

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

Important Issues and Evidence-Based Treatments

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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.

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Introduction

The practice of evidence-based medicine for children and adolescents requires health professionals and child welfare advocates to engage in a careful assessment of the risks and benefits of using psychopharmacological treatments while addressing serious concerns of over-diagnosis and overtreatment in this vulnerable population. As attention to these issues has grown, a strong undercurrent of anxiety and confusion exists about whether the use of psychotropic agents to remove undesirable impulses and behaviors of children may affect their neurological development, personality, character and temperament. Suspicions exist that over-diagnosis and overtreatment are 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 (Correll et al., 2011; Morris & Stone, 2011).

Contributing factors to the sharp growth in the use of psychotropic drugs for children and adolescents have been attributed to: (Fanton & Gleason, 2009, p. 754)

“... 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.”

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 & 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

According to the National Network of Public Health Institutes, data governance is essential to the reliable construction of the comprehensive picture of psychiatric illness in children. Data governance establishes a foundation for reliable standards in data collection and analysis critical to the understanding of the number of children and adolescents with psychiatric illness and the public and private efforts to address these needs. The reliable assessment of children’s mental health can only be determined through the best quality data that can be collected. To this end, this section begins with data obtained from Centers for Disease Control and Prevention (CDC) surveillance of child and adolescent mental health (Starks, 2021).

What are the most common mental health disorders diagnosed in children and adolescents, and how do factors such as age, gender and socioeconomic status affect the number of individuals who are

diagnosed? The most common diagnoses in children are attention deficit hyperactivity disorder (ADHD), behaviors problems, and anxiety and depression. Data from the age range of 2 or 3–17 years in US children and teens showed that over 9% were diagnosed with ADHD. This translates to 6.1 million children and teens in the US with this diagnosis. A smaller but still very significant number—over 7%—are diagnosed with behavior disorders. This translates to 4.5 million US children and teens. Close to the same number have a diagnosis of anxiety. However, depression is diagnosed in less than half that amount—over 3%—of US children were diagnosed. This translates to 1.9 million US children and teens.

In children and adolescents, co-morbidity is more often the rule rather than the exception. For example, 75% of children and teens with depression also have anxiety. About half of children and teens with depression have behavior problems. From the perspective of children and teens suffering from anxiety, about one third have behavior problems and a third have depression. Looking at the group of children and teens with behavior problems, a third have anxiety and one fifth have depression. It is crucial therefore to screen for the presence of other mental health disorders when one is found in a child or teen.

Over time, the detection of depression and anxiety in children has increased. This may be due to increased awareness of the illnesses or increased screening. However, the diagnosis of depression and anxiety appears more often in children as they age, causing there to be many more cases in the 12–17 age range than the 6–11 age range. However, most behavior disorders are found in the 6–11-year-old range.

As mentioned above, gender and socioeconomic status affect the number of children and teens with mental health issues. For example, in the 2-to 8-year-old age range, boys predominated in mental, behavioral and developmental disorders. With regard to socioeconomic status, for children living below the federal poverty level, 22% had a mental, behavioral or developmental disorder (CDC, n.d.).

The National Survey of Children's Health conducted in 2020 and 2021 screened and reported on 93,669 US children under the age of 18. The number of children and teens with at least one mental health or behavioral condition was 20,295, or 21.7% of the sample, and varied by state (Child and Adolescent Health Measurement Initiative).

Of the children and teens in the survey who were diagnosed with a mental health disorder, only 51.6% received treatment, again with considerable variation by state. The states in the top quartile for highest prevalence of not receiving needed care were (in order of highest [58%] to lowest [51%] prevalence): Utah, Florida, Texas, Missouri, West Virginia, Hawaii, Nevada, Delaware, Mississippi, Louisiana, Georgia and Idaho. The states in the bottom quartile for highest prevalence of not receiving needed care were (in order of lowest [37%] to highest [44%] prevalence): Iowa, Nebraska, Maine, New Mexico, Maryland, Massachusetts, Minnesota, Kentucky, Rhode Island, Connecticut, Ohio and the District of Columbia. Although the disparities are considerable, state policies that promote coordination of care are associated with improved treatment and a reduction in mental health disease burden (Whitney & Peterson, 2019).

Gender patterns of youth suicide have changed gradually and for many years there was a significant gap between male and female youth suicide, with prevalence being higher for males. Suicide is the second leading cause of death in youth in the US and the rate has been climbing in recent years. In females aged 10–14, the rate has tripled, and in females aged 15–19, the rate has doubled. These increases emphasize an urgent need to identify a gender- and developmentally informed approach to addressing suicide in female youth (Ruch et al., 2019).

Within the context of collaborative care, the following disorders were noted as prevalent in a study of pediatric practice settings when care was provided by pediatricians with the assistance of mental health experts: ADHD, anxiety disorder, autism spectrum disorder (ASD), conduct disorder, depressive disorder not otherwise specified, disruptive behavior disorder, dysthymia, major depressive disorder (MDD), mood disorder, oppositional defiant disorder (ODD), psychosis and substance abuse. Of these, the most frequently reported were ADHD and anxiety disorder. Fourteen percent of the participants were reported to have substance abuse, psychosis, and/or ASD (Burkhart et al., 2019).

Drug treatment effects on nervous system development

The long-term effects of psychiatric drugs on a child's physiological development, including on their skeletal system, organs and central nervous system (CNS), are unknown, and could occur:

- As a result of the child's own use
- During the child's gestation as a result of maternal psychiatric drug use
- During the child's mother's gestation as a result of maternal grandmother psychiatric drug use

A pregnant woman's use of psychotropic drugs may cause minor or 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 US Food and Drug Administration (FDA) issued warnings against the use of the following drugs during pregnancy: (Epstein et al., 2013; FDA, 2006, 2011; Kieler et al., 2012; "Paroxetine," 2021; Schatzberg et al., 2010)

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
5. Paroxetine, due to an increased risk of congenital malformations, particularly cardiovascular, in the first trimester of pregnancy, as well as complications during third trimester exposure

Psychotropic drug use among pregnant women was quantified in a large retrospective cohort study conducted by investigators at Vanderbilt University with women (n = 296,817) enrolled in Tennessee Medicaid through pregnancy who had a live birth or fetal death from 1985–2005 (Epstein et al., 2013). 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 disorder [BD], unipolar depression and others). Overall, the adjusted use of study medications during pregnancy for these agents increased from nearly 14 to 31 per 1,000 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 1,000) and anticonvulsants (4.12 to 13.2 per 1,000) during pregnancy, but decreases in the use of typical antipsychotics (7.77 to 0.99 per 1,000) and lithium (2.11 to 0.46 per 1,000) (Epstein et al., 2013).

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 (2010b) argued that inherent potential neurobehavioral toxicity deserves attention since reproductive safety associated with psychotropic drugs has typically focused on 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, 2010b). In addition, Gentile identified six out of eight articles that confirmed an association between SSRI exposure in utero and an increase in the risk of autism. Another study that did not find an association with autism, instead suggested an increased risk of ADHD. The relationship between tricyclic antidepressant exposure and autism was noted in only one study that remains non replicated. It is possible that classes of antidepressants other than SSRIs should be considered the new gold standard for treating women who develop severe depressive symptoms during pregnancy (Gentile, 2010b). However, other studies have pointed to premature delivery and its association with depression (“Paroxetine,” 2021; Schatzberg et al., 2010). Gentile (2010b) also emphasized that the neurobehavioral safety of SGAs is unknown due to a paucity of data, whereas the presumed safety of FGAs, TCAs and benzodiazepines remains preliminary for informing the decision-making process.

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 & 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 & Navalta, 2004, p. 423). Authors proposed the concept that “drug effects incubate” and noted emerging evidence suggesting “long-term effects of drug exposure are delayed and expressed once the vulnerable system reaches maturation” (Andersen & Navalta, 2011, p. 423). In another 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 and Navalta (2004) also speculated that future research would focus on development of novel therapeutic agents designed to “challenge deficit states and reprogram development rather than attempt to merely treat them” (p. 11–12).

A review of neuroimaging studies examined the effects of psychotherapeutic interventions in children and adults (Singh & Chang, 2012). Authors evaluated studies reporting on neuroimaging applications, e.g., structural magnetic resonance imaging, in selected child psychiatric diagnoses, e.g., ADHD, ASD and depressive disorders. Some of the findings are presented below (Singh & 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 BD, 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 responsivity to mood stabilizers in BD.
- Studies have demonstrated differential neural effects between risperidone and divalproex. These two medications show different patterns of neural activity in youth with BD 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” (p. 759)
- Studies discussing how lithium and other mood stabilizers exert their therapeutic effect are consistent on the effect of lithium on brain regional volume. Authors noted that studies suggest “medications appear to consistently have a normalizing effect on brain function and on some brain volumes in youth with BD” (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 anterior cingulate cortex bilaterally, normalizing brain activation in these areas.
- Authors reported results of a case 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” (p. 762).
- Authors reviewed studies suggesting that treatment with antipsychotics in youth with schizophrenia tends 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 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 is “correlated with symptom improvement” (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 health disorders, they noted the importance of studying adverse brain effects from interventions with neuroimaging.

Principles for optimal psychopharmacotherapy practice

In 2009, the American Academy of Child & Adolescent Psychiatry (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 in establishing 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 with a family’s needs and values (Walkup et al., 2009). A sound, trusting, collaborative relationship with the child and family are the foundation of pharmacologic interventions.

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 completed.

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. Clinicians should use standardized, objective measures to measure efficacy of pharmacologic interventions.

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: The child's assent and parent's consent are completed and documented before initiating, and at important points during, medication treatment.

Principle 9: The assent and consent discussion is focused on the risks and benefits of the proposed and alternative treatments.

Principle 10: Medication trials are implemented 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 the:

- Introduction of unacceptable variability into the pharmacological treatment of children
- Underuse of established psychosocial and pharmacological treatment approaches
- Prescription of ineffective/outdated treatment approaches, inappropriate medications or medication combinations

It is also important that these recommended practices are implemented 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 (RCTs) 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., 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, to enhance outcomes 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 below sections, which outline the best pharmaceutical treatment options available for children and adolescents. For many of the disorders in the below sections, information is presented from the *2018–2019 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents*. Through the Florida Medicaid Drug Therapy Management Program, the guidelines are updated every two years by a group of stakeholders, including: the Florida Expert Panel made up of nationally recognized experts, academicians, CAPs, 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. Evidence from RCTs and systematic review is emphasized. 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 for 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 (Agency for Health Care Administration [AHCA], 2019).

Mood disorders

Bipolar disorder (BD): 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 and ziprasidone. However, SGAs caused more weight gain and somnolence than mood stabilizers in youth and adults, and even greater weight gain in youth. Researchers noted that more direct head-to-head comparator trials are still needed. The relative efficacy of combining two mood stabilizers compared with one antipsychotic agent at the present time is not known (Correll et al., 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 has the most available data on effectiveness and tolerability within this age group (Gleason et al., 2007).

The Treatment of Early-Age Mania study in 6–15-year-olds concluded that risperidone was more effective than divalproex sodium or lithium for the initial treatment of childhood mania. It was noted that there is the risk of serious metabolic effects (Geller, B. et al., 2012; Walkup et al., 2015,). 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 BD (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 (AACAP, n.d. -a; Correll et al., 2010). 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 potential risk of triggering mania (Birmaher et al., 2007).

The *2018–2019 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents* recommend monotherapy with aripiprazole, risperidone, quetiapine or asenapine in children between the ages of 10–17 with mania or mixed episodes, lithium for mania (approved by FDA for ages 12 and older), and lurasidone for bipolar depression (age 10 and older) (AHCA, 2019). For children and adolescents ages 10–17 who have mania or mixed episodes and had only partial response to a single atypical antipsychotic, the guidelines recommend augmentation with lithium, a switch to a different antipsychotic listed above or olanzapine. For those with bipolar depression who had only a partial response to lurasidone, a switch to olanzapine-fluoxetine combination is advised. 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 must be reassessed. For mixed episodes and mania, the next step is to combine an antipsychotic with a mood stabilizer (lithium or, if lithium already tried, use valproic acid). For bipolar depression at this level, try adding lamotrigine to the current treatment. The final recommendation for continued non-responders is to use either clozapine or electroconvulsive therapy (ECT) in adolescents. The combination of two antipsychotics is not recommended at any level of treatment. In order to minimize side effects when switching psychotropic medications, 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 25–50% per 5 half-lives (AHCA, 2019).

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 (40–70%) but, with the exception of fluoxetine, the placebo response rate is also high (30–60%) (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 et al., 2011; Gentile, 2010a; Government Accountability Office [GAO], 2012; Magellan Health, 2014;). 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 (Cincinnati Children’s Hospital Medical Center, 2010; Sakolsky & Birmaher, 2012). The *Treatment for Adolescents with Depression Study* (TADS) compared treatments for moderate to severely depressed youth; the following response rates reflect improvement at 12 weeks: (Correll et al., 2011)

- 70% for those who received fluoxetine combined with weekly cognitive behavioral therapy (CBT)

- 60.6% for those treated with fluoxetine alone
- 43.2% for those treated with CBT alone
- 34.4% for placebo

Another important trial, the *Treatment of Resistant Depression in Adolescents* (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 et al., 2011; Sakolsky & Birmaher, 2012).

The *2018–2019 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, 2019). 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 (TCAs) or paroxetine are NOT recommended for children under age 6. For children and adolescents ages 6–17 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 CBT or interpersonal psychotherapy. For ages 12 and older, escitalopram may be considered. If after level 2 there is not an adequate response to therapy, the level 3 intervention is to switch to either fluoxetine or escitalopram; whichever has not yet been tried. If there is a poor or no response to level 3 interventions, the guidelines for level 4 recommend referral to a mental health professional to reassess the diagnosis and rule-out BD, increase the dose of current medication, and add psychotherapy like dialectical behavior therapy (DBT) or CBT. 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, 2019).

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 TADS and TORDIA studies and by relapse-prevention data that suggest durability of treatment effect” (Strawn et al., 2016, p. 3). Authors noted that results of a 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)

Revisions of the AACAP Practice Parameter for the Assessment and Treatment of Children and Adolescents with OCD continue to recommend 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.” Specifically, the use of exposure and response prevention has been shown to be highly effective in the pediatric population. The AACAP parameter further specifies that for youth with moderate to severe OCD, medication is indicated as a secondary intervention in addition to CBT (Geller, D. A. et al., 2012, p. 104). The most commonly used medications include SSRIs and a single tricyclic antidepressant (clomipramine). Three SSRI medications have FDA approval for treatment of OCD in children and adolescents: Sertraline (ages 6 and older), fluoxetine (ages 7 and older), and fluvoxamine (ages 8 and older). The tricyclic antidepressant, clomipramine, is also FDA approved for children aged 10 and over (Kodish et al., 2011). The combination of CBT and an SSRI may be more effective than CBT alone in 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. 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 SSRIs over clomipramine because of tolerability and safety in children and adolescents (Geller, D. A. 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 et al., 2011; Franklin et al., 2011; Geller, D. A. et al., 2012; Kodish 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).

In a small number of cases (< 5%), OCD symptoms may arise after a child is exposed to a streptococcal infection. While there may be controversy regarding definitive proof of the autoimmune hypothesis of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), this diagnosis may be made when OCD symptoms or a tic disorder, or both, suddenly appear or worsen following a streptococcal (strep) infection, such as strep throat or scarlet fever. In these cases, treatment may include antibiotics if there is evidence of elevated strep titer and a positive throat culture (Wilbur et al., 2019). In rare cases, plasma exchange or intravenous immunoglobulin may be a consideration for acutely and severely affected children with PANDAS. Research suggests that both active treatments can improve global functioning, depression, emotional ups and downs, and obsessive-compulsive symptoms.

Emerging research studies have suggested a possible role for the drug D-cycloserine as a possible treatment for OCD. In addition, there is emerging evidence the medications targeting glutamate receptors, such as ketamine, may be effective for OCD. A new drug, troriluzole, is undergoing pivotal phase 3 trials and has shown promise in the treatment of OCD.

Anxiety disorders

Although non-OCD disorders (i.e., GAD, 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 *Child/Adolescent Anxiety Multimodal Study* where patients (n = 488; ages 7–17 yrs.) with non-OCD anxiety disorders showed the most improvement with the combination of CBT/sertraline (81%), followed by CBT alone (60%) and sertraline alone (53%), compared to a 24% response rate with a placebo pill (Correll et al., 2011; Kodish et al., 2011). In an earlier clinical trial, the *Research Unit on Pediatric Psychopharmacology Study*, children (n = 128; 6–17 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 (Connelly et al., 2007; Correll et al., 2011; Gleason et al., 2007; Kodish et al., 2011).

The AACAP Clinical Practice Guidelines for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders recommend SSRIs for the treatment of social anxiety disorder, GAD, SAD or panic disorder in children and adolescents ages 6–18 (Walter et al., 2020). The SSRIs with sufficient data available for comparison are fluoxetine, fluvoxamine, paroxetine and sertraline (Walter et al., 2020). The AACAP Clinical Practice Guidelines also recommend CBT in this age group for the same disorders (Walter et al., 2020). The AACAP Clinical Practice Guidelines suggest that SNRIs can be utilized as treatment for these conditions as the benefits may outweigh the harms, but there is greater uncertainty when compared to use of SSRIs (Walter et al., 2020). The SNRIs with sufficient data available for comparison are venlafaxine and duloxetine (Walter et al., 2020). Duloxetine is the only SNRI to have an FDA indication for the treatment of any anxiety disorder in children and adolescents (Walter et al., 2020). The AACAP did not provide a statement in support of the use of benzodiazepines to treat anxiety in children and adolescents, due to a lack of sufficient evidence supporting the benefits (Walter et al., 2020).

The *2018–2019 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 CBT adapted to young children. If there is poor/partial response to psychotherapy, the guidelines recommend treatment with fluoxetine and concurrent psychotherapy for children ages 4–5 years. The guidelines advise a review of black box warnings with parents and monitoring for suicidal ideation. Fluoxetine, starting at 1–2 mg/day, is recommended for 8–10 weeks with maximum dosing of 5–10 mg/day. After six to nine months of treatment with medication, a gradual downward titration is recommended. Sertraline combined with psychotherapy may be considered where fluoxetine is unsuccessful. For youth ages 6–17 years, 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 either 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, either duloxetine 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 a first or second-line treatment.

