength of evidence of treatment efficacy is high for aripiprazole and moderate for risperidone, investigators have concluded that future research is unlikely to change the assessment of benefits of these agents. Because marked weight gain and risk of extrapyramidal symptoms are significant in these agents, their usage is typically reserved for cases of severe impairment or risk of injury due to their adverse-effect profiles (MacPheeters et al., 2011; Warren et al., 2011).

A recent study compared the use of psychotropic medications among children (n=7901) aged 1 to 17 in five health systems with ASD to a matched population (n=79010) with no ASD (Madden et al., 2017). Significantly more children with ASD had psychiatric comorbidities, e.g., depression, bipolar disorder, schizophrenia, and other psychoses, than the children without ASD, and those with ASD were more likely to utilize mental health services. Approximately 48.5% of children with ASD took psychotropic medications, with the most prevalent medications being those that typically target ADHD including stimulants and non-stimulant ADHD therapies, antipsychotics, antidepressants and mood stabilizer. The most frequent antidepressant was fluoxetine, and risperidone and aripiprazole led among antipsychotics. Compared to only 7.7% of the children without ASD who took psychotropic medication, almost half of those with ASD took psychotropic medications, and the largest difference was for antipsychotics. Researchers found that in the absence of other psychiatric diagnoses, “0.3% of children who had neither ASD nor ADHD diagnosis received an ADHD-associated medication, whereas 10.4% of children with ASD but no ADHD diagnosis received such medications; results for antipsychotics and antidepressants were similar” (Madden et al., p. 148). Researchers summarized that children with ASD were 11.4 times more likely to receive treatment with psychotropic medications as children without ASD, and “in the absence of relevant comorbidity diagnoses, children with ASD had far higher rates of use than peers; children with neither ASD nor these specific comorbidities rarely received psychotropics” (Madden et al., p. 149). Researchers concluded that despite a lack of strong published evidence supporting the effectiveness and safety of high usage of psychotropic medications in children with ASD, psychotropic medications are used extensively and intensively for this population (Madden et al., 2017).



## Childhood Schizophrenia

Until recently, the treatment of childhood schizophrenia was of necessity based on evidence from clinical pharmacological studies conducted with adults. The FDA approved several SGA agents for use in children and adolescents (aged 13 to 17) with schizophrenia after a wave of new placebo-controlled clinical trials were conducted and demonstrated efficacy in this population (Correll and Dratochvil, 2011; Findling et al., 2011). Findings from one international multisite trial (N=107-302 range) demonstrated that aripiprazole, olanzapine, quetiapine, risperidone and paliperidone were all superior to placebo in adolescents with schizophrenia. In addition, other published findings from head-to-head trials comparing antipsychotics in youth with schizophrenia or psychosis did not reveal any significant differences in efficacy among non-clozapine antipsychotics (i.e., olanzapine vs. risperidone; olanzapine vs. risperidone and haloperidol; olanzapine vs. molindone; olanzapine vs. quetiapine) (Correll and Dratochvil, 2011). Another systematic review of studies reviewing both first- and second-generation antipsychotics employed in childhood schizophrenia concluded that clinical improvements were greater for patients receiving SGAs than FGAs and patient adherence to medications did not differ between classes (Seida et al., 2012).

A recent systematic review and network meta-analysis compared the efficacy and safety of antipsychotics in the treatment of youth (n=2158) 8 to 19 years of age with early-onset schizophrenia-spectrum (EOS) disorders (Pagsberg et al., 2017). Authors analyzed the results from 12 short-term (six to 12 weeks) randomized trials that allocated youth with schizophrenia to a non-clozapine antipsychotic versus placebo or another antipsychotic. Outcome measures included Positive and Negative Syndrome Scale (PANSS) total and positive symptoms. Antipsychotics included aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone. Except for ziprasidone, the study found comparable acute efficacy among antipsychotics for symptom decrease based on the PANSS; except for ziprasidone and asenapine, all antipsychotics were superior to placebo. Other results included: weight gain associated with olanzapine; extrapyramidal symptoms and akathisia primarily associated with molindone; increased levels of prolactin primarily associated with risperidone, paliperidone, and olanzapine. Authors concluded that the results of this first comparison of antipsychotics (for the treatment of early onset schizophrenia in children and adolescents) with active comparators or placebo in randomized controlled trials provided useful information that was previously unavailable. They concluded: ziprasidone cannot be recommended for this treatment as it had limited or no effect and its efficacy appeared inferior to other antipsychotics; adverse events (AEs) were consistent with prior findings in adults. Authors concluded, “Aripiprazole and quetiapine had proven efficacy and reasonable tolerability in EOS, and the side effect profiles appeared less severe compared with the other antipsychotics, although both demonstrated significant AEs” (Pagsberg et al., 2017, p. 200).

## Research Evidence for Treatment Efficacy of Psychological Therapies Alone and in Combination with Psychotropic Drugs

In their recommendations about the use of psychotropic medications for children and adolescents involved in child-serving systems, the AACAP noted that “one of the most significant concerns about psychotropic medication use in youth involves the frequent absence of effective psychosocial interventions” (AACAP, 2015, p. 16). The AACAP specified that practitioners develop both a psychosocial and a psychopharmacological treatment plan based on best available evidence in the treatment of children and adolescents. Mental disorders, e.g., depression, are very debilitating, affecting psychosocial, family, and academic functioning, and are likely to continue into adulthood without evidence-based treatment. Psychotherapy, involving therapeutic conversations and interactions between therapists and children or family, can help in the resolution of problems and modification of behavior. It may include different approaches, e.g., cognitive behavior therapy, dialectical

behavior therapy, family therapy, group therapy, interpersonal therapy, play therapy, and/or psychodynamic psychotherapy. Only one of the approaches may be needed, or a combination of psychotherapy approaches may be beneficial. Sometimes a combination of psychological therapies and psychopharmacological approaches may provide the most beneficial treatment.

A large review of eleven studies from the Cochrane Library evaluated the effectiveness of psychological therapies and antidepressant medication, alone and in combination, for the treatment of depressive disorder in children and adolescents (Cox et al., 2014). Participants (n=1307) in the studies, between 6 and 18 years, had different severities of major depressive disorder and a variety of comorbid disorders which limited comparability of results. Authors reported that the majority of studies found no statistically significant differences in efficacy between the interventions compared. Two studies including 220 participants found that antidepressant medication was more effective than psychotherapy based on post-intervention remission (67.8% of participants in medication group and 53.7% in psychotherapy group in remission immediately post-intervention). Three studies involving 378 participants found that combination therapy was more effective than antidepressant medication alone based on post-intervention remission (65.9% of participants in combination therapy and 57.8% in medication alone). None of the studies suggested that combination therapy was more effective than psychotherapy alone based on post-intervention remission. In comparing suicidal ideation as an adverse effect of treatment, one study including 88 participants found significantly higher suicidal ideation in the group receiving antidepressant medication than those in the group receiving psychological therapy (18.6% of those in the medication group vs. 5.4% in the psychological therapy group). Authors noted that this effect lasted six to nine months. On rates of suicidal ideation, studies found unclear effects of combination therapy compared with either antidepressant medication alone or psychological therapy alone. Authors concluded that evidence about the relative effectiveness of psychological interventions, antidepressant medication and a combination of these interventions is very limited and that future randomized controlled trials are needed (Cox et al., 2014)

## Cautionary Guidelines for Broadened Usage of Drugs

The broadened use of psychotropic medications used in children and adolescents today has fueled a number of concerns regarding not only the number of agents prescribed but also the appropriateness of the diagnoses used to justify such use. While unsuitability of diagnosis applies across the board, Correll et al. have specified that this problem is most applicable to the improper assignment of bipolar disorder in childhood (Correll and Dratochvil, 2011). Even though SGAs were developed and initially studied as treatments for psychotic illnesses in adults, psychopharmacology experts report that aggression, and not psychosis, is the most common target symptom for which SGAs are prescribed to children and adolescents (Correll and Dratochvil, 2011; Findling et al., 2011; Crystal et al., 2009). As discussed earlier, the dramatic and steady rise in the use of antipsychotic medications has garnered the most attention and alarm since much is still not known about the efficacy, tolerability and long-term safety of these drugs in young people (Correll and Dratochvil, 2011; Fanton and Gleason, 2009; Gleason et al., 2007).

The AACAP *Practice Parameter for the Use of Atypical Antipsychotic Medication in Children and Adolescents* was developed in order to provide specific recommendations for baseline assessment and routine ongoing medical monitoring of the following significant safety issues/concerns that are associated with the SGA side effects that can develop at treatment initiation and even with sustained use: (1) weight gain, diabetes and hyperlipidemia; (2) cardiovascular problems such as prolongation of QTc interval, orthostatic hypotension, tachycardia and pericarditis and coronary artery disease associated with weight gain; (3) neutropenia and potential agranulocytosis; (4) hepatic dysfunction; (5) elevation of prolactin levels; (6) electroencephalogram (EEG) abnormalities and possible seizure activity; (7) potential for the development of extrapyramidal symptoms, tardive dyskinesia and withdrawal dyskinesias; (8) neuroleptic malignant syndrome; and (9) formation of cataracts (Findling et al., 2011).

The AACAP practice parameter summarized above also underscores the importance of prescribers in consulting the existing scientific literature before selecting the SGA agent. At the present time, SGAs clozapine, risperidone, olanzapine, quetiapine, ziprasidone, paliperidone and aripiprazole have published pediatric clinical trial data, but the more recently FDA-approved SGA, asenapine, has no data pertaining to its use in the young population (Findling et al., 2011; Seida et al., 2012).

Since the current FDA-approved indication for SGA use in children and adolescents includes only schizophrenia, bipolar disorder and specific symptoms of autism, the clinician is strongly urged to consider alternative pharmacological or psychosocial treatments for these other specific problems, i.e., disruptive behavior disorders and aggression (Findling et al., 2011).

## Drug Treatment Effects on Nervous System Development

The unknown long-term safety effects of psychiatric drugs taken by children and adolescents also includes their potential impact on developing organs, skeletal system, brain and central nervous system of a fetus in utero and throughout a child's entire growth period (Kohlstadt and Vitiello, 2010). Developmental effects of drugs may include minor and major malformations (i.e. somatic teratogenesis) in the embryonic phase or effects on the fetus and breastfeeding infant which can affect the child's subsequent behavior, cognitive abilities and/or emotional regulation, i.e., neurobehavioral teratogenesis (Schatzberg et al., 2010). The FDA recently issued warnings against the use of the following drugs during pregnancy: (1) FGA/SGA antipsychotic drugs due to the risk of abnormal muscle movements and withdrawal symptoms in newborns; (2) valproic acid for risk of neural tube birth defects; (3) topiramate for risk of cleft lip/palate defects; (4) SSRIs for increased risk (i.e., up to six times more) of neonatal persistent pulmonary hypertension (PPHN) after the 20th week of gestation; and (5) changing paroxetine assigned pregnancy category from C (i.e., risk cannot be ruled out) to D (i.e., positive evidence or risk to humans, risk may outweigh benefit) due to an increased risk of congenital malformations, particularly cardiovascular, in the first trimester of pregnancy (Schatzberg et al., 2010; FDA, 2012); Epstein et al., 2012; Paroxetine, 2013; FDA, 2013; Kieler et al., 2012).

Psychotropic drug use among pregnant women was quantified in a large retrospective cohort study conducted by investigators at Vanderbilt University using women (n=296, 817) enrolled in Tennessee Medicaid through pregnancy who had a live birth or fetal death from 1985 to 2005 (Epstein et al., 2012). These women were treated with one or a combination of antipsychotics, lithium and anticonvulsants for a variety of disorders (i.e., pain, epilepsy, schizophrenia, bipolar disorders, unipolar depression and others). Overall, the adjusted use of study medications during pregnancy for these agents increased from nearly 14 to 31 per 1000 pregnancies in the twenty-year span reviewed. In addition, the study revealed there were significant increases in the use of atypical antipsychotics (1.73 to 16.5 per 1000) and anticonvulsants (i.e., 4.12 to 13.2 per 1000) during pregnancy but decreases in the use of typical antipsychotics (7.77 to 0.99 per 1000) and lithium (2.11 to 0.46 per 1000) (Epstein et al., 2012).

