Magellan Health Services, Inc.

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

Important Issues and Evidence-Based Treatments

MAGELLAN HEALTH SERVICES®

Contents

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. Health care practitioners using these guidelines are responsible for considering their patients' particular situation in evaluating the appropriateness of these guidelines.

Introduction

In this era of evidence-based medicine, health professionals and child welfare advocates must engage in a careful assessment of the risk and benefit of using psychopharmacological treatments in children and adolescents while addressing serious concerns of overdiagnosis and overtreatment in this vulnerable population. As attention to this problem grows, a strong undercurrent of anxiety and confusion exists that current use of psychotropic agents is conveniently undertaken in order to remove undesirable impulses and behaviors of children while ignoring possible effects on neurological development, personality, character and temperament. Similarly, suspicions exist that this trend may be driven by a supply-induced demand created by pharmaceutical companies and medical providers. This has been termed a type of clinical, cultural and "social iatrogenesis" whereby the increased use of unnecessary or dangerous treatments can lead to increased injury and cost of health care (p. 300).[1, 2]

It is important to consider contributing factors to this sharp increase in use of psychotropic drugs that have been discussed in the pediatric psychopharmacology literature—i.e., "increased awareness of severe mental health problems in young children, development of medications considered safer than their older counterparts, 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" (p. 754).[3] Current challenges in psychiatric medicine are complex because the field has made tremendous strides in treating severe psychiatric disorders in very young, latency age school children and adolescents, but may be "creating equally serious problems when relying on pharmacologic interventions alone" (p. 764).[3] The call for an evidence-informed and judicious approach to the use of psychotropic medications with children and youth is urgent.

Nature and Scope of the Problem

In 2006, the American Psychological Association (APA) *Working Group on Psychotropic Medication for Children and Adolescents* summarized estimates for the morbidity associated with child and adolescent mental disorders with prevalence rates for childhood disorders ranging from 17% to 22% and where some 15% have significant functional impairment. In addition, the APA expressed significant concern that "only 1 in 5 of these children receives services provided by appropriately trained professionals" (p.19).[4] Other estimates also show that some 8 million of these youth are on one or more psychotropic medications.[1] In light of these prevalence data, increases in the number and percentage of children being treated with psychotropic drugs has been observed across populations—i.e., youth enrolled in Medicaid, foster care, preschoolers and adolescents.[3, 5]

In a published review of the clinical literature, Pidano and Honigfeld summarized recent findings from large epidemiologic studies where data portrayed the following key trends: (1) a two- to three- fold increase in the percentage of child/adolescent patients taking any psychotropic medication over a ten year (1987 – 1996) period; (2) adolescent office visits to physicians resulting in an increase in psychopharmacological prescriptions (i.e., 3.4% in 1994 – 1995 to 8.3% in 2000 – 2001) manifesting an overall child/adolescent (ages 6 – 17 years) psychopharmacological prescription rate of 8.8%; and (3) a trend for psychotropic drugs becoming more pronounced for male patients (i.e., 10% of visits). The drugs prescribed most often were various agents for treating attention-deficit hyperactive disorder, antidepressants, antipsychotics, mood stabilizers, and sedative-hypnotics.[5] Another large retrospective cohort study by Olfson et al. used data from the National Ambulatory Medical Care Survey from 1993 to 2002 and analyzed office visits to physicians by children and adolescents. Their findings revealed an approximate six-fold national increase in the absolute number of office-based visits that included prescription of antipsychotic medications in this population.[6] Further, Cooper and colleagues found that new use of antipsychotics among children and adolescents nearly doubled in the 6 years after the introduction of the atypical psychotics for young persons (aged 2 – 18 year) enrolled in Tennessee's managed Medicaid program (TennCare) from 1996 through 2001.[7]

More recent data published by the Government Accountability Office (GAO) continue to verify these trends despite efforts by providers, children's advocates and others to improve mental health treatment practices.[8] The GAO report , *Children's Mental Health/Concerns Remain about Appropriate Services for Children in Medicaid and Foster Care* (December 2012), analyzed nationwide data from the Medical Expenditure Panel Survey (MEPS) from 2007 through 2009 for children (ages 0 through 20 years) in Medicaid, State Children's Health Insurance Programs