In another study, a systematic review was performed of five randomized, double-blind, placebo-controlled trials that assessed the effects of sertraline, fluoxetine, venlafaxine ER and duloxetine in pediatric patients (n = 1,186) with GAD to examine the efficacy, safety and tolerability of psychopharmacologic interventions in youth with GAD (Dobson & 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 & Strawn, 2016, 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 & Strawn, 2016, p. 52).

Beta-blockers, traditionally used to treat hypertension, have been utilized to treat the physical symptoms of anxiety, such as elevated heart rate, sweating and shaking. This approach can work well to prevent acute symptoms of anxiety disorders, such as social phobia, e.g., when giving a presentation or performing on stage (NIMH, n.d. -b). Propranolol is a type of beta-blocker that is commonly used for this purpose. Although there is evidence for the use of beta blockers in treating anxiety related to social phobias in adults, similar evidence for use in children and adolescents is lacking (Patel et al., 2018).

Post-traumatic stress disorder (PTSD)

The diagnostic entity, PTSD, is generally disaggregated from other anxiety disorder 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). Clinical control trials studying the use and efficacy of SSRIs for the treatment of PTSD remain limited. As a result, the AACAP continues to suggest against the use of this class of medication for PTSD (Cohen 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 (TFCBT) 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 suggest a need for additional interventions (Cohen et al., 2010). Two randomized trials have been conducted on sertraline in this population. The 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). Although limited by an open label study, use of extended release guanfacine may have therapeutic effects in the treatment of PTSD symptoms, particularly re-experiencing, avoidant and overarousal symptoms (Connor et al., 2013). Other studies of α - and α -adrenergic

blocking agents (i.e., clonidine) 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). There are limited RCTs looking at the use of antipsychotics and anticonvulsant medication for treatment of PTSD in children and adolescents and are therefore not recommended.

The *2018–2019 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 SGAs 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 or clonidine, is not recommended (AHCA, 2019).

Disruptive behavioral disorders/aggression

Aggressive behavior is a common symptom which causes children and adolescents to be referred for psychiatric treatment. Experts have termed maladaptive aggression the “fever” of child psychiatry because it is common, nonspecific, and as a phenomenon, described 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 (Connor et al., 2019). The *2018–2019 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 in children under 6 years (AHCA, 2019). If psychosocial treatment is not effective, several classes of medications have been shown to be effective in addressing aggression in the pediatric population.

Aggression in youth is most often associated with ADHD, conduct disorder (CD), ODD and disruptive mood dysregulation disorder. It also co-occurs with ASD and other neurodevelopmental disorders, including intellectual disabilities. The literature makes a distinction between “hot” aggression, due to impulsivity or low frustration tolerance, and “cold” aggression, due to planned, predatory or self-controlled behavior (Connor et al., 2019). The authors make the case that “hot” aggression is more likely to benefit from medication.

A 2016 article examined the role of medication in the treatment of aggression in youth with pathological aggression (Gurnani et al., 2016). Authors advised that medications for aggression “should be used judiciously and with close patient monitoring, given potential safety concerns” (Gurnani et al., 2016, 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., Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth, and Treatment of Maladaptive Aggression in Youth, to guide implementation of appropriate therapeutic interventions (Gurnani et al., 2016).

Stimulants are the most widely prescribed class of psychotropic agents for children and youth in the US. Stimulants have demonstrated efficacy in treating symptoms of ADHD including aggression, as well as impulsivity and low frustration tolerance which leads to aggression. Side effects of stimulants can include insomnia, reduced appetite, stomachache, headache and dizziness. They have also been linked to long-term adverse events, including height and weight suppression. In rare cases, stimulants can cause vocal or motor tics or exacerbate a pre-existing tic disorder.

While stimulants are most frequently used to manage ADHD symptoms (Michelson, 2004), non-stimulant medications such as venlafaxine (Effexor), bupropion (Wellbutrin) and atomoxetine (Strattera), have been approved in the US to treat children and adolescents who fail to respond to stimulants and children who cannot tolerate stimulants due to side effects (Michelson, 2001).

Atypical antipsychotics also show benefit in the management of aggression (Schur et al., 2003; Sikich, et al., 2004). Older antipsychotics should be avoided due to the risk of serious adverse events, such as neuroleptic malignant syndrome, extrapyramidal symptoms (EPS) and tardive dyskinesia (Connor et al., 2001; McConville & Sorter, 2004). However, atypical antipsychotics are also associated with significant metabolic risks, including weight gain, type II diabetes and elevated lipid profiles.

Among first-line atypical antipsychotic agents, risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon) and aripiprazole (Abilify), have all been used to address aggression in children and youth. Risperidone has been shown to produce significantly greater reductions in aggression and persistent behavioral disturbances compared with placebo in subjects with a variety of diagnoses, including conduct disorder, ODD and ADHD (Aman et al., 2004; Buitelaar et al., 2001). Risperidone and aripiprazole (Abilify) have been shown to be effective for managing aggression in children and adolescents with ASD. The Rutgers University Center for Education and Research on Mental Health Therapeutics 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. (2011) also noted that thioridazine was found to be an effective first-generation antipsychotic agent for aggressive behavior in conduct-disordered youth.

Research shows that mood stabilizers, such as Lithium and anticonvulsant medications, which are commonly used for BD, can also reduce aggressive symptoms in children and adolescents. The use of lithium in children and adolescents, however, is often deterred by the need for frequent blood draws for dose monitoring, as well as its associations with nausea, vomiting, enuresis, ataxia and cognitive impairment (Bassarath, 2003; Malone et al., 2000). In a study of youth with explosive temper and mood lability, divalproex (Depakote) treatment was superior to placebo in reducing aggressive symptoms (Donovan et al., 2000).

Current research indicates that α -2 agonists can reduce oppositional behavior, enhance frustration tolerance, and improve hyperactivity and impulsivity in children. In these cases, the α -2 agonist appears to target aggression and poor impulse control without any impact of the inattention or distractibility. Either clonidine or guanfacine is often co-prescribed with stimulants (dosReis et al., 2005). In an RCT of 67 children (6–14 years) with ADHD and comorbid ODD or CD, a combination of clonidine and stimulant treatment improved conduct problems (Hazell & Stuart, 2003). Although α -2 agonists such as clonidine and guanfacine can produce drowsiness, sedation and weight gain, their use in combination with stimulants may allow for a lower dose of stimulant and stimulant-associated side effects.

Antidepressants, such as bupropion (Wellbutrin) and fluoxetine (Prozac), may reduce irritable mood, resulting in a decrease in aggressive behavior. The FDA has accordingly issued a black box warning related to a low but clear link between antidepressant use and increased suicidal ideation in adolescents.

Attention-deficit/hyperactivity disorder (ADHD)

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. Stimulants are generally associated with optimal reduction in symptoms, as it is estimated that at least 70% of school-aged children respond favorably to stimulant medication (Magellan Health, 2020). 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 and also reduces abuse potential.

Atomoxetine does not offer the option for a drug holiday, unlike stimulants, and should be taken daily (Magellan Health, 2020). Meta-analytic findings of clinical trials for atomoxetine and stimulants yielded a moderate effective size for atomoxetine of 0.63 and large effective sizes of 0.99 and 0.95 for immediate and extended-release stimulants, respectively (Correll et al., 2011). Atomoxetine shares some adverse effects with stimulants but appears to have much less potential for aggravation of tics and insomnia. It is purported to be a good choice when anxiety, depression, tics, substance abuse and ODD symptoms complicate ADHD in children or adults. Atomoxetine has been associated with six reported cases of hepatotoxicity but none of these cases resulted in a liver transplant. In addition, atomoxetine has a black box warning from the FDA regarding possible increased suicidality. Atomoxetine has not been found to be as effective in treating primary ADHD symptoms as stimulants and has more recently come to be considered a second-line treatment (Magellan Health, 2020).

The extended-release formulation of α -adrenergic agonists, clonidine and guanfacine were granted FDA approval for the treatment of ADHD as adjunctive agents along with stimulant medications. Alpha-adrenergic agonists impact ADHD symptoms by affecting the noradrenergic system and generally have greater benefit for hyperactivity/impulsivity symptoms than for inattention. The α -adrenergic agonists, both in monotherapy and as add-on treatment to stimulants, are significantly more effective than placebo for total and specific attention-deficit/hyperactivity disorder (ADHD) symptoms, as well as for

ODD symptoms (Magellan Health, 2020). However, given the significantly higher incidence of hypotension, bradycardia, fatigue, somnolence and sedation in participants randomized to α -2 agonists compared with placebo, clinicians should monitor these side effects routinely. The α -2 agonists are an alternative treatment for children and adolescents with ADHD who cannot tolerate psychostimulants or do not have a sufficient response to treatment with stimulants. These medications do not have FDA approval for use in preschool-aged children (Magellan Health, 2020). Nevertheless, current clinical guidelines now stipulate that children as young as 4 years of age may be diagnosed with 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, 2020).

The PPWG of the AACAP recommends methylphenidate as the first-line psychopharmacological treatment for preschool ADHD. If ineffective, a switch to an amphetamine formulation is recommended. The PPWG algorithm further allows clinicians to consider individual clinical factors in choosing between atomoxetine and α -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 and ADHD. These findings need to be corroborated with supporting evidence from future clinical studies comparing antipsychotics with behavioral intervention, combination treatments and placebo (Correll et al., 2011; Magellan Health, 2020).

There has been an increase in stimulant formulations. Most of the new formulations are long-acting formulations of methylphenidate and amphetamine with new delivery technologies. These include chewable tablets, oral dissolving tablets, transdermal patches, beaded technology and extended-release liquid formulations. The advent of these formulations has helped with medication adherence in pediatric populations and provided clinicians with more options to individualize treatment for optimal response (Steingard et al., 2019).

Recent research studies are investigating whether virtual reality and innovative brain training programs could be an effective non-pharmacological treatment for ADHD. After showing some benefits in treating phobias, pain and anxiety, virtual reality exposure is being tested as a distraction therapy. Through specialized computer games, ADHD symptoms are targeted, including inattention and distractibility. In addition, many target executive function deficits including working memory and inhibition, which are common in people with ADHD (Klingberg, 2005). Research regarding computer training methods is limited in size and shows mixed results. Although some studies show benefits in specific areas, there is limited evidence showing results will carry over into real life situations. Cogmed Working Memory Training has been shown to improve working memory and attention in children with ADHD compared to control groups (Bigorra, 2015). More research is needed to determine whether these programs will provide lasting benefits in real life situations.

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: (Wolraich, 2019; Magellan Health, 2020).

1. Evidence-based parent- and/or teacher-administered behavioral management 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 along with parent- and/or teacher-administered behavioral management and behavioral classroom intervention.
3. Medications should initially be prescribed for adolescents and behavioral treatments are optional, although preferable.
4. Educational interventions and individualized instructional supports, including school environment, class placement, instructional placement, and behavioral supports, are a necessary part of any treatment plan and often include an individualized educational plan or a rehabilitation plan (504 plan).

The *2018–2019 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents* recommend that the initial treatment for children under age 6 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, 2019). The next level of treatment, if methylphenidate is not successful, considers monotherapy with atomoxetine, as long as the child has the ability to swallow the medicine whole. The next level of treatment considers amphetamine formulation (FDA indications for ages 3–5 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. If immediate-release monotherapy has failed, extended-release stimulant medication within special dosing guidelines for preschoolers may be considered.

For the treatment of children and adolescents ages 6–17 years old, the guidelines recommend psychostimulant monotherapy as initial treatment (methylphenidate class or amphetamine class, either short or long acting), and monotherapy with another stimulant if the first choice is not effective. If supplementation of an extended-release psychostimulant is required for sufficient coverage, it is recommended to stay within same drug class. An alternative 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. A following level of treatment recommended is an immediate-release alpha-2 agonist as monotherapy or combined with other ADHD medication classes. Only after treatments at these levels, and if these treatments do not result in a satisfactory response, do the guidelines recommend bupropion or TCAs. The guidelines state that the following are not recommended in the treatment of ADHD in children and adolescents 6–17 years old: (AHCA, 2019)

- Antipsychotic medication to treat core symptoms of ADHD

- Concurrent use of two or more alpha-2 agonists
- Concurrent use of two different stimulant classes
- Desipramine

Strawn et al. (2016) reviewed literature related to medications for the treatment of ADHD in children and adolescents. 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: (Strawn et al., 2016)

- 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 (three 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 patients unable to tolerate stimulants, although may be considered first-line due to concern for abuse of stimulant medications and diversion
- FDA boxed warning carried by atomoxetine for the small risk of suicidal ideation

Developmental disabilities

Autism is a developmental disability and there is currently no pharmacologic agent that is effective in treating its core behavioral manifestations (Brasic and Pataki, 2012; Carrasco et al, 2012). Currently, risperidone and aripiprazole have been approved by the FDA for treatment of irritability (consisting primarily of physical aggression and severe tantrum behavior) associated with ASDs in children and adolescents (FDA, 2019). These drugs may be prescribed for short-term treatment by specialists with experience in treating these relatively uncommon disorders because associated metabolic side effects are concerning. Drugs may be effective in treating comorbid psychiatric disorders, e.g., OCD, depressive disorders, GAD and ADHD, or specific behaviors (Brasic & Pataki, 2012; Meyers et al., 2007). The 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 identified, the patient can be treated with the medications that are used in treating these conditions in children who do not have ASD. 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; Plauché et al., 2007, pp. 1169, 1170).

- Repetitive behavior, rigidity and obsessive-compulsive symptoms—SSRIs, i.e., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline
- Hyperactivity, impulsivity and inattention symptoms—atypical antipsychotic agents (i.e., aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone), valproic acid, stimulants (i.e., dextroamphetamine, methylphenidate and mixed amphetamine salts) and alpha agonists (i.e., clonidine and guanfacine)
- Aggression, explosive outburst and self-injury—atomoxetine, atypical antipsychotic agents (i.e., aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone), alpha agonists (i.e., clonidine and guanfacine), anticonvulsant mood stabilizers (i.e., levetiracetam, topiramate and valproic acid), SSRIs (i.e., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) and beta-blockers (i.e., nadolol, metoprolol, pindolol and propranolol)
- Sleep dysfunction—melatonin, ramelteon, alpha agonists (i.e., clonidine and guanfacine) and antihistamines (i.e., diphenhydramine and hydroxyzine)
- Anxiety—mirtazapine, SSRIs (i.e., citalopram, escitalopram, fluvoxamine, paroxetine and sertraline) and buspirone
- Depressive phenotype—SSRIs (i.e., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) and mirtazapine
- Bipolar phenotype—anticonvulsant mood stabilizers (i.e., carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate and valproic acid), atypical antipsychotic agents (i.e., aripiprazole, olanzapine, quetiapine, risperidone and 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 large studies on their usage in children with autism have been disappointing (Vega & Anderson, 2012; Williams et al., 2010). Meta-analytic findings on the efficacy of SSRIs for repetitive behaviors in ASDs showed that current published and unpublished literature overstates SSRI effectiveness. Similarly, other meta-analytic findings on the use of SSRIs for core symptoms of autism (i.e., communication, social interaction and behavior problems) showed a 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 (Vega & Anderson, 2012; Williams et al., 2010;). Atypical antipsychotics, risperidone and aripiprazole, are the two best-studied medications to treat the challenging or repetitive behaviors manifested in ASD. Since the 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 EPS 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 (McPheeters et al., 2011; Warren et al., 2011).

A study compared the use of psychotropic medications among children (n = 7,901) with ASD aged 1–17 in five health systems to a matched population (n = 79,010) with no ASD (Madden et al., 2017). Significantly more children with ASD had psychiatric comorbidities, e.g., depression, BD, 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 stabilizers. 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., 2017, p. 148). Researchers summarized that children with ASD were 11.4 times more likely to receive treatment with psychotropic medications than 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., 2017, 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).

Clinicians should specifically inquire about the use of complementary and alternative medications (CAM) in children with developmental disabilities, including ASD, as there is wide use of CAM, albeit with inconclusive evidence. More controlled studies are needed, and it is important that the family be able to voice questions to healthcare providers.

Childhood schizophrenia

Until recently, the treatment of childhood schizophrenia was based on evidence from clinical pharmacological studies conducted with adults. The FDA approved several SGA agents for use in children and adolescents (aged 13–17) with schizophrenia after a wave of new placebo-controlled clinical trials were conducted and demonstrated efficacy in this population (Correll et al., 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 et al., 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 systematic review and network meta-analysis compared the efficacy and safety of antipsychotics in the treatment of youth (n = 2,158) 8–19 years of age with early-onset schizophrenia-spectrum (EOS) disorders (Pagsberg et al., 2017). Authors analyzed the results from 12 short-term (6–12 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; EPS 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 RCTs provided useful information that was previously unavailable. They concluded that ziprasidone cannot be recommended for this treatment as it had limited or no effect and its efficacy appeared inferior to other antipsychotics; adverse events 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 adverse events” (Pagsberg et al., 2017, p. 200).

Eating disorders

Eating disorders are common, and the mortality rate, especially for anorexia nervosa is high. This rate has been predicted to increase by 5.6% for each decade that an individual remains ill. A wide variety of treatments for these disorders, which include anorexia nervosa, bulimia nervosa, binge eating disorder and avoidant-restrictive food intake disorder (ARFID), have been evaluated. Perhaps the most comprehensive recent review of these interventions is the *Canadian Practice Guidelines for the Treatment of Children and Adolescents with Eating Disorders* published in the *Journal of Eating Disorders* (Couturier et al., 2020). This review outlines the effectiveness of various therapies, including the most recent research in the use of medications, to treat these disorders. *The Practice Parameter for the Assessment and Treatment of Children and Adolescents with Eating Disorders* published by the AACAP recommends that the use of medications be reserved for comorbid conditions and refractory cases (Lock & La Via, 2015). Most current studies involve treatment of adults, and few double-blind placebo-controlled studies exist in the treatment of children and adolescents. The following review is organized by type of medication.