The marked increase in trend of psychotropic drug use in pregnant women, children and adolescents has provoked heightened research within the field of developmental neuroscience. In a published systematic review of the literature, Gentile argued that inherent potential neurobehavioral toxicity deserves attention since reproductive safety of psychotropic drugs has typically assessed the risk of congenital malformations and perinatal complications. Authors indicated that current evidence substantiates the well-known structural teratogenicity (i.e., reduced head circumference) for certain anticonvulsants (i.e., valproic acid and carbamazepine vs. clonazepam or lamotrigine), but is insufficient to suggest that behavioral teratogenicity may follow—although valproic acid exposure during pregnancy has been associated with an increased risk of autism in children (Gentile, 2010). In addition, Gentile acknowledged that preliminary data on SSRIs seems to exclude neurocognitive effects of prenatal exposure to these agents on infant development. However, other

studies have pointed toward premature delivery and its association with depression itself (Schatzberg et al., 2010; Paroxetine, 2013). Gentile also emphasized that the neurobehavioral safety of SGAs is unknown due to a paucity of data, whereas the presumed safety of FGAs, tricyclic antidepressants (TCAs) and benzodiazepines remains preliminary for informing the decision-making process (Gentile, 2010).

It is also critical to consider the dynamic effect of psychotropic drugs on the immature brain which demonstrates plasticity in its ability to adapt to the external milieu and preventive interventions. Psychotropic agents can influence brain development whereby chronic drug exposure during sensitive periods can produce permanent alterations of the nervous system that can result in either beneficial or harmful delayed consequences (Andersen and Navalta, 2011). A clinical review of developmental neuropharmacology by Andersen et al. discussed the effects of childhood psychotropic drug exposure whereby the concept of “neuronal imprinting” presumes that “drug effects outlast exposure to the drug itself” (Andersen and Navalta, 2004, p. 423). Authors proposed the concept that “drug effects incubate” and noted emerging evidence suggest “long-term effects of drug exposure are delayed and expressed once the vulnerable system reaches maturation” (Andersen and Navalta, 2011, p. 423). In a more recent discussion of neurodevelopment, Andersen et al. further stipulated that the “adult system accommodates the drug only temporarily” whereas the “drug assimilates into the juvenile brain by producing permanent alteration of the system” so that the “immature brain reprograms its developmental trajectory as if the drug was part of its local environment.” It is, therefore, theorized by neuroscientists that “chronic exposure to commonly used therapeutic agents during a sensitive period has the potential to either prevent or exacerbate symptoms later in life.” Based on this theoretical framework, Andersen also speculated that future research will focus on development of novel therapeutic agents designed to “challenge deficit states and reprogram development rather than attempt to merely treat them” (Andersen and Navalta, 2004, p. 11-12).

A review of neuroimaging studies examined the effects of psychotherapeutic interventions in children and adults (Singh and Chang, 2012). Authors evaluated studies reporting on neuroimaging applications, e.g., structural magnetic resonance imaging (MRI), in selected child psychiatric diagnoses, e.g., ADHD, ASD, depressive disorders. Some of the findings are presented below (Singh and Chang, 2012).

- A study demonstrated that a single dose of a psychostimulant normalizes levels of brain activity in performance monitoring areas of dorsomedial and left ventrolateral prefrontal cortices, thalamus, cingulate, and parietal regions in youth with ADHD;
- No direct effects on white matter microstructure were found from medications in youth and young adults with high-functioning autism although improved structural integrity in the uncinate fasciculus was found in low functioning young adults with autism who received cognitive and behavioral therapies;
- In youth with bipolar disorder (BP), studies have shown that the degree of amygdala functional connectivity predicted medication response suggesting that increased functional integration of the amygdala within the frontolimbic network may be a biomarker of broad responsiveness to mood stabilizers in BP (Singh and Chang, p. 759);
- Studies have demonstrated differential neural effects between two medications, i.e., risperidone and divalproex. These two medications show different patterns of neural activity in youth with BP during emotion process, response inhibition, and working memory tasks. Authors indicated, “Studies illustrate that psychotropic medication effects on the brain may be task dependent as well as specific for different types of medications” (Singh and Chang, p. 759).
- Studies discussing how lithium and other mood stabilizers exert their therapeutic effect are consistent with effect of lithium on brain regional volume. Authors noted that studies suggest that “medications appear to consistently have a normalizing effect on brain function and on some brain volumes in youth with BD” (Singh and Chang, p. 761).

- There is a paucity of studies examining the impact of treatment of depression on the brain in youth. One study, limited by lack of depressed youth exposed to placebo, found that fluoxetine treatment seemed to decrease activations in the amygdala, orbitofrontal cortex, and subgenual ACC bilaterally, normalizing brain activation in these areas.
- Authors reported results of a case report providing “support for a reversible glutamatergically mediated dysfunction of the caudate nucleus in OCD that may serve as a marker for pathophysiology and treatment response” (Singh and Chang, p. 762).
- Authors reviewed studies suggesting that treatment with antipsychotics in youth with schizophrenia tend to normalize brain structure. They further emphasized the current lack of knowledge related to antipsychotic effects on brain function, connectivity, and white matter of youth with schizophrenia.
- Authors summarized that understanding potential mechanisms of action of effective treatment for a range of psychiatric disorders in children and adolescents has advanced due to neuroimaging studies. “The good news is that, taken together, intervention appears to have a normalizing effect on brain structure and function in youth suffering from psychopathology” and “are correlated with symptom improvement” (Singh and Chang, p. 763).
- While authors reviewed studies that reported null effect or benefits of treatment rather than long-term risks of interventions in the treatment of children and adolescents with mental disorders, they noted the importance of studying adverse brain effects of interventions with neuroimaging.

## Conclusion

The increase in dissemination of pediatric practice parameters and the considerable progress made in implementation of pediatric psychopharmacological clinical trials may help to promote prescribing practices that are safe and of high quality for children and adolescents with mental health disorders in the US today (Correll and Dratochvil, 2011). However, the challenge of ensuring that children and adolescents receive evidence-based mental health treatment requires a multi-pronged approach where children and families access and accept treatment, providers gain the necessary skills/knowledge, and organizations and funding policies align to support them (Allen and Jensen, 2008). The appropriate use of psychotropic medication is important for all children, including those living in family homes, foster care, and other settings. The American Academy of Child and Adolescent Psychiatry (AACAP) notes recent concerning trends in the prescription of psychotropic medications: increased use, especially for youth in foster care, potential adverse effects, and cost effects. They recommend that the use of psychotropic medication for children and adolescents should be provided in a holistic way and involve “a commitment to the biopsychosocial perspective, trauma-informed care principles, and system-of-care values and principles” (AACAP, 2015). “Care that is individualized, family-driven, and youth-guided, with recognition that collaborating with children and families is both an ethical and a pragmatic imperative” is emphasized by the AACAP (AACAP, p. 1).

The AACAP indicates that evidence shows that prescriptions of psychotropic medications to youth have been increasing over the past 25 years. They note that antipsychotics were the fastest growing class of psychotropic medication among young people from 2003 to 2010, and the increase was likely due to increased use for aggression. They also reported that 85% of the use of second generation antipsychotic (SGA) medications was concurrent with use of other psychotropic medication classes, and that this occurred more among youth who were Medicaid-eligible, without comorbid ADHD or intellectual disability, than in foster care children. The AACAP stated that this pattern represents “a changing trend in prescribing practice that increasingly favors concurrent SGA use in less-impaired youth” (AACAP, p. 12).

The AACAP discusses reasons for the concern about medication prescribing for youth in foster care: vulnerable population; emotional/behavioral problems; lack of safety net; and youth being subject to inappropriate prescribing practices. While noting the need to understand and monitor current prescribing in this group, e.g.,

prescriptions of five or more concurrent psychotropic medications, high doses, and prescriptions even for infants, the AACAP acknowledged the greater exposure to traumatic experiences of foster children as well as the difficulties in coordinating their medication care.

The AACAP indicates the frequent absence of effective psychosocial interventions, including psychotherapy, which is often not combined with psychopharmacological treatment in the treatment of children with concomitant psychosocial problems. The AACAP indicates that psychotropic medication should not be the sole intervention for youth with complex mental needs where evidence-based psychosocial interventions, e.g., Trauma-Focused Cognitive Behavioral Therapy, Child-Parent Psychotherapy, Alternatives for Families Cognitive Behavior Therapy, and Parent Child Interaction Therapy, are also needed. The AACAP states, “The prescriber who does not appreciate the need for combined psychosocial and psychopharmacological treatment for children with concomitant psychosocial problems, may unnecessarily expose the child to increasingly complex pharmacological treatment strategies” (AACAP, 2015). The AACAP notes children in Medicaid receiving psychotropic medications often do not receive any psychotherapeutic behavioral health services. Of foster care youth who might have benefited from evidence-based psychosocial therapy, the AACAP noted that only about one-fifth receive “partial treatment” (AACAP, 2015).

Since most of mental health treatment is currently provided in primary care practices, there is a need for primary care clinicians and behavioral health specialists to forge new collaborative relationships that enhance the delivery of evidence-based care to affected children and their families. Well-designed pilot projects where primary care providers and child psychiatrists have used consultation, collaboration and comanagement employing telephonic, video conferencing and on-site educational case reviews/training sessions have been lauded as model programs. Professional and consumer advocacy groups along with managed care organizations have urged state governments and healthcare systems to consider them as viable alternative approaches (Pidano and Honigfeld, 2012). The AACAP recommends oversight and monitoring practices that promote collaboration among state and local agencies, managed care organizations, and professionals, with child and adolescent psychiatrists offering support, leadership and expertise (AACAP, 2015). They recommend that for children in multiple child-serving systems, collaboration among all professionals is important.

Psychotropic medication should be prescribed according to existing standards of practice, with monitoring and oversight. The AACAP has highlighted areas of concern, e.g., the greater use of psychotropic medication in foster care compared to other youth in Medicaid; and the increased rates of use of SGAs alone as well as in combination with other medication classes;

In addition, the quest for more scientifically-validated clinical information on the pharmacological treatment of children and adolescents remains urgent and is of paramount importance. The future direction for pediatric psychopharmacological research must provide a platform to: (1) identify clinical and biological response predictors of treatment; (2) generate precise benefit and risk estimates of treatment in patient subgroups; (3) increase understanding of psychotropic drug exposure on the developing brain; (4) study the moderators, mediators, biomarkers and biosignatures of treatment outcome; and (5) test multi-stage treatment strategies utilizing dynamic/multimodal treatment regimes. This clinical research agenda is necessary to accomplish the ideal goal of increased personalized treatment of our young population (Correll and Dratochvil, 2011). The AACAP cautions, “The research base on treating mental health disorders, while growing, remains limited” (AACAP, p. 27). They advise distinguishing between the absence of an evidence-base in favor of a specific practice and the evidence of ineffectiveness of that practice, and note that future research may validate some practices that currently lack evidence (AACAP, 2015).

**Note:** The following Medication Charts are intended to provide general information on dosing, clinical indications, ages approved for usage, specific drug warnings/precautions, typical side effects, teratogenic risks and appropriate patient monitoring parameters.