(CHIP) and foster care comparing them against children that were privately insured. The GAO findings showed that on average, 6.2% of noninstitutionalized children in Medicaid nationwide and 4.8% of privately insured children took at least one psychotropic medication during a calendar year and noted that boys continue to have a utilization rate twice as high as girls (i.e., 8.4% versus 3.9%). In addition, the GAO found that children in Medicaid were over twice as likely as privately insured children to take an antipsychotic medication (i.e., 1.3% versus 0.5%). Based on their findings, the GAO recommended to Congress that both "federal and state initiatives to improve monitoring and oversight are appropriate, and that continued assessment of the prescribing of psychotropic medications to vulnerable populations and of the receipt of mental health services is important" (p.38).[8] Unfortunately, despite cumulative research evidence, psychotropic medications are employed too early in the treatment regimen rather than attempting to ameliorate the child's psychiatric symptomatology with psychosocial, behavioral or family interventions as a first step or augmenting treatment.[2]

Another overarching issue to consider in pediatric psychopharmacologic practice is the fact that most medications used with preschool children are administered "off label." This means that they are used to treat symptoms/conditions for which they were not granted approval by the Food and Drug Administration (FDA).[9] Fanton et al. alerted clinicians that "children have been described as 'therapeutic orphans' in the US drug regulatory system…noting that "preschool populations have been neglected more than school-aged peers." This is evidenced by the fact in 2009, that there "were only four medications approved for psychiatric indications in children younger than 6 years of age (i.e., haloperidol, chlorpromazine, d-amphetamine and risperidone)" (p. 755).[3] Only about 31% of psychotropic medications have been approved by the FDA for use in children or adolescents. It is estimated that currently more than 75% of the prescriptions written for psychiatric illness in this population is "off label" in usage.[10]

In a historical review of debates and developments in pediatric psychopharmacology, Correll and colleagues acknowledged research data which suggest that "psychiatric disorders are often more severe, chronic and unresponsive to therapies and associated with greater functional impairments and disease burdens if their onset occurs during childhood or adolescence compared to adulthood" (p. 26).[2] Authors further indicated that most major psychiatric disorders do have their onset in childhood or adolescence and stressed that the earlier the onset, the more malignant the course of the illness. While this may help us understand why severely ill youths should be prescribed psychoactive medications, it does not, however, address the issues of overtreatment or the concerns about inadequate efficacy data from pediatric randomized controlled trials.[2] At the present time, much of the published clinical trial findings applied to children and adolescents have been extrapolated from single-agent versus placebo drug trials using adult patients while measuring acute and short-term outcomes. More recent well-designed pediatric psychotropic drugs studies have pointed to a greater or different profile of susceptibility to adverse effects in children compared to adults. Other dissimilarities include developmentally dependent variations in drug effectiveness, paradoxical drugs reactions in susceptible youth and pharmacokinetic differences based on age and developmental anatomical/physiological maturity.[2, 9]

Current widespread use of psychotropic medication in children and youth must also be understood within the context of significant changes that have occurred in the mental health services system in the United States. The American Academy of Child and Adolescent Psychiatry (AACAP) reported that over the last 10 – 15 years, a manifest shortage of child and adolescent psychiatrists, more limited insurance coverage for inpatient and residential treatment and few outpatient psychotherapy services provided by psychiatrists have developed.[11] As a result of these trends, the Bazelon Center for Mental Health Law reports that primary care providers now furnish over one-half of the mental health treatment in this country and that about 25% of all primary care recipients have a diagnosable mental disorder. Moreover, the Bazelon Center and others have reported that as many as 50% of mental health problems go undiagnosed in the primary care setting.[5, 12] In addition, there have been numerous studies showing that primary care providers prescribe the majority of psychoactive medications used by children and adolescents. While most of the prescriptions are for attention-deficit hyperactivity disorder (ADHD) and depression, data indicate that over 75% of prescriptions for anxiolytics, antipsychotics and mood stabilizers for youths have also been ordered by primary care providers and not psychiatrists.[5]

Children in Foster Care

State government public sector health systems face a trend where children in foster care have become increasingly more vulnerable to inappropriate and excessive medication use. These children have many needs related to emotional and psychological stress because they have typically experienced abuse in neglectful, serial or chaotic caretaking environments and often present with past traumatic and reactive attachments that can mimic or complicate mental disorders.[13] Studies have shown that in addition to being in foster or state care, other factors that increase the risk of improper use of psychotropic drugs in children and youth include: (1) being poor (2) living in group care (3) being hospitalized in psychiatric inpatient units and (4) being incarcerated.[10] An analysis from the Centers for Medicare and Medicaid Services (CMS) of Medicaid data (2002 – 2007) for children in foster care (n=686,000) for 47 states and the District of Columbia showed that while there was wide variation, the range of rates for polypharmacy use was 1% – 14% and 3% – 22% for antipsychotic drug usage.[14]