Atypical Antipsychotics

Olanzapine is the most common medication studied for children and adolescents, however only one double-blind placebo-controlled study is currently published on its use. Kafantaris et al. (2011) studied 20 underweight adolescents 12–22 years of age. This was a ten-week pilot study which demonstrated no differences in beneficial effect between the group treated with olanzapine and the placebo group. In addition, the olanzapine group demonstrated increased fasting glucose and insulin levels. 8.5 mg was the mean dose of olanzapine in the index group (Kafantaris et al., 2011). Three case-control studies demonstrated the use of olanzapine in anorexia nervosa. All three demonstrated issues with side effects, including sedation, dyslipidemia and reductions in activity levels. Only one of the three

studies showed weight gain, but in this study, one third of the participants discontinued olanzapine due to side effects. (Hillebrand et al., 2005; Norris et al., 2011; Spettigue, Norris, Maras, et al., 2018) A few case reports address treatment for eating disorder not otherwise specified (EDNOS) and ARFID, but they are not placebo-controlled trials. These reports show improvements on the clinical global impressions scale for EDNOS. The report regarding ARFID treatment used olanzapine with a combination of other medications including fluoxetine, fluvoxamine and cyproheptadine. (Brewerton & D’Agostino, 2017; Spettigue, Norris, Santos et al., 2018)

Risperidone is examined in one double-blind placebo-controlled study of 40 patients aged 12–21 who were randomized to risperidone or placebo. No difference in outcome was observed at the conclusion of this nine-week study (Hagman et al., 2011). This study concludes that the evidence does not support the use of risperidone in anorexia nervosa treatment of young patients. Four small case reports demonstrated some weight increase and improved willingness to eat with the use of risperidone (Kracke & Tosh, 2014; Newman-Toker, 2000; Umehara & Ohmori, 2014).

The use of **quetiapine** is reported in only a few case reports. In one of these reports, three cases of patients aged 11–15 with severe anorexia nervosa were studied. Two patients received 100 mg bid and another patient received 250 mg bid. Improvements in body image disturbance, weight phobias and paranoid ideas were reported, but sedation and constipation were disclosed as side effects (Mehler-Wex et al., 2008).

One case-control study and two case reports demonstrate the use of **aripiprazole** in the treatment of anorexia nervosa. Frank et al. (2016) compared a group of 22 adolescents receiving aripiprazole to an untreated comparison group of 84 adolescents. The treated group sustained a greater increase in body mass index (BMI) than the untreated group. The case reports suggested improvements in anxiety and rigidity with the use of aripiprazole (Frank, 2016; Frank et al., 2017).

Although some of these studies have suggested a modest benefit of atypical antipsychotics, the results have been discouraging and not conclusive. Despite the lack of efficacy of these psychotropic drugs, prescribers continue to offer them off-label for patients with anorexia nervosa (Mitchell & Peterson, 2020).

Antidepressants (Use in anorexia nervosa)

One retrospective study reports no differences in BMI, eating disorder psychopathology, and depressive and obsessive-compulsive symptoms in a group of 32 patients, 19 of whom were treated with **SSRI’s**, including **fluoxetine**, **fluvoxamine** and **sertraline**, and 13 patients who received no medication (Holtkamp et al., 2005). However, five case reports from various authors reported improvement with SSRI’s either alone or in combination with second or first-generation antipsychotics (Ercan et al., 2003; Frank et al., 2001; Gee & Telew, 1999; Lyles & Sarkis, 1990; Newman-Toker, 2000).

Mirtazapine is examined in the treatment of anorexia nervosa in one case control study and two case reports. Hrdlicka et al. reported that nine adolescent patients who were treated with mirtazapine, and nine patients who were matched in age and BMI demonstrated no significant differences (Hrdlicka et

al., 2008). Two case reports demonstrated more positive results. In one, a 16-year-old female who had been hospitalized for anorexia nervosa and depression, was treated with mirtazapine with positive results in weight restoration and mood improvement (Jaafar et al., 2007). Similarly, a 16-year-old boy responded well with weight restoration after treatment with mirtazapine (Naguy & Al-Mutairi, 2018).

Antidepressants (Use in bulimia nervosa)

Only scant evidence exists for the efficacy of SSRIs in the treatment of bulimia in children and adolescents, although fluoxetine is FDA approved for the treatment of bulimia in adults. One open-label trial studied treatment of 10 adolescents aged 12–18 years with **fluoxetine** over an 8-week period. Fluoxetine was titrated to a maximum of 60 mg qd with supportive psychotherapy. Binges decreased significantly from 6.4 to 0.4 episodes per week. 70% of patients were reported as improved or much improved. No significant side effects were noted.

Antidepressants (Use in avoidant/restrictive food intake disorder)

SSRIs were helpful in the post-traumatic type of this disorder, as described in case reports of the use of **escitalopram** and **fluoxetine**. In one report, three children with severe choking phobias were treated successfully with low-dose SSRI's (Banerjee et al., 2005).

No studies examining the use of SNRI's or mood stabilizers in eating disorders have been reported to date.

Conducting clinical trials for eating disorder treatment in this young population is complicated by methodological, ethical and legal issues. Informed consent is difficult to obtain in cases where the treatment, in this case medication, confronts the patient's symptoms directly, as in the case of olanzapine contributing to weight gain in a patient with anorexia who fears weight gain. In addition, parental consent must be obtained. Many parents do not want medications used to treat their child or adolescent. Thus, study quality in these situations can be poor and prone to bias (Couturier et al., 2020).

Despite these issues, The Canadian Clinical Practice Guideline made a weak recommendation that olanzapine or aripiprazole may be reasonable for anorexia nervosa treatment in certain populations if its use is carefully monitored and the treatment is provided by a child psychiatrist or pediatrician with experience in treating children and adolescents with eating disorders. These medications, if used off-label in the treatment of this population, should be administered at the lowest possible effective dose and should be titrated carefully. Informed consent must be obtained from the patient and parents or responsible adult (Couturier et al., 2020). This recommendation is consistent with the *Practice Parameter for the Assessment and Treatment of Children and Adolescents with Eating Disorders* published by the AACAP (Lock & La Via, 2016).

Further research is desperately needed to ascertain the efficacy and safety of medication use in the treatment of eating disorders in children and adolescents. Promising areas for research consist of examining the use of SSRIs such as fluoxetine in the treatment of bulimia. Risperidone and quetiapine

may show promise in further research in the treatment of anorexia nervosa. Further research into the use of mirtazapine may reveal efficacy in the treatment of anorexia nervosa, as well (Couturier et al., 2020). Currently there is no evidence that SNRI's or mood stabilizers have a place in the treatment of eating disorders. Bupropion, as well, is not recommended for treatment of eating disorders due to the increased risk of seizures with this medication.

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 (2015) noted that “one of the most significant concerns about psychotropic medication use in youth involves the frequent absence of effective psychosocial interventions” (p. 16). The AACAP specified that practitioners should 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 debilitating, and affect 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., CBT, DBT, 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 = 1,307) in the studies, between 6–18 years, had different severities of MDD 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 RCTs are needed (Cox et al., 2014)

Controversies in clinical management

Long-term prospective validity of psychiatric diagnoses in very young children. This consideration of pediatric psychopharmacological treatment, which is in the forefront of debate, has been highlighted by experts as an issue 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 and Gleason (2009) 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 (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 & Gleason, 2009, 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 and a half. The treatment of depression in children and adolescents was significantly altered when in October 2003 the FDA released a public health advisory alerting the healthcare profession 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. In 2006 the FDA extended the warning to include young adults, up to 25 years of age, although the increase in suicidality for the additional group was not statistically significant (Soumerai & Koppel, 2018). The 2004 warning prompted a precipitous drop of 25% in rates of both diagnosis and treatment of depression by pediatric and non-pediatric primary care physicians (PCPs) (Birmaher & 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 (Birmaher et al., 2007; Correll et al., 2011; Walkup et al., 2009). 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).

Another study examined the risk of suicide attempt and self-inflicted injury in depressed children ages 5–17 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” (Gibbons et al., 2015, 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., 2015, 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., 2015, p. 213).

Apprehension on the use of stimulants in the treatment of ADHD. While stimulant medication has strong evidence and a 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 (Wolraich et al., 2019; Texas Department of Family and Protective Services & the University of Texas at Austin College of Pharmacy 2010). In 2008, a joint advisory statement of the AAP and American Hospital Association 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, 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 (ECG) at the physician’s discretion for children being prescribed stimulants. The professional medical communities issuing this advisory recommended reasonable screening measures that would not result in reduced access to stimulant treatment (Wolraich et al., 2019; 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 in decreasing growth velocity, especially for children on higher doses. The AAP publication, *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 1–2 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., 2010; 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. The substantial role of primary care providers 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 & Honigfeld, 2012, p. 931). Pidano and Honigfeld’s (2012) 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” (p. 931). Authors also indicated that while PCPs 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 & 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 & the University of Texas at Austin College of Pharmacy, 2010).

Pharmacogenetic testing. There are several commercially available pharmacogenetic/pharmacogenomic tests being marketed for clinical practice in psychiatric medicine. Healthcare providers are increasingly using these tests, along with consumers, as some are available directly to consumers. The commercial entities claim the testing measures the metabolism of drugs and can predict a patient’s response to specific medication, based on genetic variants, and can therefore be used to guide medication choice and dosing and impact the resulting therapeutic response and side effects (AACAP, 2020).

The FDA is not aware of any data establishing that these tests can help patients or healthcare providers in making appropriate treatment decisions for the tested drugs (Ellingrod, 2019). The FDA has issued a safety warning about the use of genetic tests with unapproved claims to predict medication response. The FDA stated that changing a patient’s medication regimen based on the results of a pharmacogenetic/pharmacogenomic test leads to “inappropriate treatment decisions and potentially serious health consequences for the patient” (AACAP, 2020)

Presently, there is no standard by which to review commercial pharmacogenetic/pharmacogenomic tests as to:

1. Which genes to test
2. Which variants specific to a gene need to be included

3. How the genetic data is translated to a phenotype
4. How the phenotype is translated to a treatment recommendation

Information in the package insert of the product should be used to guide pharmacogenetic testing in treatment decisions (Ellingrod, 2019). Patient education is critical. Clinicians should use testing panels with recommendations that best align with their individual practices, their patient's needs and FDA information.

Cautionary guidelines for broadened usage of drugs

The broadened use of psychotropic medications in children and adolescents has fueled 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. (2011) have specified that this problem is most applicable to the improper assignment of BD in childhood. Even though SGAs were developed and initially studied as treatments for psychotic illnesses in adults, psychopharmacology experts report that aggression—not psychosis—is the most common target symptom for which SGAs are prescribed to children and adolescents (Correll et al., 2011; Crystal et al., 2009; Findling et al., 2011). 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 et al., 2011; Fanton & 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: (Findling et al., 2011)

- Weight gain, diabetes and hyperlipidemia
- Cardiovascular problems such as prolongation of QTc interval, orthostatic hypotension, tachycardia and pericarditis and coronary artery disease associated with weight gain
- Neutropenia and potential agranulocytosis
- Hepatic dysfunction
- Elevation of prolactin levels
- Electroencephalogram abnormalities and possible seizure activity
- Potential for the development of EPS, tardive dyskinesia and withdrawal dyskinesias
- Neuroleptic malignant syndrome
- Formation of cataracts

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. (Findling et al., 2011; Seida et al., 2012).

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

Integrated care/collaborative care in the treatment of children with behavioral and emotional problems

Although the prevalence of child and adolescent psychiatric disorders in the United States has risen to between 13% and 20%, in vulnerable populations with higher community risk factors it can be as high as 25% (Bethell, n.d.). As a result of efforts of the AAP Task Force on Mental Health to educate pediatricians on the signs and symptoms of mental health problems in children, the increased prevalence is due, in part, to the increase in the number of children and teens being identified and diagnosed by primary care providers (AAP, n.d.). However, for a number of reasons, only 15–20% of this population is receiving mental health services and treatment (Tyler et al., 2017). The collaborative care model was developed to address the impediments to children and teens with mental health issues in receiving care in pediatric primary and medical home settings (Tyler et al., 2017).

What is collaborative care? In essence, it is a partnership between the primary care physician and/or pediatrician, and a child and adolescent psychiatrist (CAP) or other mental healthcare professional. Three models of this partnership have emerged: (Burkhart et al., 2019)

1. Consultation by telehealth/telephone
2. Co-location, i.e., sharing of the same physical office space
3. Collaborative/integrated care treatment partnerships/co-management

In the consultation model, the primary care physician and/or pediatrician and CAP can have a telephonic “curbside,” a more formal consult, or an actual consult where there is an office or virtual meeting (Burkhart et al., 2019).

The Massachusetts Child Psychiatry Access Project (MCPAP) is a well-recognized consultative care model, having been replicated and adapted in over 20 states (Tyler et al., 2017). The model consists of regional teams composed of CAPs, licensed therapists, care coordinators and administrative support

personnel. During the initial consult with a CAP, there may be an in-person assessment (live or virtual), short term therapy or assistance with connection to community resources.

The co-location model facilitates mental health professionals working directly in the primary care setting to enhance care coordination.

In a collaborative/integrated care model, patient co-management occurs with a team-based approach, in which the primary care pediatrician, CAP and care manager share the medical record and schedule regular case reviews and discussions. In this model, there are five core principles: (Burkhart et al., 2019)

1. **Patient-centered care:** Conducted with patient and family engagement in primary care and mental health treatment planning.
2. **Population-based care:** A critical aspect of the collaborative care model, essential for the early identification of and intervention in mental health conditions through the patient registry, which identifies defined patient groups, e.g., those with ADHD, and systematically tracks their course.
3. **Measurement-based treatment:** Relies on an initial assessment with a symptom checklist or rating scale and serial repeats of the measure, determining efficacy of treatment with changes in score.
4. **Evidence-based care:** Incorporates treatments that are validated in research studies.
5. **Accountable care:** Groups of providers are held responsible for health outcomes of a designated population.

Through the collaborative/integrated care model, the problem of lack of familiarity and training in mental health by around two thirds of pediatricians is addressed, and comfort with care of mental health issues is improved (Tyler et al., 2017). Pediatricians may also consider seeking additional training in the following behavioral health interventions to better understand and contribute in the collaborative care model: (Burkhart et al., 2019)

1. Motivational interviewing
2. Cognitive behavioral therapy
3. Brief solution-focused intervention
4. Parent training in behavior management

As mentioned, the yardstick of effectiveness of collaborative care is a collection of behavioral health measures that are used for initial and follow up assessment of target symptoms. These clinically validated measures are as follows: (Burkhart et al., 2019)

1. Pediatric Symptom Checklist-17 (PSC-17)
2. Scale for Anxiety and Related Emotional Disorders (SCARED)
3. Center for Epidemiological Studies Depression Scale (CES-DC)
4. Patient Health Questionnaire-9 (PHQ-9)
5. Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS)

6. Modified Checklist for Autism in Toddlers (M-CHAT)
7. Social determinants of health screening
8. Adverse early life experiences screening
9. Strengths and Difficulties Questionnaire (SDQ)
10. Child Adolescent PTSD Reaction Index

Implementation of The collaborative/integrated care model has been shown to lead to better care outcomes than the traditional care model in which a referral is needed for off-site mental health management (Asarnow et al., 2015). Initiation and completion of mental health treatments as well as patient satisfaction show improvements with this care strategy over traditional approaches as well.

Children in foster care

State government health systems continue to face challenges related to increased utilization of psychotropic medications by children in foster care who often experience increased emotional and psychological stress as a result of abuse in neglectful, serial or chaotic caretaking environments and present with past trauma and reactive attachments that can mimic or complicate mental disorders (Texas Department of Family and Protective Services & the University of Texas at Austin College of Pharmacy, 2010). An analysis from the Centers for Medicare and Medicaid Services (CMS) of Medicaid data (2002–2007) for children in foster care ($n = 686,000$) in 47 states and the District of Columbia showed that while there was wide variation, the range of rates for polypharmacy was 1%–14% and 3%–22% for antipsychotic drug usage (Rubin et al., 2012).

Children in foster care must have the consent of a caregiver to receive any type of medication. However, the medication consent authority varies across the states, as some require a biological parent's permission while others require permission by a state board/panel, foster parent, the court or other designated authority (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. 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 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, use of multiple medications), involve atypical antipsychotic medications or demonstrate treatment-resistance (Solchany, 2012).

In a retrospective analysis of data on usage of mental health services and psychotropic medications among children ($n = 1,491$) age 6 and younger in foster care from 2009–2011, 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 (e.g., depression, anxiety, or posttraumatic stress disorder) (7%)

- 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 psychotropic 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 6
- Among children as young as age 4, three or more psychotropic classes began
- Likelihood of using antipsychotic, antidepressant and ADHD medications for three or more weeks per month increased with each year increase in age
- 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 medication exposure affecting brain size, neuronal circuitry and brain volume. There was also concern for metabolic adverse events in young children and authors emphasized the importance of routine metabolic monitoring to minimize adverse events and decrease prescribing. 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. The prescribing of antipsychotics to youth is significantly more common in the US than in other countries. (Mackie et al., 2021) While increasing evidence justifies the use of antipsychotics to treat primary psychotic disorders in youth and adolescents, the majority of antipsychotic use is for conditions which lack FDA approval. A study of the general pediatric population in North Carolina noted that antipsychotics were often prescribed to treat aggression (48%), irritability (19%), and impulsivity (11%). (Christian et al., 2013)

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). 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 youths not in foster care (1.4%).

- “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.” Demographic characteristics explained only a small portion of the difference. (Vanderwerker et al., 2014, p. 4)

Vanderwerker et al. suggested 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
- 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 findings of other studies 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).

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 was five times greater than in privately insured youth, and indications were mostly for clinician-reported externalizing behavior disorders rather than FDA-approved indications, e.g., psychotic disorders, BD and autism-related irritability.

Following the Substance Abuse and Mental Health Services Administration’s (SAMHSA’s) publishing of *Guidance on Strategies to Promote Best Practice in Antipsychotic Prescribing for Children and Adolescents*, from 2011–2015, prescriptions for antipsychotic medications declined for both Medicaid and commercially insured youth. Prescriptions for Medicaid-insured youth dropped from 1.6% to 1.2% and for commercially insured youth from 0.5% to 0.4%. Of note, this study reflects the same, but to a lesser extent, disparity between Medicaid and commercially insured populations with Medicaid-insured youth three times more likely to receive antipsychotics than commercially insured youth.