# Appendix

# At-A-Glance: Psychotropic Drug Information for Children and Adolescents

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Combination Antipsychotic/Antidepressant</b>			
Symbyax <i>fluoxetine &amp; olanzapine</i>	Bipolar depression: 10 and older	3mg/25 mg–12mg/50 mg daily	<p><b>Black Box Warnings:</b> 1) Usage increased the risk of suicidal thinking and behaviors in children and adolescents with major depressive disorder and other psychiatric disorders. 2) Increased mortality in elderly patients with dementia-related psychosis.</p> <p><b>Warnings and precautions:</b> 1) Avoid abrupt withdrawal. 2) Lower starting doses recommended for those with hepatic impairment, potential for slowed metabolism, and those predisposed to hypotensive reactions.</p> <p><b>Pregnancy:</b> No adequate or well controlled studies in pregnant women.</p> <p><b>Lactation:</b> Both fluoxetine and olanzapine are excreted in human breast milk. Studies of fluoxetine have shown adverse effects in breast fed infants such as crying, sleep disturbances, vomiting, and watery stools. It is recommended that women not breastfeed while taking Symbyax.</p>
<b>Antipsychotic Medications</b>			
<p><b>Black Box Warning for all atypical /second generation antipsychotics (SGA):</b> Increased mortality in elderly patients with dementia-related psychosis</p> <p><b>*Precautions which apply to all atypical or second generation antipsychotics (SGA):</b> Neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia, diabetes, weight gain, akathisia, and dyslipidemia. As such, patients on these drugs should have their weight, blood pressure, glucose, and lipids checked before starting these medications and rechecked at 12 weeks, one year, and at least once annually after that.</p> <p><b>†Precautions which apply to all typical or first generation antipsychotics (FGA):</b> Extrapyramidal symptom, tardive dyskinesia</p> <p><b>Precautions which apply to all antipsychotics:</b> neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms</p>			
Abilify <i>aripiprazole* (SGA)</i>	<p>Irritability associated with autistic disorder: 6 and older</p> <p>Tourette’s Disorder: 6 and older</p> <p>Bipolar I disorder, manic or mixed episodes, monotherapy or as an adjunct to lithium: 10 and older</p> <p>Schizophrenia: 13 and older</p>	<p>2–15 mg daily (irritability with autistic disorder)</p> <p>&lt; 50 kg: 2–10 mg daily</p> <p>&gt; 50 Kg: 2–20 mg daily (Tourette’s)</p> <p>2–30 mg daily (Bipolar I, manic or mixed, monotherapy or adjunct to lithium)</p> <p>2–30 mg daily (schizophrenia)</p>	<p><b>Additional Black Box Warning:</b> Increased risk of suicidal thinking and behavior in short-term studies in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors.</p> <p><b>Warnings and precautions:</b> 1) May cause extrapyramidal disorder, somnolence, tremor, fatigue, nausea, akathisia, blurred vision, excessive saliva, sedation, drooling, decreased appetite, lethargy, fever, headache, increased appetite, nasopharyngitis, and dizziness. 2) Patients can experience intense urges for gambling and other compulsive behaviors (shopping, eating, sexual urges, etc. 3) Abilify Maintena and Aristada, long acting injectable versions of this product, are not approved in pediatric populations.</p> <p><b>Pregnancy:</b> No adequate or well controlled studies in pregnant women. In animal studies, aripiprazole demonstrated developmental toxicity, included possible teratogenic effects.</p> <p><b>Lactation:</b> Aripiprazole is excreted in human breast milk.</p>



Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Antipsychotic Medications</b> <i>continued</i>			
Saphris <i>asenapine*</i> (SGA)	Bipolar mania: 10–17	2.5–10 mg twice daily	<p><i>Warnings and precautions:</i> 1) Can cause QT prolongation, seizures, somnolence, dizziness, nausea, increased appetite, weight gain, fatigue, metallic taste in mouth, and oral tingling. 2) Contraindicated in those with severe hepatic impairment. 3) Efficacy of asenapine was NOT demonstrated in clinical trials of adolescents aged 12-17 with schizophrenia. 4) Asenapine is a sublingual tablet. It should not be swallowed, but should be placed under the tongue and left to dissolve completely. The tablet will dissolve in saliva within seconds. Eating and drinking should be avoided for 10 minutes after administration. 5) Available in black cherry flavor.</p> <p><i>Pregnancy:</i> No adequate or well controlled studies in pregnant women.</p> <p><i>Lactation:</i> It is not known if asenapine is excreted in human breast milk. It is excreted in the milk of rats during lactation.</p>
Rexulti <i>brexpiprazole</i> (SGA)	18 and older	N/A	<p><i>Additional Black Box Warnings:</i> 1) Antidepressants increase the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behaviors. 2) Safety and effectiveness of REXULTI have not been established in pediatric patients.</p> <p><i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. No adverse developmental or teratogenic effects were seen in animal studies.</p> <p><i>Lactation:</i> It is not known if brexpiprazole and its metabolites are excreted in human breast milk. It is excreted in</p>
Vraylar <i>cariprazine</i> (SGA)	18 and older	N/A	<p><i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. No teratogenic effects were seen in animal studies but there were reports of malformations and developmental toxicities in rat pups.</p> <p><i>Lactation:</i> It is not known if cariprazine is excreted in human breast milk. It is excreted in the milk of rats during lactation.</p>

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Antipsychotic Medications</b> <i>continued</i>			
<p>Thorazine <i>chlorpromazine†</i> (FGA)</p>	<p>Severe Behavioral Problems marked by combativeness and/or explosive hyperexcitable behavior and short term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following symptoms (impulsivity, difficulty sustaining attention, aggressivity, mood lability, and poor frustration tolerance: 6 mos and older Nausea and Vomiting: 6 mos and older Presurgical Apprehension: 6 months and older</p>	<p>Outpatients: 0.25 mg/lb body weight every 4–6 hours as needed Hospitalized patients: start with low doses and increase gradually. In severe behavior disorders, higher dosages may be necessary; 50–100 mg daily. 200 mg daily in older children. (severe behavioral problems **There is little evidence that behavior improvement in severely disturbed mentally retarded patients is further enhanced by doses beyond 500 mg per day** (Severe behavioral problems) 0.25 mg/lb body weight (adjust dosage and frequency based on severity of symptoms and response of the patient) (Nausea and vomiting) 0.25mg/lb 2–3 hours before operation (presurgical apprehension)</p>	<p><i>Warnings and precautions:</i> 1) May alter cardiac conduction and cause sedation, Neuroleptic Malignant Syndrome, and weight gain. 2) Use caution with renal disease, seizure disorders, respiratory disease, and in acute illness. 3) Should generally not be used in pediatric patients under 6 months of age except where potentially lifesaving. <i>Pregnancy:</i> Safety for the use of chlorpromazine during pregnancy has not been established. Reproductive studies in rats have demonstrated potential for embryotoxicity, increased neonatal mortality, and decreased performance in offspring. The possibility of permanent neurological damage cannot be excluded. <i>Lactation:</i> Chlorpromazine is excreted in human breast milk.</p>
<p>Clozaril <i>clozapine*</i> (SGA)</p>	<p>18 and older</p>	<p>N/A</p>	<p><i>Black Box Warnings:</i> 1) Agranulocytosis 2) Seizures 3) Myocarditis and cardiomyopathy 4) Adverse cardiovascular and respiratory effects. <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. Animal studies revealed no evidence of impaired fertility or harm to the fetus. <i>Lactation:</i> Clozapine is present in human breast milk.</p>
<p>Haldol <i>haloperidol†</i> (FGA)</p>	<p>Schizophrenia: 3 and older Tourette’s Syndrome, and Disruptive Behavior Disorder and ADHD: 3 and older</p>	<p>0.05 -0.15 mg/kg/day (schizophrenia) 0.05 – 0.075 mg/kg/day (Tourette’s and ADHD)</p>	<p><i>Warnings and precautions:</i> 1) May cause sedation, orthostatic hypotension, photosensitivity, constipation, dry mouth, and prolactin elevation. 2) Haldol decanoate, the long acting injectable version of this product, is not approved in pediatrics. <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. Animal studies show haloperidol may harm fetus. <i>Lactation:</i> Infants should not be nursed while on haloperidol</p>