Children in foster care receiving any type of medication must have the consent of a caregiver. However, states differ in medication consent authority since some require biological parent permission, whereas others require a state board/panel, foster parent, the court or other designated authorities (e.g., physicians or staff in residential settings). Unfortunately, states still report many cases where children in foster care were given psychotropic drugs without the required legal consent. Child advocates and clinicians see this as an area that needs to be rectified given the importance of the decision to use psychotropic agents in children. It is critical that the caregiver with consent authority be familiar with the specific child's needs, the therapeutic agents being prescribed and the intended impact/clinical outcomes for the specific agents. Professional second opinions are uniformly recommended in cases that may be complex (e.g., children under 6 years, pregnant teens, multiple medications), involve atypical antipsychotic medications or demonstrate treatment-resistance.[10]

Controversies in Clinical Management

A few areas of pediatric psychopharmacological treatment in the forefront of debate have been highlighted by experts as issues of special concern to prescribers. As discussed previously, the use of psychotropic medication in children of preschool age is a practice that is severely limited by the lack of evidence targeted to this age group.[9] This phenomenon is compounded by serious questions concerning the long-term prospective validity of psychiatric diagnoses in very young children. Fanton et al. stressed that although ADHD and post-traumatic stress disorder (PTSD) "appear to demonstrate 'homotypic continuity', meaning that the disorder continues to be present at follow up," other studies show that "the vast majority of children with mental health problems as toddlers and preschoolers will continue to have a psychiatric diagnosis in their school-age years, though not necessarily the same condition, suggesting that heterotypic continuity has valid implications"—i.e., prescribing agents used for school age manifestations of a disorder in a pre-school child (p. 755).[3] 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 (p. 755).[3]

Another controversy in pediatric psychopharmacotherapy transpired over the last decade. The treatment of depression in children and adolescents was significantly altered when in October 2003 the FDA released a public health advisory alerting health care professions to increased suicidality (ideation and attempts) in clinical trials of antidepressants in the pediatric population. A year later, a *black box warning* was issued for all antidepressants for patients under 18 years of age prompting a precipitous drop of 25% in rates of both diagnosis and treatment of depression by pediatric and non-pediatric primary care physicians.[15] 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 completed suicide rate in children and adults.[2, 11, 15] 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" (p. 11).[16]

While stimulant medication has strong evidence and clinical history of efficacy in treating core ADHD symptoms, apprehension continues on the use of stimulants in the treatment of ADHD due to concerns about cardiovascular side effects and stunted growth rates in children.[13, 17] In 2008, a joint advisory statement of the American Academy of Pediatrics (AAP) and the American Hospital Association (AHA) responded to a very small increase in sudden death from adverse cardiac events in children taking methylphenidate and amphetamine. The advisory recommended a physical exam and expanded patient/family health history focusing on cardiovascular disease risk factors (i.e., specific cardiac symptoms, Wolf-Parkinson-White syndrome, sudden death in the family, hypertrophic cardiomyopathy and long QT syndrome) and an electrocardiogram (EKG) at the physician's discretion for children being prescribed stimulants. The professional medical communities issuing this advisory recommended reasonable screening measures which would not result in a reduction in access to stimulant treatment.[17, 18]

Another area of apprehension involves one of the most common stimulant adverse effects—i.e., appetite loss. The Multimodal Therapy of ADHD (MTA) Study three-year follow-up analysis conducted in 2007, revealed the persistent effect of stimulant agents on decreasing growth velocity, especially when children are on higher doses. The AAP publication, *ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents*, indicated these outcomes demonstrated a small reduction in growth (i.e., ranging from 1 – 3 cm), affected mainly weight and diminished after the third year of treatment as a temporary drug effect. Currently, the AACAP Parents Medical Guide Workgroup recommends that parents focus on the timing of their child's stimulant dosing so as not to interfere with appetite and maintenance of adequate caloric intake.[16, 18]

As discussed previously, the majority of treatment for behavioral health conditions occurs in pediatric primary care settings. Their substantial role in prescribing psychotropic medications is an issue of significant concern as argued by Pidano et al. because "there have been studies suggesting too much may be expected of these providers when they do not have the benefit of extensive training in behavioral health or the support of mental health specialists in their practice" (p. 931).[5] Pidano's critique noted research findings signifying pediatric primary care providers "do not always identify the disorders presented by their patients and have reported substantial variations in their comfort level with diagnosing various psychiatric disorders" (p. 931).[5] Authors also indicated that while primary care physicians are most comfortable in prescribing stimulant drugs, many do prescribe atypical antipsychotics and other combinations. This same critique also indicated that although studies have shown similarities in medications and dosing when comparing primary care and psychiatric practices, the patient retention rate beyond the first visit was much higher for psychiatrists.[5] 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.[13]