Further studies looked specifically at children aged 1–5 years and similar declines were noted with prescriptions dropping from 3.5% to 2.5% among Medicaid populations and 2.0% to 1.4% for commercially insured youths. In this age group, antipsychotic prescriptions were most commonly written for males and for diagnoses of ADHD, disruptive behavior disorders, ASDs and tic disorders. Racial disparities in prescribing existed across this age group with increased rates of prescribing antipsychotic medication among youth who were non-Hispanic Black, Hispanic and non-Hispanic Other. Decreased prescribing of antipsychotic medication to non-Hispanic Whites was noted.

Foster care populations are consistently observed to have higher rates of prescribing than other groups and one study noted that after adjusting for diagnostic and demographic variation, youth in foster care

were prescribed antipsychotics two times as often as their non-foster care Medicaid counterparts. (SAMSHA, 2019)

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. A review of antipsychotic-related Medicaid prior authorization policies for youth show: (Mackie et al., 2021; Schmid et al., 2015)

- By 2015, 31 states implemented prior authorization policies for antipsychotic medications prescribed to Medicaid youth
- By 2013, 45 states and the District of Columbia implemented at least one measure to improve psychotropic oversight in foster care youth
- 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

Authors referred to a study by Stein et al. (2014) showing minimal effect of an antipsychotic-related Medicaid prior authorization policy in one mid-Atlantic state to reduce antipsychotic use in children. They cautioned about potential unintended consequences of such a policy, 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 in children under 13 years of age and one of which required no prior authorization (Stein et al., 2014). Following the start of the prior authorization period (August 2009), authors examined the effect of the prior authorization policy on the rate of antipsychotic prescribing among Medicaid-enrolled children and found:

- In states requiring prior authorization for antipsychotics, the average monthly rate of antipsychotics usage decreased from 9.8% to 9.5% (0.3% decrease) in children 6–12 years of age, and increased from 0.32% to 2.1% in children 0–5 years of age.
- In states with no prior authorization for antipsychotics, the average monthly rate of antipsychotics usage decreased slightly to 5.9% (0.08% decrease) in children 6–12 years of age, and to 0.65% (0.009% decrease) in children 0–5 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 6–12-year-olds but did not have a significant effect on antipsychotic use among 0–5-year-olds” (Stein et al., 2014, p. 374). Authors indicated the need for further research to understand the clinical effects and effects on utilization of prior authorization policies.

A national telephone-administered survey assessed the implementation strategies of state Medicaid psychotropic-monitoring programs targeting youths using data collected from August 2011 through December 2012 (dosReis et al., 2016). Authors noted variability among the types of state Medicaid psychotropic-monitoring programs, with prior authorization being the most common model. Authors noted that, in many states, programs focused exclusively on antipsychotics, and that youths in foster care have higher rates of antipsychotic use than other Medicaid-insured youths. They advised that monitoring of 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 AACAP parameters
- Lack of metabolic monitoring was the main reason for not meeting best practices

A recent article reviewed the effectiveness of a number of interventions designed to improve use of antipsychotic medications in youth, with many of the measures focused on youth in foster care. These interventions include prior authorization, retrospective drug utilization review, consultation programs between child psychiatry and primary care, clinical education, efforts to share decision making with the clinician, youth and caregiver, and efforts to improve care delivery including improved care coordination and building evidence-based systems of care. (Mackie et al., 2021) In eight programs implementing prior authorization for antipsychotics which utilized tests of significance, seven demonstrated a significant reduction in antipsychotic use among the targeted group. The eighth program showed a significant reduction in treatment rates for youth aged 6–12 years but no impact on children younger than 5 years of age. Another study focused on prescribing trends rather than antipsychotic use. It showed that prior authorization significantly reduced prescribing by CAPs but did not have a similar impact on other prescribers including pediatricians, general psychiatrists and neurologists. (Mackie et al., 2021) In the Arkansas Medicaid program foster care population studied, antipsychotic use was seen to decrease by 85.70% for children younger than 6 years old and 36.03% for those aged 6–12, from 7/2008–7/2015, with implementation of prior authorization strategies. (Mackie et al., 2021) Two studies focused on drug utilization review among foster care youth were examined. Through implementation of best practice parameters in Texas, prescribing of antipsychotics has decreased over time. In Mississippi, no change in prescribing was noted following implementation of drug utilization review to improve cardiometabolic side effects associated with antipsychotic use. (Mackie et al., 2021) Insufficient evidence exists to assess the impact of clinician prescribing support and delivery system enhancement. Additional concerns exist related to the adequacy of utilization decreases in antipsychotic prescribing as a marker for appropriate antipsychotic prescribing and further studies are warranted to elucidate these issues. (Mackie et al., 2021)

In another study, the relationship between measures of the severity of child maltreatment and Medicaid expenditures for psychotropic medications is examined (Raghavan et al., 2016). Authors linked child participants (n = 4,453) in the first *National Survey of Child and Adolescent Well-Being* from 36 states to their Medicaid claims. They discussed how Medicaid bears most of the costs of mental health services for the principal consumers of these services, i.e., the children subject to abuse or neglect who are served by child protection agencies for suspected maltreatment. Measures of severity of child maltreatment were determined through an assessment, by the child's welfare worker, of

physical abuse, sexual abuse, neglect and abandonment, including the number of different types of abuse experienced and the 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., 2016, 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.

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 et al., 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 & 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 AACAP notes concerning trends in the prescription of psychotropic medications: increased use, especially for youth in foster care, potential adverse health 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, 2015, p. 1).

The AACAP indicates that evidence shows that prescriptions of psychotropic medications for youth have been increasing. They note that antipsychotics were the fastest growing class of psychotropic medication among young people from 2003–2010, and the increase was likely due to increased use for aggression. They also reported an increase in the use of second-generation antipsychotics (SGAs), often in combination with other psychotropic medications, which “was not restricted to youth in foster care, or to those youth presumed to have the most severe or acute mental health needs,” but seen primarily among “youth who were Medicaid-eligible due to low income, were not hospitalized, and did not have comorbid ADHD or intellectual disability” (AACAP, 2015, p. 12). The AACAP stated that this

pattern represents “a changing trend in prescribing practice that increasingly favors concurrent SGA use in less-impaired youth” (AACAP, 2015, 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 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 prescribing 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 health needs where evidence-based psychosocial interventions, e.g., TFCBT, child-parent psychotherapy, Alternatives for Families: a Cognitive Behavioral 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 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 co-management employing telephonic and 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 these programs as viable alternative approaches (Pidano & Honigfeld, 2012). The AACAP recommends oversight and monitoring practices that promote collaboration among state and local agencies, managed care organizations and professionals, with CAPs offering support, leadership and expertise (AACAP, 2015). For children in multiple child-serving systems, the AACAP recommends collaboration among all professionals.

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:

- Identify clinical and biological response predictors of treatment
- Generate precise benefit and risk estimates of treatment in patient subgroups
- Increase understanding of psychotropic drug exposure on the developing brain
- Study the moderators, mediators, biomarkers and biosignatures of treatment outcome
- Test multi-stage treatment strategies utilizing dynamic/multimodal treatment regimens

This clinical research agenda is necessary to accomplish the ideal goal of increased personalized treatment of our young population (Correll et al., 2011). The AACAP (2015) cautions, “The research base on treating mental health disorders, while growing, remains limited” (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).

References

1. Agency for Health Care Administration. (2019). *2018-19 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents*. Florida Medicaid Drug Therapy Management Program for Behavioral Health, University of South Florida. <https://floridabhcenter.org/>.
2. Allen, K., & Jensen, P. S. (2008). *The use of psychotropic medications for children Involved in child welfare* [Webinar]. Center for Health Care Strategies. http://www.chcs.org/media/child_welfare_webinar_021408.pdf.
3. American Academy of Child and Adolescent Psychiatry. (2015). *Recommendations about the use of psychotropic medications for children and adolescents involved in child-serving systems*. https://www.aacap.org/App_Themes/AACAP/docs/clinical_practice_center/systems_of_care/AACAP_Psychotropic_Medication_Recommendations_2015_FINAL.pdf.
4. American Academy of Child and Adolescent Psychiatry. (2019). *Psychotherapy for children and adolescents: Different types*. https://www.aacap.org/AACAP/Families_and_Youth/Facts_for_Families/FFF-Guide/Psychotherapies-For-Children-And-Adolescents-086.aspx.
5. American Academy of Child and Adolescent Psychiatry. (2020). *Clinical use of pharmacogenetic tests in prescribing psychotropic medications for children and adolescents*. https://www.aacap.org/aacap/Policy_Statements/2020/Clinical-Use-Pharmacogenetic-Tests-Prescribing-Psychotropic-Medications-for-Children-Adolescents.aspx.
6. American Academy of Child and Adolescent Psychiatry. (n.d. -a). *Bipolar Disorder Parents' Medication Guide for Bipolar Disorder in Children and Adolescents*. Retrieved June 24, 2021, from https://www.aacap.org/App_Themes/AACAP/docs/resource_centers/resources/med_guides/parentsmedguide_bipolar.pdf.
7. American Academy of Child and Adolescent Psychiatry. (n.d. -b). *Collaborative Mental Health Care in Pediatric Primary Care*. Retrieved March 27, 2022, from https://www.aacap.org/App_Themes/AACAP/docs/Introduction%20to%20Collaborative%20Care%20lecture.pdf.
8. American Academy of Pediatrics. (n.d.). *Mental Health Initiatives*. Retrieved March 27, 2022. <https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/About-Us.aspx>.
9. Andersen, S. L., & Navalta, C. P. (2004). Altering the course of neurodevelopment: A framework for understanding the enduring effects of psychotropic drugs. *International Journal of Developmental Neuroscience*, 22, 423–440.

10. Andersen, S. L., & Navalta, C. P. (2011). New frontiers in developmental neuropharmacology: Can long-term therapeutic effects of drugs be optimized through carefully timed early intervention? *J Child Psychol Psychiatry*, 52(4), 476–503.
11. Anderson, L. E., Chen, M. L., Perrin, J. M., & Cleave, J. C. (2015). Outpatient visits and medication prescribing for US children with mental health conditions. *Pediatrics*, 136(5), e1178–e1185.
12. APA Working Group on Psychoactive Medication for Children and Adolescents. (2006). *Report of the Working Group on Psychoactive Medications for Children and Adolescents: Psychopharmacological, psychosocial, and combined interventions for childhood disorder: Evidence base, contextual factors, and future directions*. American Psychological Association.
13. Asarnow, J. R., Rozenman, M., Wiblin, J., & Zeltzer, L. (2015). Integrated Medical-Behavioral Care Compared With Usual Primary Care for Child and Adolescent Behavioral Health: A Meta-analysis. *JAMA pediatrics*, 169(10), 929–937. <https://doi.org/10.1001/jamapediatrics.2015.1141>.
14. Banerjee, S. P., Bhandari, R. P., & Rosenberg, D. R. (2005). Use of low-dose selective serotonin reuptake inhibitors for severe, refractory choking phobia in childhood. *Journal of Developmental and Behavioral Pediatrics*, 26(2), 123–127.
15. Bassarath, L. (2003). Medication Strategies in Childhood Aggression: A Review. *Canadian journal of psychiatry*, 48, 367–73.
16. Bethell, C. (n.d.). Data Resource Center for Child & Adolescent Health. Retrieved March 27, 2022, from <https://www.childhealthdata.org/>.
17. Bigorra, A., Garolera, M., Guijarro, S., & Hervas, A. (2015). Long-term far-transfer effects of working memory training in children with ADHD: A randomized controlled trial. *European Child and Adolescent Psychiatry*, 25(8), 853–867.
18. Birmaher, B., Brent, D., & the AACAP Work Group on Quality Issues: Bernet, W., Bukstein, O., Walter, H., Benson, R. S., Chrisman, A., Farchione, T., Greenhill, L., Hamilton, J., Keable, H., Kinlan, J., Schoettle, U., & Stock, S. (2007). Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *Journal of the American Academy of Child Adolescent Psychiatry*, 46(11), 1503–1526.
19. Blader, J. C., Schooler, N. R., Jensen, P. S., Pliszke, S. R., & Karantaris V. (2009). Adjunctive divalproex versus placebo for children with ADHD and aggression refractory to stimulant monotherapy. *American Journal of Psychiatry*, 166(12), 1392–1401.
20. Brasic, J. R., & Pataki, C. (2021). *Autism management and treatment*. Medscape. <http://emedicine.medscape.com/article/912781-treatment>.

21. Brent, D., Emslie, G., Fassler, D., Kratochvil, C., March, J., Robb, A., Shaffer, D., & Singh, M. (2010). The use of medication in the treatment of childhood and adolescent depression: Information for patients and families. *Parents Med Guide*.
<http://www.parentsmedguide.org/parentsmedguide.htm#9>.
22. Brewerton, T. D., & D'Agostino, M. (2017). Adjunctive use of olanzapine in the treatment of avoidant restrictive food intake disorder in children and adolescents in an eating disorders program. *Journal of Child and Adolescent Psychopharmacology*, 27(10), 920–922.
23. Burkhart, K., Asogwa, K., Muzaffar, N., & Gabriel, M. (2019). Pediatric integrated care Models: A systematic review. *Clinical Pediatrics*, 59(2), 148–153. <https://doi.org/10.1177/0009922819890004>
24. Carrasco, M., Volkmar, F. R., & Bloch, M. H. (2012). Pharmacologic treatment of repetitive behaviors in autism spectrum disorders: Evidence of publication bias. *Pediatrics*, 129(5), e1301–e1310.
25. Cataife, G., & Weinberg, D. A. (2015). Racial and ethnic differences in antipsychotic medication use among children enrolled in Medicaid. *Psychiatric Services*, 66(9), 946–951.
26. Centers for Disease Control and Prevention. (n.d.). *Data and statistics on children's mental health*.
<https://www.cdc.gov/childrensmentalhealth/data.html>.
27. Child and Adolescent Health Measurement Initiative. 2020-2021 National Survey of Children's Health (NSCH) data query. Data Resource Center for Child and Adolescent Health supported by the U.S. Department of Health and Human Services, Health Resources and Services Administration (HRSA), Maternal and Child Health Bureau (MCHB). Retrieved 10/24/2022 from www.childhealthdata.org.
28. Christian, R. B., Farley, J. F., Sheitman, B., McKee, J. R., Wei, D., Diamond, J., Chrisman, A., Barnhill Jr., L. J., Wegner, L., Palmes, G., Trygstad, T., Pfeifferberger, T., Wegner, S. E., Best, R., & Sikich, L. (2013). A+KIDS, a web-based antipsychotic registry for North Carolina youths: An alternative to prior authorization. *Psychiatric Services*, 64(9), 893–900.
29. Cincinnati Children's Hospital Medical Center Best Evidence Statement (BESt). (2010). *Treatment of children and adolescents with major depressive disorder (MDD) during the acute phase*.
<https://www.cincinnatichildrens.org/research/divisions/j/anderson-center/evidence-based-care/recommendations>.
30. Cohen, J. A., Bukstein, O., Walter, H., Benson, R. S., Chrisman, A., Farchione, T. R., Hamilton, J., Keable, H., Kinlan, J., Schoettle, U., Siegel, M., Stock, S., Medicus, J., & AACAP Work Group on Quality Issues. (2010). Practice parameter for the assessment and treatment of children and adolescents with posttraumatic stress disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 49(4), 414–430.

31. Connor, D. F., Grasso, D. J., Slivinsky, M. D., Pearson, G. S. & Banga, A. (2013). An open-label study of guanfacine extended release for traumatic stress related symptoms in children and adolescents. *Journal of Child and Adolescent Psychopharmacology*, 23(4), 244–251.
32. Connor, D. F., Newcorn, J. H., Saylor, K. E., Amann, B. H., Scahill, L., Robb, A. S., Jensen, P. S., Vitiello, B., Findling, R. L., & Buitelaar, J. K. (2019). Maladaptive Aggression: With a Focus on Impulsive Aggression in Children and Adolescents. *Journal of Child and Adolescent Psychopharmacology*, 29(8), 576–591.
33. Cooper, W. O., Hickson, G. B., Fuchs, C., Arbogast, P. G., & Ray, W. (2004). New users of antipsychotic medications among children enrolled in TennCare. *Archives of Pediatric and Adolescent Medicine*, 158(8), 753–759.
34. Correll, C. U., Kratochvil, C. J., & March, J. S. (2011). Developments in pediatric psychopharmacology: Focus on stimulants, antidepressants, and antipsychotics. *Journal of Clinical Psychiatry*, 72(5), 655–670.
35. Correll, C. U., Sheridan, E. M., & DelBello, M. P. (2010). Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: A comparative analysis of acute, randomized, placebo-controlled trials. *Bipolar Disorders*, 12, 116–141.
36. Couturier J., Isserlin L., Norris M., Spettigue W., Brouwers M., Kimber M., McVey G., Webb C., Findlay S., Bhatnagar N., Snelgrove N., Ritsma A., Preskow W., Miller C., Coelho J., Boachie A., Steinegger C., Loewen R., Loewen T., Waite E., Ford C., Bourret K., Gusella J., Geller J., LaFrance A., LeClerc A., Scarborough J., Grewal S., Jericho M., Dimitropoulos G., Pilon D. (2020). Canadian practice guidelines for the treatment of children and adolescents with eating disorders. *Journal of Eating Disorders*, 8(4).
37. Cox, G. R., Callahan, P., Churchill, R., Hunot, V., Merry, S. N., Parker, A. G., & Hetrick, S. E. (2014). Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. *Cochrane Database of Systematic Reviews*, (11).
38. Crystal, S., Olfson, M., Huang, C., Pincus, H., & Gerhard, T. (2009). Broadened use of atypical antipsychotics: Safety effectiveness, and policy challenges. *Health Affairs (Project Hope)*, 28(5), w770–w781.
39. Department of Health & Human Services. (n.d.). *Collaborative efforts and technical assistance resources to strengthen the management of psychotropic medications for vulnerable populations*. <https://www.medicaid.gov/federal-policy-guidance/downloads/cib-08-24-12.pdf>.
40. Dobson, E. T., & Strawn, J. R. (2016). Pharmacotherapy for pediatric generalized anxiety disorder: A systematic evaluation of efficacy, safety and tolerability. *Pediatric Drugs*, 18(1), 45–53.