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Antipsychotic Medications</b> <i>continued</i>			
Fanapt <i>iloperidone*</i> (SGA)	18 and older	N/A	<i>Warnings and precautions:</i> 1) May cause prolonged QTc interval and priapism. 2) Not recommended for patients with severe liver impairment  <i>Pregnancy:</i> The limited available data in pregnant women is not sufficient to inform a drug associated risk for major defects and miscarriage.  <i>Lactation:</i> It is not known if iloperidone and its metabolites are excreted in human milk. It is excreted in the milk of rats during lactation.
Loxitane <i>loxapine†</i> (FGA)	18 and older	N/A	<i>Warnings and precautions:</i> 1) Should be used in extreme caution in patients with a history of convulsive disorders since it lowers seizure threshold. 2) Use in caution in those with cardiovascular disease.  <i>Pregnancy:</i> Safe use in pregnancy has not been established.  <i>Lactation:</i> The extent of excretion in human milk is not known, however, loxapine and its metabolites have been shown to be transported into the milk of lactating dogs. Administration to nursing women should be avoided if clinically possible.
Adasuve <i>loxapine†</i> (FGA)	18 and older	N/A	<i>Additional Black Box Warning:</i> Can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer Adasuve only in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm  <i>Warnings and precautions:</i> 1) Adasuve is an inhaled form of loxapine. 2) Is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called Adasuve REMS  <i>Pregnancy:</i> Based on animal data, may cause fetal harm.  <i>Lactation:</i> It is not known whether loxapine is present in human breast milk. Loxapine and its metabolites are present in the breast milk of lactating dogs. Discontinue drug or nursing, taking into consideration importance of drug to mother.
Latuda <i>lurasidone</i> (SGA)	Schizophrenia: 13 and older	40–80 mg daily	<i>Additional Black Box Warnings:</i> Increased risk of suicidal thinking and behavior in short-term studies in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors.  <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. No adverse developmental or teratogenic effects were seen in animal studies.  <i>Lactation:</i> It is not known if lurasidone and its metabolites are excreted in human breast milk. It is excreted in the milk of rats during lactation.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Antipsychotic Medications</b> <i>continued</i>			
Moban <i>molindone† (FGA)</i>	Schizophrenia: 12 and older	15 mg–225 mg daily depending on the severity of the disorder and response to treatment	<i>Warnings and precautions:</i> Drowsiness is the most frequently occurring adverse effect. <i>Pregnancy:</i> Animal reproductive studies have not demonstrated a teratogenic potential. The benefits must be weighed against the unknown risks to the fetus if used in pregnant patients. <i>Lactation:</i> It is not known if molindone is excreted in human breast milk.
Zyprexa <i>olanzapine* (SGA)</i>	Schizophrenia and Bipolar I Disorder, mania or mixed episodes: 13 and older	2.5–20 mg daily	<i>Warnings and precautions:</i> 1) May cause sedation, increased appetite, weight gain, dizziness, abdominal pain, fatigue, dry mouth, and headache. 2) Zyprexa Relprev, the long acting injectable formulation, is not approved in pediatrics. <i>Pregnancy:</i> No adequate and well-controlled studies in pregnant women. <i>Lactation:</i> Olanzapine is excreted in human breast milk.
Invega <i>paliperidone* (SGA)</i>	Schizophrenia: 12 and older	< 51kg: 3–6 mg daily ≥ 51kg: 3–12 mg daily	<i>Warnings and precautions:</i> 1) May cause somnolence, akathisia, tremor, dystonia, cogwheel rigidity, anxiety, weight gain, and tachycardia. 2) Use can cause an increase in the QT interval. 3) Invega Sustenna and Invega Trinza, long acting injectable formulations, are not approved in pediatrics. <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. In animal reproduction studies, there were no increases in fetal abnormalities. <i>Lactation:</i> Paliperidone is excreted in human breast milk.
Trilafon <i>perphenazine† (FGA)</i>	Schizophrenia: 12 and older	Adult dosages below. See additional information note in the next box. Oral: 2–64 mg daily (12–24 mg is average daily dose) Injection: 5 mg per dose. Injection can be repeated every 6 hours not to exceed 15 mg in ambulatory patients or 30 mg in hospitalized patients per day	<i>Warnings and precautions:</i> 1) May cause dystonia, Neuroleptic Malignant Syndrome, orthostatic hypotension, weight gain, endocrine changes and alterations in cardiac condition. 2) According to the label, pediatric dosages have not been established but they recommended that Pediatric patients over 12 years may receive the lowest limit of adult dosage. <i>Pregnancy:</i> Safe use in pregnancy has not been established. <i>Lactation:</i> Safe use during lactation has not been established.
Orap <i>pimozide† (FGA)</i>	Tourette’s Disorder: 12 and older	≥ 12 yrs: 0.05 mg/kg–0.2 mg/kg; not to exceed 10 mg daily	<i>Warnings and precautions:</i> 1) May cause dyskinesias, dry mouth, constipation, prolactin elevation, and prolonged QTc interval. 2) Avoid abrupt withdrawal. 3) A small, open label study (36 children) in children ages 2- 12 demonstrated pimozide has a similar safety profile in this age group as in older patients and there were no safety findings that would preclude its use in this age group. <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. <i>Lactation:</i> It is not known whether pimozide is excreted in human breast milk.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Antipsychotic Medications</b> <i>continued</i>			
Seroquel <i>quetiapine*</i> (SGA)	Bipolar I Disorder: 10 and older Schizophrenia: 13 and older	25–600 mg daily 25–800 mg daily	<i>Warnings and precautions:</i> 1) May cause dyskinesias, dry mouth, constipation, prolactin elevation, and prolonged QTc interval. 2) Avoid abrupt withdrawal. 3) A small, open label study (36 children) in children ages 2- 12 demonstrated pimoizide has a similar safety profile in this age group as in older patients and there were no safety findings that would preclude its use in this age group.  <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women.  <i>Lactation:</i> It is not known whether pimoizide is excreted in human breast milk.
Seroquel XR <i>quetiapine*</i> (SGA)	Bipolar I Disorder: 10 and older Schizophrenia: 13 and older	50–600 mg daily 50–800 mg daily	<i>Additional Black Box Warning:</i> Increased risk of suicidal thoughts and behaviors in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors.  <i>Warnings and precautions:</i> May cause somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, dry mouth, tachycardia, and weight gain.  <i>Pregnancy:</i> Limited human data. Based on animal data, may cause fetal harm.  <i>Lactation:</i> Quetiapine is excreted in human breast milk.
Risperdal <i>risperidone*</i> (SGA)	Irritability associated with autistic disorder: 5 and older Bipolar mania: 10 and older Schizophrenia: 13 and older	<20 kg: 0.25–3 mg daily ≥20 kg: 0.5–3 mg daily 0.5–6 mg daily 0.5–6 mg daily	<i>Warnings and precautions:</i> 1) Risperdal Consta, the long acting injectable formulation, is not approved in pediatrics. 2) Doses above 2.5 mg daily in bipolar mania and 3 mg daily in schizophrenia provided no additional clinical benefit in studies.  <i>Pregnancy:</i> No adequate and well controlled studies in pregnant women. Based on animal data, may cause fetal harm.  <i>Lactation:</i> Risperidone and its metabolite are present in human breast milk.
Mellaril <i>thioridazine†</i> (FGA)	Treatment Refractory Schizophrenia: (age not specified)	0.5–3mg/kg/day	<i>Additional Black Box Warning:</i> Dose-related prolongation of QTc interval may cause torsade de pointes-type arrhythmias and sudden death. Use restricted to schizophrenia resistant to standard antipsychotic drugs.  <i>Warnings and precautions:</i> FDA label does not include a specific age. It states medication can be used in pediatric patients with schizophrenia who are unresponsive to other agents.  <i>Pregnancy:</i> No teratogenic effects reported in product labeling.  <i>Lactation:</i> It is not known whether thioridazine is excreted in human breast milk.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Antipsychotic Medications</b> <i>continued</i>			
Navane <i>thiothixene†(FGA)</i>	Schizophrenia: 12 and older	6–60 mg daily	<i>Warnings and precautions:</i> May cause CNS collapse, CNS depression, blood dyscrasias. <i>Pregnancy:</i> Safe use of thiothixene during pregnancy has not been established. <i>Lactation:</i> It is not whether thiothixene is excreted in human breast milk.
Stelazine <i>trifluoperazine†(FGA)</i>	Behavioral Disorders: no age specified Psychosis: 6 and older	1–2 mg daily depending on the size of the child 1–15 mg daily (some older children with severe symptoms may require, and be able to tolerate, higher dosages)	<i>Warnings and precautions:</i> May cause CNS collapse, CNS depression, blood dyscrasias, bone marrow depression, and hepatic impairment. <i>Pregnancy:</i> studies in pregnant women showed no casual relationship between the drug and congenital malformations. <i>Lactation:</i> There is evidence that trifluoperazine is excreted in the milk of nursing mothers.
Geodon <i>ziprasidone* (SGA)</i>	18 and older	N/A	<i>Warnings and precautions:</i> 1) Doses should be administered with food. 2) Use can cause prolonged QTc interval. <i>Pregnancy:</i> No adequate and well-controlled studies in pregnant women. In animal studies, ziprasidone demonstrated developmental toxicity, including fetal structural abnormalities and possible teratogenic effects at doses similar to human therapeutic doses. <i>Lactation:</i> It is not known whether ziprasidone or its metabolites are excreted in human breast milk. It is recommended that women receiving ziprasidone should not breastfeed.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Antidepressant Medications</b> (also used for anxiety disorders)			
<p>⚠ ∞ <b>Black Box Warning which applies to all antidepressants:</b> Increased risk of suicidal thinking and behaviors in children, adolescents, and young adults (18–24) with major depressive disorder and other psychiatric disorders. Monitor for worsening and emergence of suicidal thoughts and behaviors.</p> <p>‡ Tricyclic antidepressants (TCAs) are not the drugs of choice for pediatric patients with depression; there is lack of high-quality data to support efficacy and safety. <b>Monitoring of cardiac function is wise when TCAs are used in children.</b></p> <p>⚠ ∞ Precautions which apply to all Selective Serotonin-Reuptake Inhibitors (SSRI) and all Serotonin and Norepinephrine Re-uptake Inhibitors (SNRI) antidepressants: Activation of mania/hypomania, discontinuation syndrome, increased risk of bleeding and use in combination with Monoamine oxidase inhibitors (MAOIs).</p> <p>⚠ ∞ ≠ Precautions which apply to all SNRIs: Use in combination with MAOIs, activation of mania/hypomania, Discontinuation syndrome, increased risk of bleeding.</p> <p><i>General precautions for MAOIs:</i> This class is usually reserved for patients that have failed other agents because of the strict dietary restrictions and side effects. Patients must avoid foods that are high in tyramine and avoid alcohol. This medication should not be used if another MAOI has been previously prescribed. Serious, life-threatening side effects can occur if isocarboxazid is consumed before another MAOI has cleared from the body.</p> <p><i>Pregnancy effects for SSRIs/SNRIs:</i> Babies exposed to SSRIs and SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Other clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying.</p>			
Elavil <i>amitriptyline</i> ‡ (tricyclic [TCA])	18 and older	N/A	<p><i>Warnings and precautions:</i> According to the label, the safety and efficacy of amitriptyline in pediatric patients has not been established. It is recommended that this drug not be used in patients under 12 years of age due to lack of experience with the use of this drug in pediatric patients.</p> <p><i>Pregnancy:</i> Amitriptyline has been shown to cross the placenta. There have been a few reports of adverse events, including CNS effects, limb deformities, or developmental delay in infants whose mothers took amitriptyline in pregnancy.</p> <p><i>Lactation:</i> Amitriptyline is excreted into breast milk. Because of the potential for serious adverse reactions in nursing infants from amitriptyline, a decision should be made whether to discontinue nursing or discontinue the drug.</p>
Asendin <i>amoxapine</i> ‡ (TCA)	18 and older	N/A	<p><i>Warnings and precautions:</i> Most common adverse events are drowsiness, dry mouth, constipation, and blurred vision.</p> <p><i>Pregnancy:</i> No teratogenic effects were observed in mice, rat, and rabbit studies. Amoxapine should only be used during pregnancy if benefit outweighs risk to fetus.</p> <p><i>Lactation:</i> Amoxapine is excreted in human breast milk. Caution should be exercised when used in nursing women.</p>

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Antidepressant Medications</b> <i>continued</i>			
Wellbutrin, WellbutrinSR, Wellbutrin XL, Zyban  <i>bupropion</i> (aminoketone class)	18 and older	N/A	<p><i>Warnings and precautions:</i> 1) Contraindicated in those with seizure disorders or a current or prior diagnosis of bulimia or anorexia. 2) Can increase blood pressure. 3) Can cause false positive urine test results for amphetamines.</p> <p><i>Pregnancy:</i> Data from international bupropion Pregnancy registry (675 first trimester patients) and a retrospective cohort study using the United Healthcare database (1213 first trimester exposures) did not show an increased risk for malformations. Animal data did not show increased risk of teratogenicity.</p> <p><i>Lactation:</i> Bupropion and its metabolites are excreted in human breast milk.</p>
Celexa  <i>citalopram*</i> (SSRI)	18 and older	N/A	<p><i>Pregnancy:</i> No adequate and well controlled studies in pregnant women . Animal reproduction studies have shown negative consequences on fetal and postnatal development including teratogenic effects when administered at doses greater than human therapeutic doses.</p> <p><i>Lactation:</i> Citalopram is excreted in human breast milk. There have been reports of infants experiencing excessive sedation, decreased feeding, and weight loss in association with breastfeeding. Caution should be exercised and breastfeeding infants should be observed for side effects when given to a nursing woman.</p>
Anafranil  <i>clomipramine‡</i> (TCA)	OCD: 10 and older	25–200 mg daily or 3 mg/kg/day, whichever is less	<p><i>Warnings and precautions:</i> 1) The most commonly observed adverse events are gastrointestinal complaints (including dry mouth, constipation, nausea, dyspepsia, anorexia, tremor, dizziness, and nervousness. 2) Seizure was the most significant risk of clomipramine use in premarket evaluation. 3) Use with caution in patients with a history of seizures or predisposing factors like brain damage.</p> <p><i>Pregnancy:</i> No teratogenic effects were observed in mice and rat studies. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers have taken clomipramine until delivery. Clomipramine should only be used during pregnancy if the benefit outweighs the risk to the fetus.</p> <p><i>Lactation:</i> Clomipramine is excreted in human breast milk.</p>
Pristiq  <i>desvenlafaxine</i> ∞ ¥ (SNRI)	18 and older	N/A	<p><i>Pregnancy:</i> No adequate and well-controlled studies in pregnant women. Based on animal data, desvenlafaxine may cause fetal harm.</p> <p><i>Lactation:</i> Desvenlafaxine is excreted in human breast milk.</p>



Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Antidepressant Medications</b> <i>continued</i>			
Sinequan <i>doxepin</i> ‡ (TCA)	18 and older	N/A	<i>Warnings and precautions:</i> While the safety and effectiveness in the pediatric population have not been established, the product labeling specifically says use of doxepin in children under 12 years of age is not recommended because safe conditions for its use have not been established. Anyone considering the use of doxepin in a child or adolescent must balance the risk versus the benefit.  <i>Pregnancy:</i> Safety in pregnancy has not been established.  <i>Lactation:</i> There have been reports of apnea and drowsiness occurring in nursing mothers taking doxepin.
Cymbalta <i>duloxetine</i> ∞¥ (SNRI)	Generalized Anxiety Disorder (GAD): 7 and older	30–120 mg daily	<i>Pregnancy:</i> No adequate and well controlled studies in pregnant women; Use in pregnancy only if the potential benefit justifies the potential risk to the fetus.  <i>Lactation:</i> Duloxetine is excreted in human breast milk.
Lexapro <i>escitalopram</i> * (SSRI)	Major Depressive Disorder (MDD): 12 and older	10–20 mg daily	<i>Pregnancy:</i> No adequate and well controlled studies in pregnant women; Use in pregnancy only if the potential benefit justifies the potential risk to the fetus.  <i>Lactation:</i> Escitalopram is excreted in human breast milk. There have been reports of infants experiencing excessive sedation, decreased feeding, and weight loss in association with breastfeeding. Caution should be exercised and breastfeeding infants should be observed for side effects when escitalopram is given to a nursing woman.
Prozac <i>fluoxetine</i> * (SSRI)	MDD: 8 and older Obsessive compulsive disorder (OCD): 7 and older	10–20 mg daily (MDD) 10–60 mg daily (OCD)	<i>Pregnancy:</i> The effect on labor and delivery in humans is unknown. Prozac does cross the placenta so there is a possibility that it may have adverse effects on the newborn. Prozac should be used in pregnancy only if the potential benefit justifies the potential risks to the fetus.  <i>Lactation:</i> Fluoxetine is excreted in human breast milk. Nursing while taking fluoxetine is not recommended.
Luvox <i>fluvoxamine</i> * (SSRI)	OCD: 8 and older	25–200 mg daily (kids over age 11 may need doses up to 300 mg daily)	<i>Warnings and precautions:</i> 1) Luvox CR is not indicated in children/adolescents. 2) May cause decreased appetite and weight loss have been observed with pediatric use. Regular monitoring of weight and growth is recommended.  <i>Pregnancy:</i> The effect on labor and delivery in humans is unknown.  <i>Lactation:</i> Fluvoxamine is excreted in human breast milk so the decision of whether to discontinue nursing or discontinue the drug should take into account the potential for serious adverse effects from exposure to fluvoxamine in the nursing infants as well as the potential benefit of therapy to the mother.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Antidepressant Medications</b> <i>continued</i>			
Tofranil <i>imipramine</i> ‡ (TCA)	Bedwetting: 6 and older	Ages 6–11: 25-50 mg daily Ages 12 and older: 25–75 mg daily *Do not exceed 2.5 mg/kg/ day* *Give one hour before bedtime*	<i>Warnings and precautions:</i> 1) The most common adverse effects in children with bedwetting are nervousness, sleep disorders, tiredness, and mild stomach disturbances. The adverse events usually disappear during <i>continued</i> use or when the dosage is decreased. 2) Imipramine should only be used for short term, add on therapy. 3) Tofranil-PM is not indicated in children. It is generally recommended that Tofranil-PM should not be used in children because of the increased potential for acute overdose due to the high unit potency (75, 100, 125, and 150 mg). Anyone considering the use Tofranil-PM (imipramine pamoate) in a child or adolescent must balance the potential risks with the clinical need.  <i>Pregnancy:</i> Should not be used in women who are or might become pregnant as there have been clinical reports of congenital malformations associated with the use of imipramine.  <i>Lactation:</i> Likely to be excreted in human breast milk.
Marplan <i>isocarboxazid</i> (MAOI)	18 and older	N/A	<i>Warnings and precautions:</i> 1) The safety and effectiveness in pediatric populations has not been demonstrated but the product labeling specifically says marplan is not recommended for use in patients under 16 years of age. 2) Because of adverse reactions and numerous drug interactions, marplan is considered a second line agent in those who have failed other agents.  <i>Pregnancy:</i> Safety in pregnancy has not been established.  <i>Lactation:</i> Levels of excretion into breast milk and effects on nursing infants is unknown.
Fetzima <i>levomilnacipran</i> (SNRI)	18 and older	N/A	<i>Pregnancy:</i> Safety in pregnancy has not been established.  <i>Lactation:</i> It is not known if levomilnacipran is excreted in human breast milk. Studies have shown that it is present in the milk of lactating rats.
Ludiomil <i>maprotiline</i> ‡ (TCA)	18 and older	N/A	<i>Pregnancy:</i> Safety in pregnancy has not been established.  <i>Lactation:</i> Maprotiline is excreted in human breast milk. Caution should be exercised when given to a nursing mother.
Remeron <i>mirtazapine</i> (tetracyclic)	18 and older	N/A	<i>Warnings and precautions:</i> 1) Two trials in 258 pediatric patients with depression were conducted by the manufacturer and the data was not sufficient to support a claim for use. 2) Do not take if an MAOI was used within the past 14 days.  <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. There were no teratogenic effects seen in animal studies.  <i>Lactation:</i> Mirtazapine may be excreted into human breast milk so caution should be exercised when administered to nursing women.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Antidepressant Medications</b> <i>continued</i>			
Pamelor <i>nortriptyline</i> ‡ (TCA)	18 and older	N/A	<i>Warnings and precautions:</i> Safety and effectiveness in the pediatric population has not been established. However, the package labeling did provide dosing for adolescents: 30-50 mg/day (no specific age was given for “adolescent”). <i>Pregnancy:</i> Safe use during pregnancy has not been established. Animal studies have yielded inconclusive results. <i>Lactation:</i> Safe use during lactation has not been established. Animal studies have yielded inconclusive results.
Paxil, Paxil CR <i>paroxetine</i> * (SSRI)	18 and older	N/A	<i>Warnings and precautions:</i> 1) Three placebo controlled trials in 752 patients with depression were conducted with paroxetine and the data was not sufficient to support a claim for use in pediatric patients. 2) May cause nausea, somnolence, sweating, tremor, abnormal physical weakness or lack of energy, dry mouth, insomnia, sexual dysfunction, constipation, diarrhea, and decreased appetite. <i>Pregnancy:</i> Pregnancy Category D as a result of scientific evidence of positive teratogenic effects, particularly cardiovascular malformations. Paroxetine should be avoided in pregnancy if possible. <i>Lactation:</i> Paroxetine is excreted in human breast milk.
Nardil <i>phenelzine</i> (MAOI)	18 and older	N/A	<i>Pregnancy:</i> Safety in pregnancy has not been established. <i>Lactation:</i> Safety in lactation has not been established.
Vivactil <i>protriptyline</i> ‡ (TCA)	18 and older	N/A	<i>Warnings and precautions:</i> Safety and effectiveness in the pediatric population has not been established. However, the package labeling does provide dosing guidelines for adolescents: 5 mg three times daily, increase gradually if necessary (no specific age was given for “adolescent” and maximum doses were not given). <i>Pregnancy:</i> Safety in pregnancy has not been established. <i>Lactation:</i> Safety in lactation has not been established.
Emsam (patch) <i>selegiline</i> (MAO-B inhibitor/ <i>phenethylamine</i> class)	18 and older	N/A	<i>Pregnancy:</i> No adequate and well-controlled studies in pregnant women. <i>Lactation:</i> It is not known if selegiline is excreted in human breast milk. Studies have shown that it is present in the milk of lactating rats.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Antidepressant Medications</b> <i>continued</i>			
Zoloft <i>sertraline*</i> (SSRI)	OCD: 6 and older	25–200 mg daily	<i>Warnings and precautions:</i> 1) Solution contains 12% alcohol. 2) Studies in depression were not sufficient to support an indication for pediatric use.  <i>Pregnancy:</i> Overall, available published studies suggest no difference in major birth defect risk. No teratogenicity was observed in animal studies.  <i>Lactation:</i> Sertraline is excreted in human breast milk. In a published pooled analysis of 53 mother infant pairs, exclusively human milk fed, showed no adverse reactions in the breastfed infants.
Parnate <i>tranylcypromine</i> (MAOI)	18 and older	N/A	<i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. Animal reproductive studies show that tranylcypromine passes through the placental barrier to the fetus of rats.  <i>Lactation:</i> Tranylcypromine is excreted in human breast milk.
Desyrel, Oleptro <i>trazodone</i> (serotonin antagonist and reuptake inhibitor [SARI] class)	18 and older	N/A	<i>Warnings and precautions:</i> 1) Should not be used within 14 days of MAOI treatment. 2) Monitor for emergence of mania/hypomania. 3) May cause prolongation of the QT/QTc interval, increased risk of bleeding, priapism and possible hyponatremia.  <i>Pregnancy:</i> No adequate and well-controlled studies in pregnant women. Some rat and rabbit studies show adverse effects on the fetus at doses higher than the maximum human dose.  <i>Lactation:</i> Trazodone and its metabolites are found in the milk of lactating rats.
Surmontil <i>trimipramine‡</i> (TCA)	18 and older	N/A	<i>Warnings and precautions:</i> Though safety and effectiveness in the pediatric population has not been established, the FDA labeling provides dosing recommendations for adolescent patients of an initial dose of 50 mg daily with gradual increases up to 100 mg per day (no age range was given for “adolescent”).  <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. Trimipramine has shown evidence of embryotoxicity and/or increased incidence of major anomalies in rats or rabbits with doses beyond those approved in humans.  <i>Lactation:</i> Effects in the nursing infant are unknown.
Effexor, Effexor XR <i>venlafaxine∞</i> (SNRI)	18 and older	N/A	<i>Warnings and precautions:</i> According to the FDA labeling, two placebo-controlled trials in 766 pediatric patients with depression and two placebo controlled trials in 793 pediatric patients with anxiety have been conducted with Effexor XR, and the data were not sufficient to support a claim for use in pediatric patients.  <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. Rat and rabbit studies did not show teratogenicity. Effects on labor and delivery in humans are unknown.  <i>Lactation:</i> Venlafaxine is excreted in human breast milk.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Antidepressant Medications</b> <i>continued</i>			
Viibryd <i>vilazodone (atypical antidepressant)</i>	18 and older	N/A	<i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. There were no teratogenic effects seen when given to pregnant rats or rabbits.  <i>Lactation:</i> No data on the presence of vilazodone in human breast milk, the effects on breastfed infants, or the effects of the drug on milk production. It is present in the milk of lactating rats.
Trintellix <i>Vortioxetine (atypical antidepressant – serotonin modulator)</i>	18 and older	N/A	<i>Warnings and precautions:</i> Product underwent a name change from Brintellix to Trintellix on 5/2/16 to decrease the risk of prescribing and dispensing errors due to name confusion with Brilanta, an antiplatelet medication.  <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. Based on animal data, vortioxetine may cause fetal harm. Vortioxetine caused developmental delays when administered to pregnant rats and rabbits. There were no teratogenic effects seen in rats or rabbits.  <i>Lactation:</i> It is not known whether vortioxetine is excreted in human breast milk. It is present in the milk of lactating rats.
<b>Mood Stabilizing and Anticonvulsant Medications</b>			
Tegretol, Tegretol XR, Carbatrol, Epilex <i>carbamazepine</i>	Seizures: any age	Under 6: 10–35 mg/kg/day Sge 6–12: 20–1000 mg daily Age 13–15: 400–1000 mg daily Age 16 and older: 400–1200 mg daily **Recommended therapeutic serum levels: 4-12 mcg/mL**	<i>Black Box Warning:</i> 1) Stevens-Johnson Syndrome (particularly among Asians) 2) Aplastic anemia 3) Agranulocytosis.  <i>Warnings and precautions:</i> 1) May cause neutropenia and hyponatremia. 2) Induces metabolism of itself and some other drugs. 3) May decrease efficacy of oral contraceptives. 4) Causes teratogenicity. 5) Don't use within 14 days of an MAOI. 6) Tegretol XR does not have dosing recommendations for patients under 6.  <i>Pregnancy:</i> May cause fetal harm when administered to pregnant women. Data suggest that there may be an association with congenital malformations (including spina bifida), congenital anomalies, and development disorders.  <i>Lactation:</i> Carbamazepine and its metabolite are excreted into human breast milk.
Equetro <i>carbamazepine extended release capsules</i>	18 and older	N/A	<i>Black Box Warning:</i> 1) Stevens-Johnson Syndrome (particularly among Asians) 2) Aplastic anemia 3) Agranulocytosis  <i>Pregnancy:</i> May cause fetal harm when administered to pregnant women. Data suggest that there may be an association with congenital malformations (including spina bifida), congenital anomalies, and development disorders.  <i>Lactation:</i> Carbamazepine and its metabolite are excreted into human breast milk.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Mood Stabilizing and Anticonvulsant Medications</b> <i>continued</i>			
Depakote, Depakote ER, Depakote Sprinkles <i>divalproex sodium</i> — Depakene, Stavzar <i>valproic acid</i>	Seizures (monotherapy and adjunctive): 10 and older	10–60 mg/kg/day Recommended therapeutic serum levels: 50–100 mcg/mL	<b>Black Box Warning:</b> 1) Hepatotoxicity 2) Teratogenicity 3) Pancreatitis <b>Warnings and precautions:</b> 1) May cause urea cycle disorders, multi-organ hypersensitivity reaction, thrombocytopenia, withdrawal seizures, suicidal ideation, and polycystic ovaries. 2) Use may decrease the efficacy of birth control pills so alternative contraception should be used. 3) Depakote Sprinkles may be swallowed whole or the contents of the capsule may be sprinkled on soft food. The food should be swallowed and not chewed. <b>Pregnancy:</b> Can cause congenital malformations including neural tube defects and decreased IQ. <b>Lactation:</b> Excreted in human breast milk.
Neurontin <i>gabapentin</i>	Seizures (adjunct): 3 and older	Ages 3–11: 10–50 mg/kg/day Ages 12 and older: 900–2400 mg daily (Doses of 3600 mg/day have also been administered to a small number of patients for short duration and have been well tolerated)	<b>Warnings and precautions:</b> Dosage adjustments necessary for renal impairment or those undergoing hemodialysis. <b>Pregnancy:</b> No adequate or well controlled studies in pregnant women. Based on animal data, may cause fetal harm. <b>Lactation:</b> Gabapentin is excreted in human breast milk.
Lamictal, Lamictal XR <i>lamotrigine</i>	Epilepsy (adjunct): 2 and older Epilepsy (monotherapy): 16 and older	<b>Adjunct dosing:</b> Age 2–12: 0.15–15 mg/kg/day or maximum 300 mg daily (max dose is 400 mg daily if taking conflicting medications) 12 and older: 25 mg every other day – 375 mg daily (max dose is 500 mg daily if taking conflicted medications) **above doses may have to be increased or decreased for those patients taking concomitant valporate, carbamazepine, phenytoin, phenobarbital, or primidone** <b>Monotherapy dosing:</b> 16 and older: 200–500 mg daily	<b>Black Box Warning:</b> Life threatening serious rashes including Stevens-Johnson Syndrome. The rate of serious rash is greater in pediatric patients than in adults. <b>Warnings and precautions:</b> 1) May cause vomiting, infection, fever, accidental injury, diarrhea, abdominal pain, and tremor. Can also cause acute-multi-organ failure, withdrawal seizures, blood dyscrasias, hypersensitivity, and suicidal ideation. 2) Has been reported to cause false positive readings for phencyclidine (PCP) in some urine drug screens. 3) Some estrogen containing contraceptives have been shown to decrease serum concentrations of lamotrigine so dosage adjustments may be necessary. 4) Safety and efficacy for 10-17 year olds with bipolar disorder or 1 to 2 year olds for adjunct therapy for seizures was not established. <b>Pregnancy:</b> No adequate and well controlled studies in pregnant women. In animal studies, lamotrigine was developmentally toxic at doses lower than those administered clinically. <b>Lactation:</b> Lamotrigine is excreted in human breast milk. Apnea, drowsiness, and poor sucking have been reported in milk fed infants exposed to lamotrigine.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Mood Stabilizing and Anticonvulsant Medications</b> <i>continued</i>			
Eskalith, Lithobid  <i>lithium carbonate/ citrate</i>	Bipolar Mania: 12 and older	300–2,400 mg daily  Therapeutic serum levels: 0.6–1.2 mEq/L (toxic concentrations seen at levels greater than 1.5 mEq/L)	<i>Black Box Warning:</i> Toxicity above therapeutic serum levels.  <i>Warnings and precautions:</i> 1) May cause renal function impairment, polyuria, tremor, diarrhea, nausea, and hypothyroid. 2) Patients with significant renal or cardiovascular disease, severe debilitation, dehydration, or sodium depletion are at higher risk of toxicity.  <i>Pregnancy:</i> Lithium may cause fetal harm when administered to a pregnant woman. Data from lithium birth registries suggest an increase in cardiac and other abnormalities. If possible, lithium should be withdrawn for at least the first trimester.  <i>Lactation:</i> Lithium is excreted in human breast milk. It is recommended to try to avoid breastfeeding while on lithium.
Trileptal  <i>oxcarbazepine</i>	Seizures (monotherapy): 4 and older  Seizures (adjunct): 2 and older	Monotherapy: 600–2100 mg daily (initiate at 8–10 mg/kg/day)  Adjunct: 150–1,800 mg daily (8–60 mg/kg/day)  **Max doses are dependent on patient's weight**	<i>Warnings and precautions:</i> 1) May cause hyponatremia and suicidal ideation. 2) May decrease the effectiveness of hormonal contraceptives. 3) Dose adjustments necessary in those with a creatinine clearance less than 30 ml/min.  <i>Pregnancy:</i> No adequate or well controlled clinical studies in pregnant women. Closely related structurally to carbamazepine which is considered to be teratogenic in humans. Animal studies show the potential for harm to the fetus as well.  <i>Lactation:</i> Oxcarbazepine and its active metabolite are excreted in human breast milk.
Topamax, Topamax XR  <i>topiramate</i>	Epilepsy (monotherapy and adjunctive): 2 and older  Migraine: 12 and older	<i>Monotherapy:</i>  10 and older: 25–400 mg daily (for those < 10, there are specific weight based maxes)  <i>Adjunctive:</i>  Age 2–16: 25 mg daily–9 mg/kg/day (Recommended dose: 5–9 mg/kg/day)  17 and older: 25–400 mg daily  25–100 mg daily (migraines)	<i>Warnings and precautions:</i> 1) Because of the bitter taste, tablets should not be broken. 2) Decreases the efficacy of contraceptives and can cause increased breakthrough bleeding.  <i>Pregnancy:</i> Topiramate can cause fetal harm when administered to a pregnant woman. Infants exposed to topiramate have an increased risk of cleft lip and /or palate.  <i>Lactation:</i> Topiramate is excreted in human breast milk. The effects of topiramate exposure on breastfed infants are unknown.
Trokendi XR, Qudexy XR  <i>topiramate</i>	Epilepsy (monotherapy and adjunctive therapy): 6 and older	<i>Monotherapy:</i>  Ages 6–9: 25 mg–400 mg daily  Age 10 and older: 50–400 mg daily  <i>Adjunctive:</i>  25 mg daily–9 mg/kg/day (Recommended dose: 5–9 mg/kg/day)  **Max doses are dependent on the child's weight**	<i>Warnings and precautions:</i> 1) Decreases the efficacy of contraceptives and can cause increased breakthrough bleeding. 2) Capsules have to be swallowed whole and may not be sprinkled on food, crushed or chewed.  <i>Pregnancy:</i> Topiramate can cause fetal harm when administered to a pregnant woman. Infants exposed to topiramate have an increased risk of cleft lip and /or palate.  <i>Lactation:</i> Topiramate is excreted in human breast milk. The effects of topiramate exposure on breastfed infants are unknown.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>Anti-anxiety Medications</b> (Drugs below are <i>benzodiazepines</i> except buspirone)			
<p><i>Classification of buspirone:</i> anxiolytic psychoactive drug of the azapirones chemical class</p> <p><i>Warnings/precautions for all benzodiazepines:</i> 1) Avoid abrupt withdrawal. These agents should be used for a limited time period and discontinuation of these drugs requires tapering. 2) Benzodiazepines should be administered cautiously to patients with renal impairment or renal failure, hepatic disease or hepatic encephalopathy. 3) Liver and renal function should be monitored regularly during prolonged therapy. 4) Associated with serious adverse events when combined with opioids, benzodiazepines, alcohol, or other drugs that depress the central nervous system.</p> <p><i>Warnings in pregnancy/lactation for benzodiazepines:</i> 1) Have been associated with negative outcomes in pregnant women including <i>teratogenicity</i>. Use of benzodiazepines during pregnancy, particularly in the first trimester, generally increases the risk of congenital malformations and decreases viability. 2) Because of the potential for adverse effects in nursing infants, such as sedation, feeding difficulties, breathing difficulties, feeding difficulties, and weight loss, it is generally not recommended to breast feed during use.</p>			
Xanax <i>alprazolam</i>	18 and older	N/A	
Buspar <i>buspirone</i>	Generalize Anxiety Disorder: 6–17 years	7.5 mg–60 mg daily	<i>Lactation:</i> The extent of excretion of buspirone and its metabolites into human milk is not known. Buspirone and its metabolites are excreted in the milk of lactating rats.
Librium <i>chlordiazepoxide</i>	Anxiety: 6 and older	10–30 mg daily	
Klonopin <i>clonazepam</i>	18 and older	N/A	
Tranxene <i>clorazepate</i>	Partial Seizures: 9–12 years	15–60 mg daily	<i>Warnings and precautions:</i> Recommended to monitor blood count and liver function tests.
Valium <i>diazepam</i>	Anxiety: 6 months and older	1 mg to 2.5 mg, 3 or 4 times daily initially; increase gradually as needed and tolerated	<i>Warnings and precautions:</i> According to the manufacturer, oral diazepam tablets are contraindicated in those with severe hepatic disease. In general, all forms of diazepam should be administered cautiously to patients with mild to moderate hepatic disease, cirrhosis, hepatic fibrosis, and acute or chronic hepatitis, because its elimination half-life can be prolonged, possibly resulting in toxicity.
Ativan <i>lorazepam</i>	Anxiety: 12 and older	2–10 mg daily	
Serax <i>oxazepam</i>	18 and older	N/A	
<b>ADHD Medications</b> (Drugs below are stimulants, except atomoxetine, clonidine and guanfacine)			
<p><i>Classification of non-stimulant drugs:</i> (1) atomoxetine is a selective norepinephrine reuptake inhibitor or NRI; (2) clonidine and (3) guanfacine are classified as alpha-2 receptor agonists.</p> <p><i>Black Box Warning for all stimulants:</i> Abuse potential. Risk of sudden death and serious cardiovascular events.</p> <p><i>Warnings/precautions for all stimulants:</i> May cause sudden death in those with pre-existing structural cardiac abnormalities or serious heart problems. May cause hypertension, psychiatric adverse events and possible growth suppression.</p> <p><i>Warnings for all amphetamines:</i> Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. These infants may experience symptoms of withdrawal as demonstrated by dysphoria, agitation, and significant fatigue.</p>			
Evekeo <i>amphetamine sulfate</i>	ADHD: 3 and older Narcolepsy: 6 and older Exogenous obesity: 12 and older	2.5–40 mg daily (ADHD) 5–60 mg daily (Narcolepsy) Up to 30 mg daily (take in divided doses) 30–60 minutes before meals (exogenous obesity)	<i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. Based on animal data, may cause fetal harm. <i>Lactation:</i> Amphetamines are excreted in human breast milk.



Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>ADHD Medications</b> <i>continued</i>			
Adzenys XR <i>amphetamine extended release</i>	ADHD: 6 and older	Ages 6–12: 6.3–18.8 mg daily Ages 13 and older: 6.3–12.5 mg daily	<i>Warnings and precautions:</i> 1) Adzenys XR is the first amphetamine extended release orally disintegrating tablet. 2) Do not substitute for other amphetamine products on a mg/mg basis. <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. Based on animal data, may cause fetal harm. <i>Lactation:</i> Amphetamines are excreted in human breast milk.
Dyanavel XR <i>amphetamine extended release</i>	ADHD: 6 and older	2.5–20 mg daily	<i>Warnings and precautions:</i> 1) Liquid solution that needs to be shaken prior to use. 2) Do not substitute for other amphetamine products on a mg/mg basis <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. Based on animal data, may cause fetal harm. <i>Lactation:</i> Amphetamines are excreted in human breast milk.
Adderall <i>Mixed amphetamine salts</i>	ADHD: 3 and older Narcolepsy: 6 and older	2.5–40 mg daily (ADHD) 5-60 mg daily (Narcolepsy)	<i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. Based on animal data, may cause fetal harm. <i>Lactation:</i> Amphetamines are excreted in human breast milk.
Adderall XR <i>Mixed amphetamine salts extended release</i>	ADHD: 6 and older	Ages 6–12: 10-30 mg daily Ages 13 and older: 10-20 mg daily	<i>Warnings and precautions:</i> Capsule may be opened and sprinkled on soft foods. <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. Based on animal data, may cause fetal harm. <i>Lactation:</i> Amphetamines are excreted in human breast milk.
Strattera <i>atomoxetine</i>	ADHD: 6 and older	Up to 70 kg: 0.5–1.4 mg/ kg (lesser of 1.4 mg/kg or 100 mg) Over 70 kg: 40–100 mg daily	<i>Black Box Warning:</i> Increased risk of suicidal ideation in children or adolescents. <i>Warnings and precautions:</i> 1) Do not open capsule; must be swallowed whole. 2) May cause liver injury, adverse psychiatric events, increase blood pressure and heart rate, and serious cardiovascular events including sudden death, particularly in those with pre-existing structural cardiac abnormalities or serious heart problems. <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. <i>Lactation:</i> It is not known if atomoxetine is excreted in human breast milk. Atomoxetine and / or its metabolites are excreted in the breast milk of rats.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>ADHD Medications</b> <i>continued</i>			
Kapvay <i>clonidine extended release (ER)</i>	ADHD (monotherapy or adjunct to stimulants): 6–17	0.1–0.4 mg daily	<i>Warnings and precautions:</i> 1) Can lower blood pressure and cause sedation. 2) Do not crush, chew, or break tablets before swallowing. 3) Do not administer with high fat meals due to increased exposure. 4) May not see effects until 4-6 weeks. 5) Do not abruptly discontinue to avoid rebound hypertension. 6) Immediate release forms of clonidine (Catapres) are not FDA approved for use in children.  <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women.  <i>Lactation:</i> Clonidine is excreted in human breast milk.
Focalin <i>dexmethylphenidate</i>	ADHD: 6–17	5–20 mg daily	<i>Pregnancy:</i> Limited human data. Based on animal data, may cause fetal harm.  <i>Lactation:</i> It is not known whether dexmethylphenidate is excreted in human breast milk.
Focalin XR <i>dexmethylphenidate extended release</i>	ADHD: 6 and older	5–30 mg daily	<i>Warnings and precautions:</i> 1) Capsule contents can be sprinkled on applesauce and swallowed whole. 2) Capsule should not be crushed, chewed, or divided.  <i>Pregnancy:</i> Limited human data. Based on animal data, may cause fetal harm.  <i>Lactation:</i> It is not known whether dexmethylphenidate is excreted in human breast milk.
Dexedrine, ProCentra Oral Solution, Zenzedi, DextroStat <i>dextroamphetamine</i>	ADHD: 3 and older Narcolepsy: 6 and older	2.5–40 mg daily (ADHD) 5–60 mg daily (narcolepsy)	<i>Warnings and precautions:</i> Extended release spanules can be used once a day when appropriate, tablets need to be given multiple times per day at intervals of 4–6 hours.  <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. Based on animal data, may cause fetal harm.  <i>Lactation:</i> Amphetamines are excreted in human breast milk.
Intuniv <i>guanfacine extended release</i>	ADHD (monotherapy and adjunct to stimulants): 6 and older	Ages 6–12: 1–4 mg daily (lesser of 0.12 mg/kg or 4 mg daily) Ages 13–17: 1–7 mg daily **max dose depends on weight of child**	<i>Warnings and precautions:</i> 1) Sedation, somnolence, and fatigue are common and tend to decline over time. 2) Do not crush, chew or break tablets. 3) Do not administer with high fat meal. 4) Do not discontinue abruptly. 5) Dosage adjustments necessary if used with Strong 3A4 inhibitors or inducers. 6) Immediate release guanfacine/Tenex is only approved for hypertension in patients 12 and older.  <i>Pregnancy:</i> No adequate or well controlled studies in pregnant women.  <i>Lactation:</i> It is not known whether guanfacine is excreted in human breast milk; however it is excreted in rat milk.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>ADHD Medications</b> <i>continued</i>			
Vyvanse <i>lisdexamfetamine dimesylate</i>	ADHD: 6–17	30–70 mg daily	Additional Information: 1) Dosage adjustments needed for renal impairment. 2) Capsules can be opened and mixed in yogurt, water, or orange juice. The contents should be mixed until completely dispersed and the entire mixture should be consumed immediately.  <i>Pregnancy:</i> Limited available data from published literature and postmarketing reports are not sufficient to inform a drug associated risk for birth defects and miscarriage.  <i>Lactation:</i> Amphetamines are present in human breast milk.
Desoxyn <i>methamphetamine</i>	ADHD: 6 and older  Obesity (short term): 12 and older	5–25 mg daily  5 mg thirty minutes before each meal; treatment should not exceed a few weeks.	<i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. Based on animal data, may cause fetal harm.  <i>Lactation:</i> Amphetamines are excreted in human breast milk.
Ritalin, Methylin <i>methylphenidate</i>	ADHD: 6 and older	10–60 mg daily	<i>Warnings and precautions:</i> Methylin is a chewable tablet. It should be taken with at least 8 ounces of water or other fluid to prevent choking.  <i>Pregnancy:</i> There are limited published studies and small case series that report on the use of methylphenidate in pregnant women; however the data are insufficient to inform any drug associated risks.  <i>Lactation:</i> Limited published literature reports that methylphenidate is present in human breast milk.
Methylin ER, Metadate ER, Ritalin SR, Aptensio XR <i>methylphenidate extended release</i>	ADHD: 6 and older	10–60 mg daily	<i>Warnings and precautions:</i> 1) Aptensio XR capsules can be opened and the contents can be sprinkled over a spoonful of applesauce. This mixture should be consumed in its entirety. 2) Ritalin SR tablets must be swallowed whole and never crushed or chewed.  <i>Pregnancy:</i> There are limited published studies and small case series that report on the use of methylphenidate in pregnant women; however the data are insufficient to inform any drug associated risks.  <i>Lactation:</i> Limited published literature reports that methylphenidate is present in human breast milk.