41. dosReis, S., Tai, M. H., Goffman, D., Lynch, S. E., Reeves, G., & Shaw, T. (2014). Age-related trends in psychotropic medication use among very young children in foster care. *Psychiatric Services*, 65(12), 1452–1457.
42. dosReis, S., Tai, M. H., Camelo, W. C., & Reeves, G. (2016). A national survey of state Medicaid psychotropic-monitoring programs targeting youths. *Psychiatric Services*, 67(1), 1146–1148.
43. Eghaneyan, B. H., Sanchez, K., & Mitschke, D. B. (2014). Implementation of a collaborative care model for the treatment of depression and anxiety in a community health center: Results from a qualitative case study. *Journal of Multidisciplinary Healthcare*, 7, 503–513.
44. Ellingrod, V. L. (2019). Pharmacogenomic testing: What the FDA says. *Current Psychiatry*, 18(4), 29–33.
45. Epstein, R. A., Bobo, W. V., Shelton, R. C., Arbogast, P. G., Morrow, J. A., Wang, W., Chandrasekhar, R., & Cooper, W. O. (2013). Increasing use of atypical antipsychotics and anticonvulsants during pregnancy. *Pharmacoepidemiology and Drug Safety*, 22(7), 794–801.
46. Ercan, E. S., Copkunol, H., Cykoethlu, S., & Varan, A. (2003). Olanzapine treatment of an adolescent girl with anorexia nervosa. *Human Psychopharmacology*, 18(5), 401–403.
47. Fanton, J., & Gleason, M. M. (2009). Psychopharmacology and preschoolers: A critical review of current conditions. *Child and Adolescent Psychiatric Clinics of North America*, 18(3), 753–771.
48. Findling, R. L., Drury, S. S., Jensen, P. S., Rappoport, J. L., the AACAP Committee on Quality Issues: Bukstein, O. G., Walter, H. J., Benson, S., Chrisman, A., Farchione, T. R., Hamilton, J., Keable, H., Kinlan, J., Schoettle, U., Siegel, M., & Stock, S. (2011). Practice parameter for the use of atypical antipsychotic medication in children and adolescents. American Academy of Child and Adolescent Psychiatry.
49. Frank, G. K. (2016). Aripiprazole, a partial dopamine agonist to improve adolescent anorexia nervosa-A case series. *International Journal of Eating Disorders*, 49(5), 529–533.
50. Frank, G. K., Kaye, W. H., & Marcus, M. D. (2001). Sertraline in underweight binge eating/purging-type eating disorders: Five case reports. *International Journal of Eating Disorders*, 29(4), 495–498.
51. Frank, G. K., Schott, M. E., Hagman, J. O., Schiel, M. A., DeGuzman, M. C., & Rossi, B. (2017). The partial dopamine D2 receptor agonist aripiprazole is associated with weight gain in adolescent anorexia nervosa. *International Journal of Eating Disorders*, 50(4), 447–450.
52. Franklin, M. E., Sapyta, J., Freeman, J. B., Khanna, M., Compton, S., Almirall, D., Moore, P., Choate-Summers, M., Garcia, A., Edson, A. L., Foa, E. B., & March, J. S. (2011). Cognitive behavior therapy augmentation of pharmacotherapy in pediatric obsessive-compulsive disorder. *JAMA*, 306(11), 1224–1232.

53. Garcia, A. M., Sapyta, J. J., Moore, P. S., Freeman, J. B., Franklin, M. E., March, J. S., & Foa, E. B. (2010). Predictor and moderators for treatment outcome in pediatric obsessive compulsive treatment study (POTS I). *Journal of the American Academy of Child and Adolescent Psychiatry*, 49(10), 1024–1033.
54. Gee, R. L., & Telew, N. (1999). Obsessive-compulsive disorder and anorexia nervosa in a high school athlete: A case report. *Journal of Athletic Training*, 34(4), 375–378.
55. Geller, D. A., March, J., & the AACAP Committee on Quality Issues: Walter, H. J., Bukstein, O. G., Benson, R. S., Chrisman, A., Farchione, T. R., Hamilton, J., Keable, H., Kinlan, J., Schoettle, U., Siegel, M., & Stock, S. (2012). Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 51(1), 98–113.
56. Geller, B., Luby, J. L., Joshi, P., Wagner, K. D., Emslie, G., Walkup, J. T., Axelson, D. A., Bolhofner, K., Robb, A., Wolf, D. V., Riddle, M. A., Birmaher, B., Nusrat, N., Ryan, N. D., Vitiello, B., Tillman, R., & Lavori, P. (2012). A randomized controlled trial of risperidone, lithium, or divalproex sodium for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents. *Archives of General Psychiatry*, 69(5), 515–528.
57. Gentile, S. (2010a). Antidepressant use in children and adolescents diagnosed with major depressive disorder: What can we learn from the published data? *Reviews on Recent Clinical Trials*, 5(1), 63–75.
58. Gentile S. (2010b). Review: Neurodevelopmental effects of prenatal exposure to psychotropic medications. *Depression and Anxiety*, 27, 675–686.
59. Gibbons, R. D., Perrignon, M. C., Hur, K., Conti, R. M., Valuck, R. J., & Brent, D. A. (2015). Antidepressant treatment suicide attempts and self-inflicted injury in children and adolescents. *Pharmacoepidemiology and Drug Safety*, 24(2), 208–214.
60. Gleason, M. M., Egger, H. L., Emslie, G. J., Greenhill, L. L., Kowatch, R. A., Lieberman, A. F., Luby, J. L., Owens, J., Scahill, L. D., Scheeringa, M. S., Stafford, B., Wise, B., & Zeanah, C. H. (2007). Psychopharmacological treatment for very young children: Context and guidelines. *Journal of the American Academy of Child Adolescent Psychiatry*, 46(12), 1532–1572.
61. Government Accountability Office. (2012). *Children’s mental health: Concerns remain about appropriate services for children in Medicaid and foster care*. <https://www.gao.gov/assets/gao-13-15.pdf>.
62. Guo, T., Xiang, Y., Xiao, L., Hu, C-Q., Chiu, H. F. K., Ungvari, G. S., Correll, C. U., Lai, K. Y., Feng, L., Geng, Y., Feng, Y., & Wang, G. (2015). Measurement-based care versus standard care for major

depression: A randomized controlled trial with blind raters. *American Journal of Psychiatry*, 172(10), 1004–1013.

63. Gurnani, T., Ivanov, L., & Newcorn, J. H. (2016). Pharmacotherapy of aggression in child and adolescent psychiatric disorders. *Journal of Child and Adolescent Psychopharmacology*, 26(1), 65–73.
64. Hagman, J., Gralla, J., Sigel, E., Ellert, S., Dodge, M., Gardner, R., O’Lonergan, T., Frank, G., & Wamboldt, M. Z. (2011). A double-blind, placebo-controlled study of risperidone for the treatment of adolescents and young adults with anorexia nervosa: A pilot study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 50(9), 915–924.
65. Hillebrand, J. J. G., van Elburg, A. A., Kas, M. J. H., van Engeland, H., & Adan, R. A. H. (2005). Olanzapine reduces physical activity in rats exposed to activity-based anorexia: possible implications for treatment of anorexia nervosa. *Biological Psychiatry*, 58(8), 651–657.
66. Hilt, R. J. (2012). Monitoring psychiatric medications in Children. *Pediatric Annals*, 41(4), 157–163.
67. Holtkamp, K., Konrad, K., Kaiser, N., Ploenes, Y., Heussen, N., Grzella, I., & Herpertz-Dahlmann, B. (2005). A retrospective study of SSRI treatment in adolescent anorexia nervosa: Insufficient evidence for efficacy. *Journal of Psychiatric Research*, 39(3), 303–310.
68. Howie, L. D., Pastor, P. N., & Lukacs, S. L. (2014). Use of medication prescribed for emotional or behavioral difficulties among children aged 6-17 years in the United States, 2011-2012. *NCHS Data Brief*, 148, 1–8.
69. Hrdlicka, M., Beranova, I., Zamecnikova, R., & Urbanek, T. (2008). Mirtazapine in the treatment of adolescent anorexia nervosa. Case-control study. *European Child and Adolescent Psychiatry*, 17(3), 187–189.
70. Jaafar, N. R., Daud, T. I. M., Rahman, F. N. A., & Baharudin, A. (2007). Mirtazapine for anorexia nervosa with depression. *Australian and New Zealand Journal of Psychiatry*, 41(9), 768–769.
71. Kafantaris, V., Leigh, E., Hertz, S., Berest, A., Schebendach, J., Sterling, W. M., Saito, E., Sunday, S., Higdon, C., Golden, N. H., & Malhotra, A. K. (2011). A placebo-controlled pilot study of adjunctive olanzapine for adolescents with anorexia nervosa. *Journal of Child and Adolescent Psychopharmacology*, 21(3), 207–212.
72. Kieler, H., Artama, M., Engeland, A., Ericsson, O., Furu, K., Gissler, M., Nielsen, R. B., Norgaard, M., Stephansson, O., Valdimarsdottir, U., Zoega, H., & Haglund, B. (2012). Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: Population based cohort study from the five Nordic countries. *BMJ*, 344, d8012.

73. Klingberg, T., Fernell, E., Olesen, P., Johnson, M., Gustafsson, P., Dahlström, K., Gillberg, C. G., Forssberg, H., & Westerberg, H. (2005) Computerized training of working memory in children with ADHD - A randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, 44, 177–186.
74. Kodish, I., Rockhill, C., & Varley, C. (2011). Pharmacotherapy for anxiety disorders in children and adolescents. *Dialogues in Clinical Neuroscience*, 13(4), 439–452.
75. Kohlstadt, I., & Vitiello, B. (2010). Use of atypical antipsychotics in children: Balancing safety and effectiveness. *American Family Physician*, 81(5), 585–589.
76. Kracke, E. J., & Tosh, A. K. (2014) Treatment of anorexia nervosa with long-term risperidone in an outpatient setting: A case study. *Springerplus*, 3, 706.
77. Kudriakova, T. B., Sirota, L. A., Rozova, G. I., & Gorkov, V. A. (1992). Autoinduction and steady-state pharmacokinetics of carbamazepine and its major metabolites. *British journal of clinical pharmacology*, 33(6), 611–615.
78. Larsen, E. R., Damkier, P., Pedersen, L. H., Fenger-Gron, J., Mikkelsen, Nielsen, R. E., Linde, V. J., Knudsen, H. E. D., Skaarup, L., & Videbech, P. (2015). Use of psychotropic drugs during pregnancy and breast-feeding. *Acta Psychiatrica Scandinavica Supplementum*, 445, 1–28.
79. Lexicomp. (n.d.). <https://online.lexi.com>.
80. Liu, H. Y., Potter, M. P., Woodworth, Y., Yorks, D., Petty, C. R., Wozniak, J. R., Faraone, S. V., & Biederman, J. (2011). Pharmacologic treatment for pediatric bipolar disorder: A review and meta-analysis. *Journal of the American Academy of Child Adolescent Psychiatry*, 50(8), 749–762.
81. Lock, J., & La Via, M. C. (2015). Practice parameter for the assessment and treatment of children and adolescents with eating disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, 54(5), 412–425.
82. Lorberg, B., Davico, C., Martsenkovskyi, D., & Vitiello, B. (2019). Principles in using psychotropic medication in children and adolescents. In Rey, J. M. & Martin, A. (Eds.), *IACAPAP e-Textbook of Child and Adolescent Mental Health*. International Association for Child and Adolescent Psychiatry and Allied Professions.
83. Lyles, B., Sarkis, E., & Kempf, J. P. (1990), Fluoxetine and anorexia. *Journal of the American Academy of Child and Adolescent Psychiatry*, 29(6), 984–985.
84. Mackie, T. I., Schaefer, A. J., Karpman, H. E., Lee, S. M., Bellonci, C., & Larson, J. (2021). Systematic review: System-wide interventions to monitor pediatric antipsychotic prescribing and promote best practice. *Journal of the American Academy of Child and Adolescent Psychiatry*, 60(1), 76–104.

85. Madden, J. M., Lakoma, M. D., Lynch, F. L., Rusinak, D., Owen-Smith, A. A., Coleman, K. J., Quinn, V. P., Yau, V. M., Qian, Y. X., & Croen, L. A. (2017). Psychotropic medication Use among insured children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 47(1), 144–154.
86. Magellan Health, Inc. (2020). *Clinical practice guideline for patients with attention deficit/hyperactivity disorder*.
<https://www.magellancompletecareoffl.com/documents/2020/09/magellan-health-services-clinical-guidelines-for-adhd.pdf/>.
87. McClellan, J., Kowatch, R., Findling, R. L., & the Work Group on Quality Issues. (2007). Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46(1), 107–125.
88. Mehler-Wex, C., Romanos, M., Kirchheiner, J., & Schulze U. M. E. (2008). Atypical antipsychotics in severe anorexia nervosa in children and adolescents--Review and case reports. *European Eating Disorders Review*, 16(2), 100–108.
89. Meyers, S. M., Plauché, J. C., & the Council on Children with Disabilities. (2007). Management of children with autism spectrum disorders. *Pediatrics*, 120(5), 1162–1182. Reaffirmed September 2010.
90. Micromedex. (n.d.). <https://www.ibm.com/watson-health/about/micromedex>.
91. Mitchell, J. E., & Peterson, C. B. (2020). Anorexia nervosa. *New England Journal of Medicine*, 382, 1343–1351.
92. Morris, J., & Stone, G. (2011). Children and psychotropic medication: A cautionary note. *Journal of Marital and Family Therapy*, 37(3), 299–306.
93. Naguy, A., & Al-Mutairi, A. (2018). An adolescent male with anorexia nervosa favorably responded to mirtazapine. *American Journal of Therapeutics*, 25(6), e675–e676.
94. National Institute of Mental Health. (n.d. -a). *Mental Health Medications*.
<https://www.nimh.nih.gov/health/topics/mental-health-medications>.
95. National Institute of Mental Health. (n.d. -b). *Anxiety Disorders*.
<https://www.nimh.nih.gov/health/topics/anxiety-disorders>.
96. Newman-Toker, J. (2000). Risperidone in anorexia nervosa. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39(8), 941–942.
97. Norris, M. L., Spettigue, W., Buchholz, A., Henderson, K. A., Gomez, R., Maras, D., Gaboury, I., & Ni, A. (2011). *Journal of Child and Adolescent Psychopharmacology*, 21(3), 213–220.

98. Pacchiarotti, I., León-Caballero, J., Murru, A., Verdolini, N., Furio, M. A., Pancheri, C., Valenti, M., Samalin, L., Roigé, E. S., Gonzalez-Pinto, A., Montes, J. M., Benabarre, A., Crespo, J. M., Perrino, C. D., Goikolea, J. M., Gutierrez-Rojas, L., Carvalho, A. F., & Vieta, E. (2016). Mood stabilizers and antipsychotics during breastfeeding: Focus on bipolar disorder. *European Neuropsychopharmacology*, 26(10), 1562–1578.
99. Pagsberg, A. K., Tarp, S., Glintborg, D., Stenstrøm, A. D., Fink-Jensen, A., Correll, C. U., & Christensen, R. (2017). Acute antipsychotic treatment of children and adolescents with schizophrenia-spectrum disorders: A systematic review and network meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*, 56(3), 191–202.
100. *Paroxetine pregnancy and breastfeeding warnings*. (2021). Drugs.com. <http://www.drugs.com/pregnancy/paroxetine.html?printable=1>.
101. Patel, D. R., Feucht, C., Brown, K., & Ramsay, J. (2018). Pharmacological treatment of anxiety disorders in children and adolescents: a review for practitioners. *Translational pediatrics*, 7(1), 23–35.
102. Pernia, S., & Demaagd, G. (2016). The new pregnancy and lactation labeling rule. *P & T*, 41(11), 713–715.
103. Pidano, A. E., & Honigfeld, L. (2012). Pediatric psychopharmacology: Context, model programs, and considerations for care. *Psychiatric Services*, 63(9), 929–934.
104. Plauché, J. C., Meyers, S. M., & the Council on Children with Disabilities. (2007). Identification and evaluation of children with autism spectrum disorders. *Pediatrics*, 120(5), 1183–1215. Reaffirmed September 2010.
105. Raghavan, R., Brown, D. S., Allaire, B., Ross, R. E., & Landsverk, J. (2016). Associations between magnitude of child maltreatment and Medicaid expenditures for psychotropic medications. *Psychiatric Services*, 67(8), 916–919.
106. Rosato, N. S., Correll, C. U., Pappadopulos, E., Chait, A., Crustal, S., & Jensen, P. S. (2012). Treatment of maladaptive aggression in youth: CERT guidelines II. Treatments and ongoing management. *Pediatrics*, 129(6), e1577–e1586.
107. Rubin, D., Matone, M., Huang, Y-S., dosReis, S., Feudtner, C., & Localio, R., (2012). *Psychotropic medication use among children in foster care: A national and state-level perspective*. Policy Lab, Center to Bridge Research, Practice and Policy. http://policylab.us/images/pdf/hsr_1pager_final.pdf.