Drug Brand Name / Generic Name	FDA Approved Age/Indication	Pediatric Dosage/ Serum Level when applicable	Black Box Warnings/Warnings and Precautions/ Additional Information
<b>ADHD Medications</b> <i>continued</i>			
Ritalin LA, Metadate CD, QuilliChewER, Quillivant XR  <i>methylphenidate extended release</i>	ADHD: 6 and older	20–60 mg daily	<i>Warnings and precautions:</i> 1) Ritalin LA and Metadate CD capsules can be opened and the contents can be sprinkled over a spoonful of applesauce. This mixture should be consumed in its entirety. 2) QuilliChew ER is the first once daily long lasting methylphenidate chewable tablet. It can be broken in half. 3) Quillivant XR is the first once daily long lasting methylphenidate liquid. It needs to be shaken vigorously for at least 10 seconds before use.  <i>Pregnancy:</i> There are limited published studies and small case series that report on the use of methylphenidate in pregnant women; however the data are insufficient to inform any drug associated risks.  <i>Lactation:</i> Limited published literature reports that methylphenidate is present in human breast milk.
Concerta  <i>methylphenidate long acting</i>	ADHD: 6 and older	Ages 6–12: 18–54 mg daily Ages 13–17: 18–72 mg daily (not to exceed 2mg/ kg/day)	<i>Warnings and precautions:</i> Should be swallowed whole and not chewed or crushed.  <i>Pregnancy:</i> There are limited published studies and small case series that report on the use of methylphenidate in pregnant women; however the data are insufficient to inform any drug associated risks.  <i>Lactation:</i> Limited published literature reports that methylphenidate is present in human breast milk.
Daytrana  <i>methylphenidate patch</i>	ADHD: 6-17	10-30 mg daily	<i>Warnings and precautions:</i> Should be applied to the hip area two hours before an effect is needed and removed nine hours after application (alternate hips).  <i>Pregnancy:</i> There are limited published studies and small case series that report on the use of methylphenidate in pregnant women; however the data are insufficient to inform any drug associated risks.  <i>Lactation:</i> Limited published literature reports that methylphenidate is present in human breast milk.

Sources: (1) *Mental Health Medications*. National Institutes of Mental Health US Department of Health and Human Services National Institutes of Health. [<http://www.nimh.nih.gov/health/publications/mental-health-medications/index.shtml>] December 12, 2012. (2) Vitiello B. *Principles in using psychotropic medication in children and adolescents*. In Rey JM (ed), *IACAPAP e-Textbook of Child and Adolescent Mental Health*. Geneva: International Association for Child and Adolescent Psychiatry and Allied Professions 2012. (3) Schatzberg AF, Cole JO, DeBattista C. (2010) *Manual of Clinical Psychopharmacology*. (7th ed.). Arlington VA: American Psychiatric Publishing, Inc. (4) Epocrates Online [<https://online.epocrates.com/u/1000/Drugs?ICID=search-drugs>] San Mateo CA. December 12, 2012. (5) Texas Department of Family and Protective Services and the University of Texas at Austin College of Pharmacy. *Psychotropic Medication Utilization Parameters for Foster Children*. December 2010. (6) Thioridazine Official FDA information, side effects and usage. [[www.drugs.com/pro/thioridazine.html](http://www.drugs.com/pro/thioridazine.html)] December 12, 2012. (7) *Children's Mental Health. Concerns Remain about Appropriate Services for Children in Medicaid and Foster Care*. GOA Highlights. GAO-13-15, Washington, D.C

# Psychotropic Drugs—Side Effects and Teratogenic Risks (interference with embryo/fetal growth)

Class of Drugs	Typical Side Effects	Possible Teratogenic Risk	Risk Category*
Antipsychotic Medications	<ul style="list-style-type: none"> <li>Akathisia and dystonic reactions are seen in children treated with SGAs but risk of tardive dyskinesia is small compared to FGAs.</li> <li>Weight gain is a significant problem with SGAs. Other side effects: constipation, dry mouth, dizziness.</li> <li>Sedation/cognitive blunting may occur with FGAs and SGAs.</li> <li>Adolescent males at much greater risk for dystonic reactions than adults.</li> <li>Significant drop in neutrophils and increased risk of seizures with clozapine (should be used as treatment of last resort).</li> </ul>	FGAs: Rare anomalies, fetal jaundice, fetal anticholinergic effects at birth.	C
		SGAs: Gestational diabetes, large birthweight.	BC
Antidepressant Medications	<ul style="list-style-type: none"> <li>TCAs: May cause significant slowing of cardiac conduction (PR interval over 0.20 msec, QRS interval over 0.12 msec) may require lowering dose. Cardiac long QT syndrome may be mechanism be responsible for 4 cases of reported sudden death in children. Other effects: Dry mouth, urinary retention, sedation, constipation, weight gain and hypotension.</li> </ul>	TCAs: Fetal tachycardia, fetal withdrawal, fetal anticholinergic effects, urinary retention, bowel obstruction.	D-amitriptyline, Imipramine, nortriptyline C- (other TCAs)/ B- maprotiline
	<ul style="list-style-type: none"> <li>In addition to strict dietary restrictions with MAOIs: Daytime sleepiness, dizziness, lightheadedness, low blood pressure, difficulty urinating, dry mouth, altered sense of taste, nervousness, muscle aches, insomnia and weight gain.</li> </ul>	MAOIs: Rare fetal malformations: rarely used in pregnancy due to hypertension.	C
	<ul style="list-style-type: none"> <li>Safety /side effect profiles of SSRIs are superior to those of TCAs. Other SSRI side effects: insomnia, sedation, appetite changes (up or down), nausea, dry mouth, headache, sexual dysfunction, Treatment- emergent akathisia from SSRIs may be more evident in pediatric depression associated with bipolar disorder and greater suicide risk.</li> </ul>	SSRIs: Perinatal and cardiovascular complications, spontaneous abortions. Potential premature delivery and neonatal persistent pulmonary hypertension (PPHN).	C/D (paroxetine)
	<ul style="list-style-type: none"> <li>Side effects and other concerns with SNRIs: nausea, insomnia, sedation, sexual dysfunction, sweating, hypertension and discontinuation syndrome.</li> </ul>	SNRIs: Potential premature delivery. Clinical outcome data sparse compared to SSRIs or TCAs.	C
	<ul style="list-style-type: none"> <li>Bupropion (aminoketone class) common side effects: headache, agitation, restless insomnia, weight loss, anorexia, sweating, tremor and hypertension.</li> </ul>	Bupropion: Risks unknown, but not recommended over SSRIs in pregnancy.	C

\*Note: Risk Categories: A: controlled studies show no risk to humans. B: No evidence of risk in humans, but adequate human studies may not have been performed. C: Risk cannot be ruled out. D: Positive evidence or risk to humans; risk may be outweighed by potential benefit. X: Contraindicated in pregnancy.