108. Ruch, D. A., Sheftall, A. H., Schlagbaum, P., Rausch, J., Campo, J. V., & Bridge, J. A. (2019). Trends in suicide among youth aged 10 to 19 years in the United States, 1975 to 2016. *JAMA Network Open*, 2(5), e193886.
109. Sakolsky, D., & Birmaher, B. (2012). Developmentally informed pharmacotherapy for child and adolescent depressive disorders. *Child and Adolescent Psychiatric Clinics of North America*, 21(2), 313–325.
110. Schatzberg, A. F., Cole, J. O., & DeBattista, C. (2010). *Manual of clinical psychopharmacology* (7th ed.). American Psychiatric Association Publishing, Inc.
111. Schatzberg, A. F., & DeBattista, C. (2019). *Manual of clinical psychopharmacology* (9th ed.). American Psychiatric Association Publishing, Inc.
112. Schmid, I., Burcu, M., & Zito, J. M. (2015). Medicaid prior authorization policies for pediatric use of antipsychotic medications. *JAMA*, 313(9), 966–967.
113. Seida, J. C., Schouten, J. R., Boylan, K., Newton, A. S., Mousavi, S. S., Beaith, A., Vandermeer, B., Dryden, D. M., & Carrey, N. (2012). Antipsychotics for children and young adults: A comparative effectiveness review. *Pediatrics*, 129, e771.
114. Singh, M. K., & Chang, K. (2012). The neural effects of psychotropic medications in children and adolescents. *Child and Adolescent Psychiatric Clinics of North America*, 21(4), 753–771.
115. Solchany, J. (2012). *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. https://www.americanbar.org/groups/public_interest/child_law/resources/child_law_practiceonline/child_law_practice/vol_31/Feb12/psychotropic_medicationandchildreninfostercaretipsforadvocatesan/.
116. Soumerai, S., & Koppel, R. (2018, August 29). *FDA’s continuing use of ‘black box’ for antidepressants ignores the harms of this warning*. STAT. <https://www.statnews.com/2018/08/29/fda-antidepressants-black-box-warnings-harms/comment-page-1/>.
117. Spettigue, W., Norris, M. L., Maras, D., Obeid, N., Feder, S., Harrison, M. E., Gomez, R., Fu, M. C., Henderson, K., & Buchholz, A. (2018). Evaluation of the effectiveness and safety of olanzapine as an adjunctive treatment for anorexia nervosa in adolescents: An open label trial. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, 27(3), 197–208.
118. Spettigue, W., Norris, M. L., Santos, A., & Obeid, N. (2018). Treatment of children and adolescents with avoidant/restrictive food intake disorder: A case series examining the feasibility of family therapy and adjunctive treatments. *Journal of Eating Disorders*, 6(20), 1–11.

119. Starks, M. (2021). *Data Governance for Children's Mental Health: What Is It and Why Is It Important?* National Network of Public Health Institutes. https://nnphi.org/resource/data-governance-for-childrens-mental-health-what-is-it-and-why-is-it-important/?parent_id=94.
120. Stein, B. D., Leckman-Westin, E., Okeke, E., Scharf, D. M., Sorbero, M., Chen, Q., Chor, K. H., Finnerty, M., & Wisdom, J. P. (2014). The effects of prior authorization policies on Medicaid-enrolled children's use of antipsychotic medications: evidence from two mid-Atlantic states. *Journal of child and adolescent psychopharmacology*, 24(7), 374–381. <https://doi.org/10.1089/cap.2014.0008>.
121. Steingard, R., Taskiran, S., Connor, D. F., Markowitz, J. S., & Stein, M. A. (2019). New Formulations of Stimulants: An Update for Clinicians. *Journal of child and adolescent psychopharmacology*, 29(5), 324–339. <https://doi.org/10.1089/cap.2019.0043>.
122. Strawn, J. R., Dobson, E. T., & Giles, L. L. (2016). Primary pediatric care psychopharmacology: Focus on medications for ADHD, depression, and anxiety. *Current Problems in Pediatric and Adolescent Health Care*, 47(1), 3–14.
123. Strawn, J. R., Keeshin, B. R., DelBello, M. P., Geraciotti, T. D., & Putnam, F. W. (2010). Psychopharmacological treatment of posttraumatic stress disorder in children and adolescents: A review. *Journal of Clinical Psychiatry*, 71(7), 932–941.
124. Substance Abuse and Mental Health Services Administration. (2019). *Guidance on strategies to promote best practice in antipsychotic prescribing for children and adolescents* (HHS publication No. PEP19- ANTIPSYCHOTIC-BP). U.S. Department of Health and Human Services.
125. Texas Department of Family and Protective Services & the University of Texas at Austin College of Pharmacy. (2010). *Psychotropic medication utilization parameters for foster children*.
126. The Parameters Workgroup of the Psychiatric Executive Formulary Committee, Health and Specialty Care Division, & Texas Health and Human Services Commission. (2019). *Psychotropic medication utilization parameters for children and youth in Texas public behavioral health* (6th version). <https://www.hhs.texas.gov/sites/default/files/documents/doing-business-with-hhs/provider-portal/facilities-regulation/psychiatric/psychotropic-medication-utilization-parameters.pdf>.
127. Tyler, E. T., Hulkower R. L., & Kaminski, J. W. (2017). *Behavioral Health Integration in Pediatric Primary Care: Considerations and Opportunities for Policymakers, Planners, and Providers*. Millbank Memorial Fund.
128. Uguz, F. (2016). Second-generation antipsychotics during the lactation period: a comparative systematic review on infant safety. *Journal of Clinical Psychopharmacology*, 36(3), 244–252.

129. Umehara, H., Iga, J., & Ohmori, T. (2014). Successful treatment of anorexia nervosa in a 10-year-old boy with risperidone long-action injection. *Clinical Psychopharmacology and Neuroscience*, 12(1), 65–66.
130. U.S. Food and Drug Administration. (2006). *Increased risk of neonatal persistent pulmonary hypertension* [FDA Alert]. <http://www.fda.gov/DrugsDrugSafetyPostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm084319.htm>.
131. U.S. Food and Drug Administration. (2011). *Antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns* [FDA Safety Communication]. <http://www.womensmentalhealth.org/posts/new-fda-warning-on-the-use-of-antipsychotic-medications-in-pregnancy/>.
132. U.S. Food and Drug Administration. (2019). *Be aware of potentially dangerous products and therapies that claim to treat autism*. <https://www.fda.gov/consumers/consumer-updates/be-aware-potentially-dangerous-products-and-therapies-claim-treat-autism>.
133. Vanderwerker, L., Akincigil, A., Olsson, M., Gerhard, T., Neese-Todd, S., & Crystal, S. (2014). Foster care, externalizing disorders, and antipsychotic use among Medicaid-enrolled youths. *Psychiatric Services*, 65(10), 1281–1284.
134. Vega, C. P., & Anderson, P. (2012). *SSRIs not recommended for autism in children or adults based on current evidence*. Medscape. <http://www.medscape.org/viewarticle/726999print>.
135. Walkup, J., & the Work Group on Quality Issues: Bernet, W., Bukstein, O., Walter, H., Arnold, V., Benson, R. S., Beitchman, J., Chrisman, A., Farchione, T. R., Hamilton, J., Keable, H., Kinlan, J., McClellan, J., Schoettle, U., Shaw, J., Siegel, M., & Stock, S. (2009). Practice parameter on the use of psychotropic medication in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, 48(9), 961–973.
136. Walkup, J. T., Wagner, K. D., Miller, L., Yenokyan, G., Luby, J. L., Joshi, P. T., Axelson, D. A., Robb, A., Salpekar, J. A., Wolf, D., Sanyal, A., Birmaher, B., Vitiello, B., & Riddle, M. A. (2015). Treatment of early-age mania: Outcomes for partial and nonresponders to initial treatment. *Journal of the American Academy of Child and Adolescent Psychiatry*, 54(12), 1008–1019.
137. Walter, H. J., Bukstein, O. G., Abright, A. R., Keable, H., Ramtekkar, U., Ripperger-Suhler, J., & Rockhill, C. (2020). Clinical practice guideline for the assessment and treatment of children and adolescents with anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, 59(10), 1107–1124.
138. Warren, Z., McPheeters, M. L., Sathe, N., Foss-Feig, J. H., Glasser, A., & Veenstra-VanderWeele, J. A. (2011). Systematic review of early intensive intervention for autism spectrum disorders. *Pediatrics*, 127(5), e1303–e1311.

139. Whitney, D. G., & Peterson, M. D. (2019). US national and state-level prevalence of mental health disorders and disparities of mental health care use in children. *JAMA Pediatrics*, 173(4), 389.
140. Wilbur, C., Bitnun, A., Kronenberg, S., Laxer, R. M., Levy, D. M., Logan, W. J., Shouldice, M., & Yeh, E. A. (2019). PANDAS/PANS in childhood: Controversies and evidence. *Paediatrics & child health*, 24(2), 85–91.
141. Williams, K., Wheeler, D. M., Silove, N., & Hazell, P. (2010). Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorder (ASD) (Review). *Cochrane Database of Systematic Reviews*, 4(8).
142. Wolraich, M. L., Hagan, J. F., Allan, C., Chan, E., Davison, D., Earls, M., Evans, S. W., Flinn, S. K., Froehlich, T., Frost, J., Holbrook, J. R., Lehmann, C. U., Lessin, H. R., Okechukwu, K., Pierce, K. L., Winner, J. D., Zurehellen, W., & SUBCOMMITTEE ON CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVE DISORDER. (2019). Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *Pediatrics*, 144 (4): e20192528. <https://doi.org/10.1542/peds.2019-2528>.
143. Yonkers K. A., Wisner K. L., Stewart D. E., Oberlander T. F., Dell D. L., Stotland N., Ramin, S., Chaudron, L., & Lockwood, C. (2009). The management of depression during pregnancy: A report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Obstetrics and Gynecology*, 114(3), 703–713.

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 A. At-a-glance: Psychotropic drug information for children and adolescents

Antipsychotic Medications

Black Box Warning for all atypical/second generation antipsychotics (SGAs): Increased mortality in elderly patients with dementia-related psychosis.

**Precautions which apply to all atypical or SGAs:* Neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia, diabetes, weight gain, akathisia and dyslipidemia.

†Precautions which apply to all typical or first-generation antipsychotics (FGAs): EPS, tardive dyskinesia.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
Abilify aripiprazole* (SGA)	Irritability associated with autistic disorder: 6 and older	2–15 mg daily < 50 kg: 2–10 mg daily	<i>Additional Black Box Warning:</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>Warnings and precautions:</i> 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.
	Tourette's Disorder: 6 and older	> 50 kg: 2–20 mg daily	
	Bipolar I disorder, acute manic or mixed episodes, monotherapy or as an adjunct to lithium: 10 and older	2–30 mg daily	

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
	Schizophrenia: 13 and older	2–30 mg daily 30 mg/day was not found to be more effective than the 10 mg/day dose	<i>Pregnancy:</i> No adequate or well controlled studies in pregnant women. In animal studies, aripiprazole demonstrated developmental toxicity, included possible teratogenic effects. If treatment is initiated during pregnancy, use of an agent other than aripiprazole is preferred. <i>Lactation:</i> Aripiprazole is excreted in human breast milk. use of agents other than aripiprazole in breastfeeding women is preferred.
Saphris <i>asenapine</i> * (SGA)	Bipolar mania: 10–17	2.5–10 mg twice daily	<i>Warnings precautions and administration:</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. <i>Pregnancy:</i> No adequate or well-controlled studies in pregnant women. If treatment is needed in a woman planning a pregnancy, use of an agent other than asenapine is preferred.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<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.
Rexulti <i>brexpiprazole</i> (SGA)	18 and older	Safety and efficacy of brexpiprazole in pediatric patients have not been established	<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. <i>Pregnancy:</i> No adequate or well-controlled studies in pregnant women. No teratogenic effects were seen in animal studies. <i>Lactation:</i> It is not known if brexpiprazole and its metabolites are excreted in human breast milk. It is distributed into milk in rats.
Vraylar <i>cariprazine</i> (SGA)	18 and older	N/A	<i>Pregnancy:</i> No adequate or well-controlled studies in pregnant women. There are no available data use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. The major active metabolite of cariprazine, didesmethyl-cariprazine, has been detected in adult patients up to 12 weeks after discontinuation. Based on animal data, may cause fetal harm. <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.
Thorazine <i>chlorpromazine</i> [†] (FGA)	Severe behavioral problems marked by combativeness	Hospitalized patients: start with low doses and increase gradually. In severe behavior disorders,	<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

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
	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 months and older Nausea and vomiting: 6 months and older Presurgical apprehension: 6 months and older	higher dosages may be necessary; 50–100 mg daily. 200 mg daily in older children. Oral: 0.55 mg/kg/dose every 4–6 hours as needed **There is little evidence that behavior improvement in severely disturbed mentally retarded patients is further enhanced by doses beyond 500 mg per day** Maximum recommended daily doses: Children younger than 5 years or weighing less than 22.7 kg: 40 mg/day Children ≥ 5 years and adolescents or weighing ≥ 22.7 kg: 75 mg/day; a maximum total dose of 100 mg has been used	disorders, respiratory disease and in acute illness. 3) Should generally not be used in pediatric patients under 6 months of age except when 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; concentrations may be higher than what is in the maternal plasma. A decision should be made whether to discontinue breastfeeding or to discontinue the drug, due to potential for serious adverse reactions in the infant.
Clozaril <i>clozapine</i> * (SGA)	18 and older	Limited data in pediatric and adolescent populations	<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. Clozapine crosses the placenta and can be detected in fetal blood and amniotic fluid.

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			<i>Lactation:</i> Clozapine is present in human breast milk. Use is not recommended.
Haldol <i>haloperidol</i> † (FGA)	Schizophrenia: 3 and older	Children 3–12 years weighing 15–40 kg: Oral: Initial: 0.5 mg/day in 2–3 divided dose Children > 40 kg and Adolescents: Oral: 0.5–5 mg/day in 2–3 divided doses	<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. Haloperidol crosses the placenta in humans. Animal studies show haloperidol may harm fetus.
	Tourette’s syndrome, and disruptive behavior disorder and ADHD: 3 and older	3–12 years weighing 15–40 kg: Oral: Initial: 0.5 mg/day in 2–3 divided doses > 40 kg and adolescents: Oral: 0.25–15 mg/day in 2–3 divided doses	<i>Lactation:</i> Is found in breast milk and has been detected in the plasma and urine of breastfeeding infants. Breastfeeding is not recommended.
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. 3) Use with caution in patients at risk of seizures or seizure history. <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. Not recommended.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
Adasuve <i>loxapine</i> [†] (FGA)	18 and older	N/A	<i>Additional Black Box Warning:</i> The inhalation powder formulation (Adasuve) can cause acute bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. <i>Warnings and precautions:</i> 1) Adasuve is contraindicated in patients with pulmonary disease associated with bronchospasms. 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. Loxapine causes elevated prolactin levels, and thus may interfere with proper lactation in some patients. It should be avoided during breast feeding if clinically possible.
Loxitane <i>loxapine</i> [†] (FGA)	18 and older	N/A	<i>Warnings and precautions:</i> 1) Should be used with extreme caution in patients with a history of convulsive disorders since it lowers seizure threshold. 2) Use with caution in those with cardiovascular disease. <i>Pregnancy:</i> Adverse events have been observed in animal reproduction studies, may cause fetal harm. <i>Lactation:</i> The extent of excretion in human milk is not known.

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Caplyta <i>lumateperone</i> (SGA)	18 and older	N/A	<i>Warnings, precautions and administration:</i> Avoid use in patients with moderate to severe hepatic disease or impairment. Use caution in patients at risk for seizures. Administer with food. <i>Pregnancy:</i> May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Data collection to monitor pregnancy and infant outcomes following exposure to lumateperone is ongoing. If treatment is needed in a woman planning a pregnancy, use of another agent is preferred. <i>Lactation:</i> It is not known if lumateperone is present in breast milk. There is a potential for toxicity based on animal studies and serious adverse reactions if breastfed; breastfeeding is not recommended during treatment.
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 of 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.
	Bipolar depression: 10 and older	20–80 mg daily	

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Moban <i>molindone</i> [†] (FGA)	Schizophrenia: 12 and older	15–225 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> Adverse events were observed in some animal reproduction studies. 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</i> * (SGA)	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</i> * (SGA)	Schizophrenia: 12 and older	3 mg once daily Max dose is weight dependent: < 51kg: 6 mg daily ≥ 51kg: 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.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<i>Lactation:</i> Paliperidone is excreted in human breast milk.
Trilafon <i>perphenazine</i> [†] (FGA)	Schizophrenia: 12 and older	Oral: 2–64 mg daily in divided doses 2–4 times daily (12–24 mg is average daily dose)	<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> Jaundice or hyper-/hyporeflexia have been reported in newborn infants following maternal use of phenothiazines. Safe use in pregnancy has not been established. <i>Lactation:</i> Perphenazine is present in breast milk. Safe use during lactation has not been established.
Orap <i>pimozide</i> [†] (FGA)	Tourette’s disorder: 12 and older	≥ 12 years: 0.05–0.2 mg/kg once daily; 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. Adverse events were observed in some animal reproduction studies. <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
Seroquel <i>quetiapine*</i> (SGA)	Bipolar I disorder: 10 and older	25–600 mg daily	<i>Warnings and precautions:</i> May cause somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, dry mouth, tachycardia and weight gain. May cause hyperprolactinemia, which may decrease reproductive function in both males and females. The clinical significance of hyperprolactinemia in patients with breast cancer or other prolactin-dependent tumors is unknown. Use with caution in patients with decreased gastrointestinal motility as anticholinergic effects may exacerbate underlying condition. Use with caution in patients with hepatic disease or impairment; dosage adjustment may be required. Use with caution in patients at risk of seizures, or on concurrent therapy with medications which may lower seizure threshold.
	Schizophrenia: 13 and older	25–800 mg daily	
Seroquel XR <i>quetiapine*</i> (SGA)	Bipolar I disorder: 10 and older	50–600 mg daily	<i>Pregnancy:</i> Crosses the placenta and can be detected in cord blood. Based on available data, congenital malformations have not been observed in humans. Antipsychotic use during the third trimester of pregnancy has a risk for abnormal muscle movements (EPS) and/or withdrawal symptoms in newborns following delivery. <i>Lactation:</i> Quetiapine is excreted in human breast milk. When an antipsychotic medication is needed in a breastfeeding woman, quetiapine may be used. In general, infants exposed to SGAs via breast milk should be monitored weekly for the first month of exposure for symptoms such as appetite changes, insomnia, irritability or lethargy.
	Schizophrenia: 13 and older	50–800 mg daily	

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
Risperdal <i>risperidone</i> * (SGA)	Irritability associated with autistic disorder: 5 and older	15–20 kg: 0.25–3 mg daily ≥ 20 kg: 0.5–3 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 and are associated with an increase incidence of adverse effects. <i>Pregnancy:</i> No adequate and well controlled studies in pregnant women; crosses the placenta. Based on animal data, may cause fetal harm. <i>Lactation:</i> Risperidone and its metabolite are present in human breast milk. Infants exposed to second generation antipsychotics via breast milk should be monitored weekly for the first month of exposure for symptoms, such as appetite changes, insomnia, irritability or lethargy.
	Bipolar mania: 10 and older	0.5–6 mg daily	
	Schizophrenia: 13 and older	0.5–6 mg daily	
Mellaril <i>thioridazine</i> † (FGA)	Treatment-refractory schizophrenia: (Age not specified)	0.5–3 mg/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 patients who fail to show an acceptable response 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. Jaundice or hyper-/hyporeflexia have been reported in newborn infants following maternal use of phenothiazines.