Class of Drugs	Typical Side Effects	Possible Teratogenic Risk	Risk Category*
<b>Mood Stabilizing and Anticonvulsant Medications</b>	<ul style="list-style-type: none"> <li>Lithium common reactions: tremor, polyuria, polydipsia, weight gain, diarrhea, vomiting, drowsiness, cognitive impairment, muscle weakness, impaired coordination, anorexia, nausea, blurred vision, xerostomia, fatigue, alopecia, reversible leukocytosis, acne and edema.</li> </ul>	Lithium: Associated with increase in birth defects including cardiac anomalies (esp. Ebstein's anomaly) and behavioral effects.	D
	<ul style="list-style-type: none"> <li>Valproate: Children younger than 2 yrs. are at greatest risk for hepatotoxicity. Common reactions: headache, nausea/vomiting, loss of muscle strength, somnolence, thrombocytopenia, dyspepsia, dizziness, diarrhea, abdominal pain, tremor.</li> </ul>	Valproate: Neural tube defects (i.e., rate 6-20%); high rates of mental retardation and lower IQ measures	D
	<ul style="list-style-type: none"> <li>Carbamazepine: May cause dizziness, drowsiness, unsteadiness, impaired coordination, nausea/vomiting, blurred vision, nystagmus, rash, confusion.</li> </ul>	Carbamazepine: Neural tube defects, minor anomalies	D
	<ul style="list-style-type: none"> <li>Oxcarbazepine: May cause dizziness, somnolence, diplopia, visual changes, fatigue, headache, nausea, vomiting, and ataxia.</li> </ul>	Oxcarbazepine: Unknown	C
	<ul style="list-style-type: none"> <li>Lamotrigine: Children are at greater risk for rash than adults. May cause nausea, vomiting, dizziness, vertigo, visual disturbance, somnolence, ataxy, pruritus/rash, headache, pharyngitis, rhinitis, diarrhea, fever, loss of muscle strength.</li> </ul>	Lamotrigine: Unknown but there appears to be a high rate of cleft lip and palate (i.e., 4-9/1,000)	C
	<ul style="list-style-type: none"> <li>Gabapentin: May cause dizziness, somnolence, ataxia, fatigue, peripheral edema, nystagmus, nausea, vomiting, and viral infection.</li> </ul>	Gabapentin/pregabalin: Unknown	C
	<ul style="list-style-type: none"> <li>Pregabalin: May cause dizziness, somnolence, xerostomia, peripheral edema, blurred vision, weight gain, abnormal thinking, constipation, impaired coordination, pain, decreased platelets.</li> </ul>		C
<b>Anti-anxiety Medications</b>	<ul style="list-style-type: none"> <li>Benzodiazepines (BZDs): If used for daytime anxiety, can increase activity and produce or aggravate behavior disorders (particularly in ADHD). Drugs cause tolerance and physical/psychological dependence. May cause somnambulism and amnesia. Other side effects include psychomotor retardation, memory impairment, paradoxical disinhibition (i.e., increased excitement, irritability, aggression, hostility and impulsivity), depression and emotional blunting.</li> </ul>	BZDs: "Floppy baby", withdrawal, increased risk of cleft lip or palate. Hypnotic BZDs: Decreased intrauterine growth Buspirone: Unknown	D/X (hypnotic BZDs)
	<ul style="list-style-type: none"> <li>Sedative antihistamines may have some antianxiety or hypnotic ability. Prolonged use of these agents may lead to anticholinergic side effects and cognitive impairment.</li> </ul>		C
	<ul style="list-style-type: none"> <li>Buspirone can cause drowsiness, dizziness, impaired concentration, nausea and headache. Depression, hostility and akathisia, dystonia, tardive dyskinesia and EPS can occur.</li> </ul>		

Sources: (1) Schatzberg AF, Cole JO, DeBattista C. (2010) *Manual of Clinical Psychopharmacology*. (7th ed.). Arlington VA: American Psychiatric Publishing, Inc. (2) Hilt RJ. *Monitoring Psychiatric Medications in Children*. *Pediatric Annals*. April 2012, Volume 41, Issue 4: 157-163. (3) Solchany J. *Psychotropic Medication and Children in Foster Care: Tips for Advocates and Judges*. *Practice and Policy Brief*, American Bar Association Center on Children and the Law. October 2011. (4) FDA Alerts [7/2006]: *Increased Risk of Neonatal Persistent Pulmonary Hypertension*. *Information for Healthcare Professionals: Paroxetine (Marketed as Paxil)*. Accessed website on February 20, 2013 <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm084319.htm> (5) Yonkers KA, Wisner KL, Stewart DE, Oberlander TF, Dell DL, Stotland N, Ramine S, Chaudron L, Lockwood C. *The Management of Depression During Pregnancy: A Report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists*. *Focus*, Winter 2012, Vol. X, No. 1.

# Recommended Clinical Monitoring of Children and Adolescents for Select Psychotropic Drugs

Class of Drugs	Monitoring Recommendation	Frequency Suggestion
<b>Atypical Antipsychotic Medications</b>	<ol style="list-style-type: none"> <li>1. Height and weight</li> <li>2. Labs: fasting blood sugar, fasting triglyceride/cholesterol</li> <li>3. Screen for dyskinesia movements</li> <li>4. Labs: CBC with differential values (diff)</li> <li>5. Blood Pressure/pulse</li> <li>6. Cardiac history</li> <li>7. Determine if treatment responsive.</li> </ol>	<ol style="list-style-type: none"> <li>1. At baseline and at each follow-up visit (at least every 6 months)</li> <li>2. At least every 6 months</li> <li>3. At least every 6 months</li> <li>4. Once, 2 – 3 months after start of drug</li> <li>5. At least once after start of drug</li> <li>6. At baseline and obtain ECG if in doubt about risk from a mild QT increase</li> <li>7. Repeat disorder-specific rating scales(s) until remission is achieved. Increase at 4 – 6 week intervals if insufficient drug benefit</li> </ol>
<b>Antidepressant (SSRI) Medications</b>	<ol style="list-style-type: none"> <li>1. Blood pressure monitoring</li> <li>2. Hepatic Function testing</li> <li>3. Assess for suicidal thinking/behaviors, clinical worsening or other changes in behaviors</li> <li>4. Inquire about activation symptoms</li> <li>5. Inquire about bleeding/bruising</li> <li>6. Measure height and weight</li> <li>7. Determine treatment response</li> <li>8. Pregnancy testing</li> </ol>	<ol style="list-style-type: none"> <li>1. Prior to treatment and with dose titration</li> <li>2. Baseline and as clinically indicated</li> <li>3. Ongoing—usually around week 2, weeks 4 – 6 and other visits</li> <li>4. Screen for new irritability or agitation around week 2 and weeks 4–6</li> <li>5. At least once after treatment begins</li> <li>6. At baseline and each F/U visit, at least every 6 months</li> <li>7. Repeat disorder-specific rating scales(s) until remission is achieved. Increase at 4–6 week intervals if insufficient drug benefit</li> <li>8. As clinically indicated</li> </ol>
<b>Antidepressant (SNRI) Medications</b>	<ol style="list-style-type: none"> <li>1. Blood pressure</li> <li>2. Hepatic function</li> <li>3. Monitor for emergence of suicidal ideation or behavior</li> <li>4. Pregnancy testing</li> </ol>	<ol style="list-style-type: none"> <li>1. Prior to initiating treatment, during dosage titration and as clinically indicated</li> <li>2. At baseline and as clinically indicated</li> <li>3. Ongoing—usually around week 2, weeks 4–6 and other visits</li> <li>4. As clinically indicated</li> </ol>
<b>Tricyclic Antidepressant Medications</b>	<ol style="list-style-type: none"> <li>1. Electrocardiograms (ECGs)</li> <li>2. Obtain outside consultation</li> <li>3. Lower dosage with significant slowing of cardiac conduction</li> <li>4. Monitor for emergence of suicidal ideation or behavior</li> </ol>	<ol style="list-style-type: none"> <li>1. Prior to starting TCA therapy, when dose exceeds 3mg/kg and then every 2 weeks if dose is being increased</li> <li>2. When prescribing doses &gt; 5 mg/kg</li> <li>3. In cases with ECG findings: PR interval over 0.20 msec, QRS interval over 0.12 msec</li> <li>4. Ongoing—usually around week 2, weeks 4–6 and other visits</li> </ol>

Class of Drugs	Monitoring Recommendation	Frequency Suggestion
<b>Stimulant Medications</b>	<ol style="list-style-type: none"> <li>1. Height and weight</li> <li>2. Blood pressure and pulse</li> <li>3. Cardiac history</li> <li>4. Refill monitoring</li> <li>5. CBC with diff</li> <li>6. Determine if treatment response.</li> </ol>	<ol style="list-style-type: none"> <li>1. At baseline and each F/U visit, at least every 6 months</li> <li>2. At baseline and at least once on a given dose of medication</li> <li>3. At baseline to determine if any risks from adrenergic stimulation</li> <li>4. Track date of each refill to identify signs of drug diversion</li> <li>5. For methylphenidate only, at least once every 6 months</li> <li>6. Repeat ADHD-specific rating scale(s) until remission is achieved. Increase at 2 to 4 weeks if insufficient response</li> </ol>
<b>Mood Stabilizing and Anticonvulsant Medications</b>	<ol style="list-style-type: none"> <li>1. Lithium: (a) Chemistry Panel, CBC with platelets, serum creatinine, thyroid function tests, pregnancy test, ECG. (b) Once dose is stable—lithium levels, renal and thyroid function and urinalysis.</li> <li>2. Divalproex sodium: (a) Chemistry Panel, CBC with platelets, liver function tests, pregnancy test. (b) Serum drug levels, hepatic and hematological indices.</li> <li>3. Carbamazepine: (a) CBC, electrolytes and liver function tests. (b) Therapeutic drug levels.</li> </ol>	<ol style="list-style-type: none"> <li>1. Baseline monitoring (b) every 3–6 months</li> <li>2. Baseline monitoring (b) every 3–6 months</li> <li>3. Baseline monitoring (b) Routine monitoring in growing children to check for autoinduction of carbamazepine—usually occurring after one week and/or dosage changes</li> </ol>

Sources: (1) Hilt RJ. *Monitoring Psychiatric Medications in Children. Pediatric Annals. April 2012, Volume 41, Issue 4: 157-163.* (2) Texas Department of Family and Protective Services and the University of Texas at Austin College of Pharmacy. *Psychotropic Medication Utilization Parameters for Foster Children. December 2010.* (3) Schatzberg AF, Cole JO, DeBattista C. (2010) *Manual of Clinical Psychopharmacology. (7th ed).* Arlington VA: American Psychiatric Publishing, Inc. (4) McClellan J, Kowatch, Findling RL, and the Work Group on Quality Issues. *Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder. J Am Acad Child Adolesc Psychiatry 46:1, January 2007.* (5) Epocrates Online [<https://online.epocrates.com/u/1000/Drugs?ICID=search-drugs>] (6) Autoinduction and steady-state pharmacokinetics of carbamazepine and its major metabolites. *Br J Clin Pharmacol (1992), 33, 611-615.*



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