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			<i>Lactation:</i> It is not known whether thioridazine is excreted in human breast milk.
Navane <i>thiothixene</i> [†] (FGA)	Schizophrenia: 12 and older	6–60 mg daily	<i>Warnings and precautions:</i> May cause CNS collapse, CNS depression and blood dyscrasias. Avoid use in patients with underlying QT prolongation or taking medicines that prolong the QT interval or cause polymorphic ventricular tachycardia. <i>Pregnancy:</i> Safe use of thiothixene during pregnancy has not been established. Adverse events were observed in some animal reproduction studies. <i>Lactation:</i> It is not known whether thiothixene is excreted in human breast milk.
Stelazine <i>trifluoperazine</i> [†] (FGA)	Behavioral disorders: no age specified	1–2 mg daily depending on the size of the child	<i>Warnings and precautions:</i> May cause CNS collapse, CNS depression, blood dyscrasias, bone marrow depression and hepatic impairment. <i>Pregnancy:</i> Adverse events have not been observed in animal reproduction studies, except when using doses that were also maternally toxic. Prolonged jaundice, extrapyramidal signs or hyporeflexia have been reported in newborn infants following maternal use of phenothiazines. <i>Lactation:</i> There is evidence that trifluoperazine is excreted in the milk of nursing mothers. Milk concentrations may be higher than those found in the maternal serum.
	Psychosis: 6 and older	1–15 mg daily (some older children with severe symptoms may require, and be able to tolerate, higher dosages until 40 mg daily)	
Geodon <i>ziprasidone</i> [*] (SGA)	18 and older	In June 2009, an FDA advisory panel advised that ziprasidone is effective in patients 10–17 years	<i>Warnings, precautions and administration:</i> 1) Doses should be administered with food. 2) Use can cause prolonged QTc interval.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
		of age for the treatment of mixed and manic episodes of BD but did not conclude that it was safe due to a large number of subjects lost in follow-up and ambiguity within QTc prolongation data.	<i>Pregnancy:</i> No adequate and well-controlled studies in pregnant women. Animal data suggests there may be risks. <i>Lactation:</i> It is present in breast milk. There is limited data. Monitor infants exposed to ziprasidone via breast milk for excess sedation, irritability, poor feeding and EPS.

Antidepressant Medications (also used for anxiety disorders)

∞ ‡ *Black Box Warning which applies to all antidepressants:* Increased risk of suicidal thinking and behaviors in children, adolescents and young adults (18–24) with MDD and other psychiatric disorders. Monitor for worsening and emergence of suicidal thoughts and behaviors.

‡ TCAs are not the drugs of choice for pediatric patients with depression; there is lack of high-quality data to support efficacy and safety. Monitoring of cardiac function is wise when TCAs are used in children.

∞ *Precautions which apply to all SSRI and all SNRI antidepressants:* Activation of mania/hypomania, discontinuation syndrome, increased risk of bleeding and use in combination with monoamine oxidase inhibitors (MAOIs).

∞ ¥ *Precautions which apply to all SNRIs:* Use in combination with MAOIs, activation of mania/hypomania, discontinuation syndrome, increased risk of bleeding.

General precautions for MAOIs: This class is usually reserved for patients who have failed other agents due to the strict dietary restrictions and side effects. Patients must avoid foods that are high in tyramine and 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.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
Elavil <i>amitriptyline</i> † (tricyclic [TCA])	12 and older	50–200 mg daily	<i>Warnings and precautions:</i> Controlled clinical trials have not shown TCAs to be superior to placebo for the treatment of depression in children and adolescents; not recommended as a first-line medication. <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. <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.
Asendin <i>amoxapine</i> † (TCA)	18 and older	N/A	<i>Warnings and precautions:</i> Most common adverse events are drowsiness, dry mouth, constipation and blurred vision. <i>Pregnancy:</i> It is not known if amoxapine or its metabolite cross the human placenta. Reproductive studies in mice, rats and rabbits have found no teratogenicity, but embryotoxicity was observed in rats and rabbits given oral doses approximating the human dose. <i>Lactation:</i> Amoxapine is excreted in human breast milk. Caution should be exercised when used in nursing women.
Zulresso <i>brexanolone</i>	15 and older females for postpartum depression (PPD)	Administered as a continuous IV infusion protocol over a total of 60 hours	<i>Warnings and precautions and administration:</i> Available through a restricted REMS program due to the possibility of excessive sedation or sudden loss of consciousness.

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			Zulresso can lead to an increased risk of suicidal thoughts and behaviors. Consider changing regimen or discontinuing Zulresso if PPD worsens or if emergent suicidal thoughts and behaviors are experienced. Patients must be monitored for hypoxia using continuous pulse oximetry equipped with an alarm. If hypoxia occurs, discontinue the infusion and do not re-initiate treatment. Assess for excessive sedation every two hours during planned, non-sleep periods, and stop the infusion if excessive sedation occurs until the symptom resolves. <i>Pregnancy:</i> May cause fetal harm; insufficient data. <i>Lactation:</i> Present in breast milk at limited concentrations likely due to the low oral bioavailability in adults.
Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban <i>bupropion</i> (<i>aminoketone class</i>)	18 and older	N/A	<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. <i>Pregnancy:</i> Bupropion and its metabolites cross the placenta. An increased risk of congenital malformations has not been observed following maternal use of bupropion during pregnancy; however, data specific to cardiovascular malformations is inconsistent. The long-term effects on development and behavior have not been studied. If treatment for MDD is initiated for the first time during pregnancy, agents other than bupropion are preferred.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<i>Lactation:</i> Bupropion and its metabolites are excreted in human breast milk.
Celexa <i>citalopram</i> * (SSRI)	18 and older	N/A	<i>Pregnancy:</i> No adequate and well-controlled studies in pregnant women. Citalopram and its metabolites cross the human placenta. An increased risk of teratogenic effects, including cardiovascular defects, may be associated with maternal use of citalopram or other SSRIs; however, available information is conflicting. <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.
Anafranil <i>clomipramine</i> ‡ (TCA)	OCD: 10 and older	25–200 mg daily or 3 mg/kg/day, whichever is less	<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. <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. <i>Lactation:</i> Clomipramine 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
Pristiq <i>desvenlafaxine</i> ∞ ¥ (SNRI)	18 and older	N/A	<i>Pregnancy:</i> No adequate and well-controlled studies in pregnant women. Based on animal data, desvenlafaxine may cause fetal harm. <i>Lactation:</i> Desvenlafaxine is excreted in human breast milk.
Auvelity <i>dextromethorphan- bupropion</i> (NMDA antagonist)	18 and older	N/A	<i>Warnings and Precautions:</i> There is a dose-related seizure risk. May increase blood pressure and cause hypertension. For patients with bipolar disorder, it may activate mania or hypomania. Psychosis and other neuropsychiatric reactions may occur. <i>Pregnancy:</i> Based on animal data, may cause fetal harm. Alternate treatment is recommended for women planning to become pregnant. <i>Lactation:</i> Bupropion and its metabolites are present in human milk. It is not known whether dextromethorphan is present in human milk. Due to the potential of neurotoxicity, it is not recommended to breastfeed during treatment and for five days following the final dose.
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.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<i>Lactation:</i> Doxepin and metabolite are present in breast milk. Drowsiness, vomiting, poor feeding and muscle hypotonia were noted in a breastfeeding infant following maternal use of doxepin.
Cymbalta <i>duloxetine</i> ∞ ¥ (SNRI)	GAD: 7 and older	30–120 mg daily	<i>Pregnancy:</i> No adequate and well-controlled studies in pregnant women; crosses the placenta. May impair platelet aggregation; the risk of postpartum hemorrhage may be increased when used within the month prior to delivery. <i>Lactation:</i> Duloxetine is excreted in human breast milk.
Lexapro <i>escitalopram</i> * (SSRI)	MDD: 12 and older	10–20 mg daily	<i>Pregnancy:</i> No adequate and well controlled studies in pregnant women; crosses the placenta and is distributed into the amniotic fluid. <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.
Spravato <i>esketamine</i> (NMDA antagonist)	18 and older	N/A	<i>Additional Black Box Warning:</i> 1) Has the potential to be abused and misused. 2) Patients are at risk for sedation after administration. Because of the risks of sedation, patients must be monitored for at least two hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting. 3) Patients are at risk for dissociative or perceptual changes after administration. Because of the risks of dissociation, patients must be monitored for at least two hours at each treatment session, followed by an assessment to determine when the patient

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			is considered clinically stable and ready to leave the healthcare setting <i>Warnings and precautions:</i> Must be given in conjunction with an oral antidepressant. Indicated for treatment-resistant depression and MDD with suicidality. Esketamine is not recommended in patients with severe hepatic impairment. <i>Pregnancy:</i> Based on animal data, use of medications that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid activity, may affect brain development. Females of reproductive potential should consider pregnancy planning and prevention during therapy. <i>Lactation:</i> Esketamine is present in breast milk. Due to the potential for adverse events in a nursing infant, breastfeeding is not recommended.
Prozac <i>fluoxetine*</i> (SSRI)	MDD: 8 and older	10–20 mg daily	<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. <i>Lactation:</i> Fluoxetine is excreted in human breast milk. Nursing while taking fluoxetine is not recommended.
	OCD: 7 and older	10–60 mg daily	
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, which have been observed with pediatric use. Regular monitoring of weight and growth is recommended.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<i>Pregnancy:</i> Crosses the placenta. If treatment for MDD is initiated for the first time in females planning a pregnancy, agents other than fluvoxamine are preferred. <i>Lactation:</i> Fluvoxamine is excreted in human breast milk.
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 the lesser of 2.5 mg/kg/ day or 50 mg/day if younger than 12 or 75 mg/day if older than 12* *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> Present in human breast milk. Breastfeeding is not recommended by the manufacturer.
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)

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			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. Animal reproduction studies have not been conducted. <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, though there is limited information. Crosses the placenta.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<i>Lactation:</i> Mirtazapine may be excreted into human breast milk so caution should be exercised when administered to nursing women.
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. Crosses the placenta and can be detected in cord blood. Animal studies have yielded inconclusive results. <i>Lactation:</i> Safe use during lactation has not been established. Present in breast milk.
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. Caution should be used.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
Nardil <i>phenelzine</i> (MAOI)	18 and older	N/A	<i>Pregnancy:</i> Safety in pregnancy has not been established. Adverse events have been observed in animal reproduction studies <i>Lactation:</i> Safety in lactation has not been established. It is not known if phenelzine is excreted in breast milk.
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 adolescents 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. It is not known if protriptyline is excreted in breast milk.
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.
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.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<i>Lactation:</i> Sertraline is excreted in human breast milk. In a published pooled analysis of 53 mother infant pairs, exclusively human milk fed, no adverse reactions in the breastfed infants were shown.
Parnate <i>tranylcypromine</i> (MAOI)	18 and older	N/A	<i>Pregnancy:</i> No adequate or 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 (serotonin antagonist and reuptake inhibitor class)</i>	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 adolescents).

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<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, venlafaxine [∞] (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 was 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. Crosses the placenta. <i>Lactation:</i> Venlafaxine is excreted in human breast milk.
Viibryd vilazodone (atypical antidepressant)	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.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
Trintellix <i>Vortioxetine</i> (atypical antidepressant – serotonin modulator)	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 Brilinta, 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. <i>Lactation:</i> It is not known whether vortioxetine is excreted in human breast milk. It is present in the milk of lactating rats.
Combination Antipsychotic/Antidepressant Medications			
Symbyax <i>fluoxetine</i> & <i>olanzapine</i>	Bipolar depression: 10 and older	3 mg/25 mg–12 mg/50 mg daily	<i>Black Box Warnings:</i> 1) Usage increased the risk of suicidal thinking and behaviors in children and adolescents with MDD and other psychiatric disorders. 2) Increased mortality in elderly patients with dementia-related psychosis treated with antipsychotics. <i>Warnings and precautions:</i> 1) Avoid abrupt withdrawal. 2) Lower starting doses recommended for those with hepatic impairment, potential for slowed metabolism and those predisposed to hypotensive reactions. <i>Pregnancy:</i> No adequate or well-controlled studies in pregnant women. Refer to individual agents in the combination product.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<i>Lactation:</i> Both fluoxetine and olanzapine are excreted in human breast milk. The mean dosage of olanzapine received by an infant at steady state is estimated to be about 1.8% of the maternal dosage. 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.

Mood Stabilizing and Anticonvulsant Medications

Black Box Warnings and warnings/precautions are specific to each medication. Please see chart for detailed information. Prior to prescribing, medical comorbidities, hepatic function, renal function, potential drug-drug interactions, alterations in protein binding and sensitivity to adverse events must be considered.

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.
Tegretol, Tegretol XR, Carbatrol, Epitol <i>carbamazepine</i>	Seizures: any age	Under 6: 10–35 mg/kg/day Ages 6–12: 20–1,000 mg daily Ages 13–15: 400–1,000 mg daily Ages 16 and older: 400–1,200 mg daily **Recommended therapeutic serum levels: 4–12 mcg/mL**	<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 age 6. <i>Pregnancy:</i> May cause fetal harm when administered to pregnant women. Data suggest 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
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	<i>Black Box Warning:</i> 1) Hepatotoxicity, 2) Teratogenicity, 3) Pancreatitis. <i>Warnings, precautions and administration:</i> 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. <i>Pregnancy:</i> Can cause congenital malformations including neural tube defects and decreased IQ. Should not be used to treat women with epilepsy or BD who plan to become pregnant, due to risks of adverse fetal events. <i>Lactation:</i> 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: 900–2,400 mg daily (Doses of 3,600 mg/day have also been administered to a small number of patients for short duration and have been well tolerated)	<i>Warnings and precautions:</i> Dosage adjustments necessary for renal impairment or those undergoing hemodialysis. <i>Pregnancy:</i> No adequate or well-controlled studies in pregnant women. Based on animal data, may cause fetal harm. Crosses the placenta. <i>Lactation:</i> Gabapentin 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
Lamictal, Lamictal XR <i>lamotrigine</i>	Epilepsy (adjunct): 2 and older	Ages 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 conflicting medications) **Above doses may have to be increased or decreased for those patients taking concomitant valproate, carbamazepine, phenytoin, phenobarbital or primidone**	Black Box Warning: Life threatening serious rashes including Stevens-Johnson syndrome. The rate of serious rash is greater in pediatric patients than in adults. Warnings and precautions: 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 BD or 1–2-year-olds for adjunct therapy for seizures was not established. Pregnancy: No adequate and well-controlled studies in pregnant women. In animal studies, lamotrigine was developmentally toxic at doses lower than those administered clinically. Lactation: Lamotrigine is excreted in human breast milk. Apnea, drowsiness and poor sucking have been reported in milk fed infants exposed to lamotrigine.
	Epilepsy (monotherapy): 16 and older	16 and older: 200–500 mg daily	
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)	Black Box Warning: Toxicity above therapeutic serum levels. Warnings and precautions: 1) May cause renal function impairment, polyuria, tremor, diarrhea, nausea and

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable		Black Box Warnings / Warnings and Precautions / Additional Information
				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	**Max doses are dependent on patient's weight**	600–2,100 mg daily (initiate at 8–10 mg/kg/day)	<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 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.
	Seizures (adjunct): 2 and older		150–1,800 mg daily (8–60 mg/kg/day)	
Topamax, Topamax XR <i>topiramate</i>	Epilepsy (monotherapy)	10 and older: 25–400 mg daily (for those younger than 10, there are specific weight-based maxes)		<i>Warnings, precaution and administration:</i> 1) Because of the bitter taste, tablets should not be broken. 2) Decreases the efficacy of contraceptives and can cause increased

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
	Epilepsy (adjunctive)	Ages 2–16: 25–9 mg/kg/day (Recommended dose: 5–9 mg/kg/day) 17 and older: 25–400 mg daily	breakthrough bleeding. 3) Capsules have to be swallowed whole and may not be sprinkled on food, crushed or chewed. 4) Acute myopia and secondary angle closure glaucoma can lead to permanent vision loss; discontinue Topamax as soon as possible if symptoms occur. <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.
	Migraine: 12 and older	25–100 mg daily	
Trokendi XR, Qudexy XR <i>topiramate</i>	Epilepsy (monotherapy)	Ages 6–9: 25–400 mg daily Ages 10 and older: 50–400 mg daily	
	Epilepsy (adjunctive)	25–9 mg/kg/day (Recommended dose: 5–9 mg/kg/day) **Max doses are dependent on the child's weight**	

Anti-Anxiety Medications (Drugs below are *benzodiazepines* except buspirone)

Classification of buspirone: Anxiolytic psychoactive drug of the azapirones chemical class

Warnings/precautions for all benzodiazepines: 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 CNS.

Xanax <i>alprazolam</i>	18 and older	N/A	<i>Pregnancy:</i> Crosses the placenta. <i>Lactation:</i> Present in breast milk.
Buspar <i>buspirone</i>	GAD: 6–17 years	7.5–60 mg daily	<i>Pregnancy:</i> Adverse events have not been observed in animal reproduction studies.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<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	<i>Pregnancy:</i> Chlordiazepoxide crosses the human placenta, and fetal serum concentrations are similar to those in the mother. <i>Lactation:</i> Excreted in breast milk.
Klonopin <i>clonazepam</i>	18 and older	N/A	<i>Pregnancy:</i> Crosses the placenta. <i>Lactation:</i> Present in breast milk.
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. <i>Pregnancy:</i> Metabolite crosses the placenta and is measurable in cord and amniotic fluid. <i>Lactation:</i> Present in breast milk and measurable in serum of breastfeeding infants.
Valium <i>diazepam</i>	Spasticity / muscle spasms: 6 months and older	1–2.5 mg, 3–4 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. <i>Pregnancy:</i> Crosses the placenta.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<i>Lactation:</i> Present in breast milk.
Ativan <i>lorazepam</i>	Anxiety: 12 and older	0.25–2 mg/dose 2 or 3 times daily; maximum dose: 2 mg/dose	<i>Pregnancy:</i> Crosses the placenta. <i>Lactation:</i> Present in breast milk.
Serax <i>oxazepam</i>	12 and older	30–120 mg	<i>Warnings and precautions:</i> Label states it is not indicated for under 6 years of age and absolute dosage for pediatric patients 6–12 years old is not established. <i>Pregnancy:</i> Crosses the placenta. <i>Lactation:</i> Present in breast milk.
ADHD Medications (Drugs below are stimulants, except atomoxetine, clonidine and guanfacine)			
<i>Classification of non-stimulant drugs:</i> (1) Atomoxetine is a SNRI. (2) Clonidine and guanfacine are classified as alpha-2 receptor agonists.			
<i>Black Box Warning for all stimulants:</i> Abuse potential. Risk of sudden death and serious cardiovascular events.			
<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. Infants born to mothers who are 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.			
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.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<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, precautions and administration:</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.
Evekeo <i>amphetamine sulfate</i>	ADHD: 3 and older	2.5–40 mg daily	<i>Pregnancy:</i> No adequate or well-controlled studies in pregnant women. Based on animal data, may cause fetal harm.
	Narcolepsy: 6 and older	5–60 mg daily	
	Exogenous obesity: 12 and older	Up to 30 mg daily (take in divided doses) 30–60 minutes before meals	<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. 3) Upon

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			treatment initiation, behavior should be monitored for emergence or worsening of aggression or hostility. <i>Pregnancy:</i> No adequate or well-controlled studies in pregnant women. An agent other than atomoxetine is preferred for the treatment of ADHD in women planning a pregnancy. 3) Upon treatment initiation, behavior should be monitored for emergence or worsening of aggression or hostility. <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.
Kapvay <i>clonidine extended release</i>	ADHD (monotherapy or adjunct to stimulants): 6–17	0.1–0.4 mg daily	<i>Warnings, precautions and administration:</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. Crosses the placenta; concentrations in the umbilical cord plasma are similar to those in the maternal serum and concentrations in the amniotic fluid may be four times those in the maternal serum. <i>Lactation:</i> Clonidine 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
Focalin <i>dexmethylphenidate</i>	ADHD: 6–17	5–20 mg daily	<i>Warnings and precautions:</i> 1) Do not co-administer with MAOIs, or within 14 days following discontinuing a MAOI. 2) May induce psychotic or manic symptoms. <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, precautions and administration:</i> 1) Do not co-administer with MAOIs, or within 14 days following discontinuing a MAOI. 2) May induce psychotic or manic symptoms. 3) Capsule contents can be sprinkled on applesauce and swallowed whole. 4) 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. Dexmethylphenidate is the more active enantiomer of racemic methylphenidate, and methylphenidate is present in breast milk.
Dexedrine, ProCentra Oral Solution, Zenzedi, Dextrostat <i>dextroamphetamine</i>	ADHD: 3 and older	2.5–40 mg daily	<i>Warnings and precautions:</i> Extended release Spansules 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.
	Narcolepsy: 6 and older	5–60 mg daily	

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<i>Lactation:</i> Amphetamines are excreted in human breast milk.
Xelstrym <i>dextroamphetamine</i>	ADHD: 6–17	Starting dose is 4.5 mg/9 hours. Titrate dosage in weekly increments of 4.5 mg up to a max dose of 18 mg/9 hour	<i>Warnings, precautions and administration:</i> Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities or coronary artery disease. May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to use.
	ADHD: Adults	Starting dose is 9 mg/9 hours. Maximum recommended dose is 18 mg/9 hours	Apply Xelstrym to one of the following sites: hip, upper arm, chest, upper back or flank. Apply one Xelstrym transdermal system two hours before an effect is needed and remove within nine hours. <i>Pregnancy:</i> No adequate or well-controlled studies in pregnant women. Based on animal data, may cause fetal harm. <i>Lactation:</i> Breastfeeding is not recommended.
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, precautions and administration:</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.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<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.
Vyvanse <i>lisdexamfetamine dimesylate</i>	ADHD: 6–17	30–70 mg daily	<i>Warnings, precautions and administration:</i> 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 post marketing reports. Lisdexamfetamine is converted to dextroamphetamine. <i>Lactation:</i> Amphetamines are present in human breast milk.
Desoxyn <i>methamphetamine</i>	ADHD: 6 and older	5–25 mg daily	<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.
	Obesity (short term): 12 and older	5 mg thirty minutes before each meal; treatment should not exceed a few weeks.	
Adhansia XR, <i>methylphenidate</i>	ADHD: 6 and older	25 mg daily initially; may titrate up in increments 10–15 mg at least every 5 days Doses > 70 mg/day are associated with increased side effects	<i>Administration:</i> May be swallowed whole or capsule opened and sprinkled onto 1 tablespoon of applesauce or yogurt and consumed within 10 minutes. <i>Pregnancy:</i> There are limited published studies and a small case series that reported on the use of methylphenidate in pregnant women; however, the data are insufficient to inform any drug associated risks.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<i>Lactation:</i> Limited published literature reports that methylphenidate is present in human breast milk.
Ritalin, Methylin <i>methylphenidate</i>	ADHD: 6 and older	10–60 mg daily	<i>Warnings, precautions and administration:</i> Methylin is a chewable tablet. It should be taken with at least eight ounces of water or other fluid to prevent choking. <i>Pregnancy:</i> There are limited published studies and a small case series that reported 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</i> <i>extended release</i>	ADHD: 6 and older	10–60 mg daily	<i>Warnings, precautions and administration:</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.
Ritalin LA, Metadate CD,	ADHD: 6 and older	20–60 mg daily	<i>Warnings, precautions and administration:</i> 1) Ritalin LA and Metadate CD capsules can be opened, and the contents can be sprinkled over a spoonful of applesauce. This mixture

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
QuilliChew ER, Quillivant XR <i>methylphenidate extended release</i>			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 a small case series that reported on the use of methylphenidate in pregnant women; however, the data is conflicting and insufficient to inform any drug associated risks. <i>Lactation:</i> 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 2 mg/kg/day)	<i>Administration:</i> Should be swallowed whole and not chewed or crushed. <i>Pregnancy:</i> There are limited published studies and a small case series that reported 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>Administration:</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 a small case series that reported on the use of methylphenidate in

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			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.
Relexxii <i>methylphenidate extended release</i>	ADHD: 6 and older	Ages 6–17: Starting dose is 18 mg once daily	<i>Administration:</i> May be administered without regard to meals. Administer whole; do not cut, crush or chew. Duration of action is approximately 8 hours. Administer the last dose of the day several hours before bedtime. <i>Pregnancy:</i> There are limited published studies and a small case series that reported 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.
	Adults younger than 65	Adults: Starting dose is 18 or 36 mg once daily	
Adderall <i>Mixed amphetamine salts</i>	ADHD: 3 and older	2.5–40 mg daily	<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.
	Narcolepsy: 6 and older	5–60 mg daily	
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>Administration:</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.

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
			<i>Lactation:</i> Amphetamines are excreted in human breast milk.
Azstarys, <i>Serdexmethylphenidate/dexmethylphenidate</i>	ADHD: 6–12	Initial: 39.2 mg/7.8 mg After one week, can increase 52.3 mg/10.4 mg OR decrease to 26.1 mg/ 5.2 mg	<i>Warnings, precautions and administration:</i> 1) Do not co-administer with MAOIs, or within 14 days following discontinuing a MAOI. 2) May induce psychotic or manic symptoms. 3) Capsule may be taken whole or opened and sprinkled over applesauce or added to water. <i>Pregnancy:</i> Limited human data. Based on animal data, may cause fetal harm. <i>Lactation:</i> It is unknown whether Serdexmethylphenidate/dexmethylphenidate is excreted in human breast milk. Methylphenidate is present in human breast milk.
	ADHD: 13–17	Initial: 39.2 mg/7.8 mg After one week, can increase 52.3 mg/ 10.4 mg	
Qelbree, <i>Viloxazine</i> (Not a stimulant medication)	ADHD: 6–11	Initial: 100 mg daily May increase in weekly 100 mg increments Max dose: 400 mg once daily	<i>Black Box Warning:</i> Increased risk of suicidal thoughts and behaviors. <i>Warnings, precautions and administration:</i> 1) Do not co-administer with MAOIs, or within 14 days following discontinuing a MAOI. 2) Coadministration of CYP1A2 substrates may increase the risk of adverse events. 3) Capsule may be taken with or without food or sprinkled over a teaspoon of applesauce. 4) May induce mania or mixed episode in patients with bipolar. 5) Suicidal thoughts and behaviors were reported. 6) Caution should be taken due to somnolence and fatigue. 7) Blood pressure and
	ADHD: 12–17	Initial: 200 mg daily May increase in weekly 200 mg increments Max dose: 400 mg once daily	

Drug Brand Name / Generic Name	FDA Approved Age / Indication	Pediatric Dosage / Serum Level When Applicable	Black Box Warnings / Warnings and Precautions / Additional Information
	Adults	Initial: 200 mg once daily May increase in weekly 200 mg increments Max dose: 600 mg once daily	heart rate increases should be monitored prior to treatment initiation and periodically after. <i>Pregnancy:</i> Based on animal studies, maternal harm may occur. <i>Lactation:</i> It is unknown if viloxazine is excreted in human breast milk.

Sources: (Larsen et al., 2015; Lexicomp, n.d.; NIMH, n.d. -a; Micromedex, n.d.; Schatzberg & DeBattista, 2019; Pacchiarotti et al., 2019; The Parameters Workgroup of the Psychiatric Executive Formulary Committee, Health and Specialty Care Division, Texas Health and Human Services Commission, 2019; Uguz, 2016)

Appendix B. Psychotropic drugs: Side effects and teratogenic risks

Class of Drugs	Typical Side Effects	Possible Teratogenic Risk	Legacy Pregnancy Risk Category ¹
Antipsychotic medications	- Akathisia and dystonic reactions are seen in children treated with SGAs, but risk of tardive dyskinesia is small compared to FGAs. - Weight gain is a significant problem with SGAs. Other side effects: constipation, dry mouth and dizziness. - Sedation/cognitive blunting may occur with FGAs and SGAs. - Adolescent males at much greater risk for dystonic reactions than adults. - Significant drop in neutrophils and increased risk of seizures with clozapine (should be used as treatment of last resort).	FGAs: Rare anomalies, fetal jaundice, fetal anticholinergic effects at birth.	C
		SGAs: Gestational diabetes, large birthweight.	BC
Antidepressant medications	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 responsible for four cases of reported sudden death in children. Other effects: Dry mouth, urinary retention, sedation, constipation, weight gain and hypotension.	TCAs: Fetal tachycardia, fetal withdrawal, fetal anticholinergic effects, urinary retention, bowel obstruction.	D-amitriptyline, Imipramine, nortriptyline

¹ In 2015, the FDA new labeling requirements, “Pregnancy and Lactation Labeling Rule” (PLLR), went into effect, effectively phasing out the previous pregnancy risk categories (A, B, C, D, and X; descriptions below), which made risk-to-benefit assessments challenging. The previous pregnancy risk categories were replaced with a standardized summary of available clinical evidence, supporting data and an explanation of risks to provide more detailed information regarding the safety and efficacy of medications in pregnancy and lactation and enable better evidence-based decision making. Pregnancy risk categories are included in this chart for reference, but please note the FDA has moved away from utilizing these. (Pernia & DeMaagd, 2016)

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	Legacy Pregnancy Risk Category ¹
			C- (other TCAs) / B- maprotiline
	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.	MAOIs: Rare fetal malformations: rarely used in pregnancy due to hypertension.	C
	- 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 BD and greater suicide risk.	SSRIs: Perinatal and cardiovascular complications, spontaneous abortions. Potential premature delivery and neonatal PPHN.	C/D (paroxetine)
	Side effects and other concerns with SNRIs: nausea, insomnia, sedation, sexual dysfunction, sweating, hypertension and discontinuation syndrome.	SNRIs: Potential premature delivery. Clinical outcome data sparse compared to SSRIs or TCAs.	C
	Bupropion (aminoketone class) common side effects: headache, agitation, restless insomnia, weight loss, anorexia, sweating, tremor and hypertension.	Bupropion: Risks unknown, but not recommended over SSRIs in pregnancy.	C
Mood stabilizing and anticonvulsant medications	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.	Lithium: Associated with increase in birth defects including cardiac anomalies (esp. Ebstein's	D

Class of Drugs	Typical Side Effects	Possible Teratogenic Risk	Legacy Pregnancy Risk Category ¹
		anomaly) and behavioral effects.	
	Valproate: Children younger than 2 years are at greatest risk for hepatotoxicity. Common reactions: headache, nausea/vomiting, loss of muscle strength, somnolence, thrombocytopenia, dyspepsia, dizziness, diarrhea, abdominal pain and tremor.	Valproate: Neural tube defects (i.e., rate 6–20%); high rates of mental retardation and lower IQ measures.	D
	Carbamazepine: May cause dizziness, drowsiness, unsteadiness, impaired coordination, nausea/vomiting, blurred vision, nystagmus, rash and confusion.	Carbamazepine: Neural tube defects, minor anomalies.	D
	Oxcarbazepine: May cause dizziness, somnolence, diplopia, visual changes, fatigue, headache, nausea, vomiting and ataxia.	Oxcarbazepine: Unknown.	C
	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 and loss of muscle strength.	Lamotrigine: Unknown but there appears to be a high rate of cleft lip and palate (i.e., 4–9/1,000).	C
	Gabapentin: May cause dizziness, somnolence, ataxia, fatigue, peripheral edema, nystagmus, nausea, vomiting and viral infection.	Gabapentin / pregabalin: Unknown.	C
	Pregabalin: May cause dizziness, somnolence, xerostomia, peripheral edema, blurred vision, weight gain, abnormal thinking, constipation, impaired coordination, pain and decreased platelets.		C
Anti-anxiety medications	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.	BZDs: “Floppy baby,” withdrawal, increased risk of cleft lip or palate. Hypnotic BZDs: Decreased intrauterine growth Buspirone: Unknown	D/X (hypnotic BZDs)

Class of Drugs	Typical Side Effects	Possible Teratogenic Risk	Legacy Pregnancy Risk Category ¹
	- Sedative antihistamines may have some antianxiety or hypnotic ability. Prolonged use of these agents may lead to anticholinergic side effects and cognitive impairment. - Buspirone can cause drowsiness, dizziness, impaired concentration, nausea and headache. Depression, hostility and akathisia, dystonia, tardive dyskinesia and EPS can occur.		

Sources: (Hilt, 2012; Lexicomp, n.d.; Micromedex, n.d.; Schatzberg & DeBattista, 2019; Yonkers et al., 2009)

Appendix C. Recommended clinical monitoring of children and adolescents for select psychotropic drugs

Class of Drugs	Monitoring Recommendation	Frequency Suggestion
Atypical antipsychotic medications	1. Height and weight 2. Labs: Fasting blood sugar, fasting triglyceride/cholesterol 3. Screen for dyskinesia movements 4. Labs: Complete blood count (CBC) with differential values (diff) 5. Blood pressure/pulse 6. Cardiac history 7. Determine if treatment responsive	1. At baseline and at each follow-up visit (at least every six months) 2. At least every six months 3. At least every six months 4. Once, two to three months after start of drug 5. At least once after start of drug 6. At baseline and obtain ECG if in doubt about risk from a mild QT increase 7. Repeat disorder-specific rating scales(s) until remission is achieved. Increase at four-to-six-week intervals if insufficient drug benefit
Antidepressant (SSRI) medications	1. Blood pressure monitoring 2. Hepatic function testing 3. Assess for suicidal thinking/behaviors, clinical worsening or other changes in behaviors 4. Inquire about activation symptoms 5. Inquire about bleeding/bruising 6. Measure height and weight 7. Determine treatment response 8. Pregnancy testing	1. Prior to treatment and with dose titration 2. Baseline and as clinically indicated 3. Ongoing—usually around week two, weeks four to six and other visits 4. Screen for new irritability or agitation around week two and weeks four to six 5. At least once after treatment begins 6. At baseline and each F/U visit, at least every six months 7. Repeat disorder-specific rating scales(s) until remission is achieved. Increase at four-to-six-week intervals if insufficient drug benefit 8. As clinically indicated
Antidepressant (SNRI) medications	1. Blood pressure 2. Hepatic function 3. Monitor for emergence of suicidal ideation or behavior 4. Pregnancy testing	1. Prior to initiating treatment, during dosage titration and as clinically indicated 2. At baseline and as clinically indicated 3. Ongoing—usually around week two, weeks four to six and other visits 4. As clinically indicated
Tricyclic antidepressant medications	1. ECGs 2. Obtain outside consultation	1. Prior to starting TCA therapy, when dose exceeds 3 mg/kg and then every two weeks if dose is being increased 2. When prescribing doses > 5 mg/kg

	3. Lower dosage with significant slowing of cardiac conduction 4. Monitor for emergence of suicidal ideation or behavior	3. In cases with ECG findings: PR interval over 0.20 msec, QRS interval over 0.12 msec 4. Ongoing—usually around week two, weeks four to six and other visits
Stimulant medications	1. Height and weight 2. Blood pressure and pulse 3. Cardiac history 4. Refill monitoring 5. CBC with diff 6. Determine if treatment response	1. At baseline and each F/U visit, at least every six months 2. At baseline and at least once on a given dose of medication 3. At baseline to determine if any risks from adrenergic stimulation 4. Track date of each refill to identify signs of drug diversion 5. For methylphenidate only, at least once every six months 6. Repeat ADHD-specific rating scale(s) until remission is achieved. Increase at two to four weeks if insufficient response
Mood stabilizing and anticonvulsant medications	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. 2. Divalproex sodium: (a) Chemistry Panel, CBC with platelets, liver function tests, pregnancy test. (b) Serum drug levels, hepatic and hematological indices. 3. Carbamazepine: (a) CBC, electrolytes and liver function tests. (b) Therapeutic drug levels.	1. Baseline monitoring (b) every three to six months 2. Baseline monitoring (b) every three to six months 3. Baseline monitoring (b) Routine monitoring in growing children to check for autoinduction of carbamazepine— usually occurring after one week and/or dosage changes

Sources: (Hilt, 2012; Kudriakova et al., 1992; Lexicomp, n.d., McClellan et al., 2007; Micromedex, n.d., Schatzberg & DeBattista, 2019; The Parameters Workgroup of the Psychiatric Executive Formulary Committee, Health and Specialty Care Division, Texas Health and Human Services Commission, 2019)