Principles for Optimal Psychopharmacotherapy Practice

In 2009, the AACAP published the *Practice Parameter on the Use of Psychotropic Medication in Children and Adolescents*, in order 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.[11] The AACAP developed these guidelines to accommodate the wide range of appropriate psychopharmacological practice by prescribers from different clinical specialties operating in today's varied practice settings. The AACAP practice parameter underscores the importance of the prescriber to establish routine procedures for **consistent** approaches to assessment and treatment along with active family participation and their understanding of the illness and challenges facing the patient. In addition, this parameter emphasizes that the practice of pediatric psychopharmacotherapy requires the integration of information from the scientific evidence base, while also employing state-of-the-art clinical skills in accordance to a family's needs and values.[11]

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:[11]

- **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.
- **Principle 6:** Prescribers Should Be Cautious When Implementing a Treatment Plan That Cannot Be Appropriately Monitored.
- **Principle 7:** The Prescriber Provides Feedback About the Diagnosis and Educates the Patient and Family Regarding the Child's Disorder and the Treatment and Monitoring Plan.
- **Principle 8:** Complete and Document the Assent of the Child and Consent of the Parents Before Initiating Medication Treatment and at Important Points During Treatment.
- **Principle 9:** The Assent and Consent Discussion Focuses on the Risks and Benefits of the Proposed and Alternative Treatments.
- **Principle 10:** Implement Medication Trials Using an Adequate Dose and for an Adequate Duration of Treatment.
- **Principle 11:** The Prescriber Reassesses the Patient if the Child Does Not Respond to the Initial Medication Trial as Expected.
- **Principle 12:** The Prescriber Needs a Clear Rationale for Using Medication Combinations.
- **Principle 13:** Discontinuing Medication in Children Requires a Specific Plan.

The AACAP practice parameter also specifies that this approach is necessary for safe, effective and proactive treatment and should help decrease the stigma that some children and their parents may experience from participating in psychiatric care. This consistent and rigorous method for assessment and treatment should also safeguard against: (1) the introduction of unacceptable variability into the pharmacological treatment of children; (2) the underuse of established psychosocial and pharmacological treatment approaches; and (3) the prescription of ineffective/outdated treatment approaches, inappropriate medications or medication combinations. Also important, these recommended practices are implemented in an effort to eliminate demoralization experienced by patients and families receiving substandard treatment, "dropping out" of care or not seeking necessary treatment in the future.[11]

Research Evidence for Treatment Efficacy of Psychotherapeutic Agents

The AACAP practice parameter discussed above verifies a current evidence base in pediatric psychopharmacology that now includes data from randomized controlled trials on both pharmacokinetics (what the body does to the medication) and pharmacodynamics (what the medication does to the body).[11] To that end, this parameter specifies that efficacy and safety data are available for single pharmacological agents in the short-term treatment of a number of childhood psychiatric disorders—i.e., major depressive disorder (MDD), ADHD, obsessive-compulsive disorder (OCD), other anxiety disorders including separation anxiety disorder (SAD), social phobia and generalized anxiety disorder (GAD), mania, tic disorders, and aggression/impulse control as evidenced in autism and disruptive behavior disorders. However, the AACAP parameter indicates that extensive clinical practice and data from adult studies currently guide medication choices for schizophrenia since the clinical presentations are similar for patients across all age groups. Additionally, this parameter recognizes the smaller evidence base supporting psychotropic medication combinations which may be justifiably used in complex comorbid presentations, enhancement of outcome for treatment-refractory or partially responsive patients or to manage side effects.[11]

Key findings from the clinical research literature using analysis from published clinical systematic reviews by recognized experts and professional consensus guidelines are summarized below in order to outline the best pharmaceutical treatment options available for children and adolescents:

Mood Disorders

Bipolar Disorder: Children and adolescents seem to have more modest benefits from traditional mood stabilizers (i.e., lithium and antiepileptics) than adults where study findings support greater benefits (i.e., reduction in mania) with second generation antipsychotics (SGAs) studied—i.e., aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone. However, SGAs caused more weight gain and somnolence than mood stabilizers in youth than adults and SGAs caused greater weight gain in youth than adults. Researchers noted that more direct head-to-head comparator trials are still needed. Also, the relative efficacy of combining two mood stabilizers compared with one antipsychotic agent at the present time is not known.[2, 19, 20] Currently, the *Preschool Psychopharmacology Working Group (PPWG)* of the AACAP recommends a trial of risperidone after the failure of psychotherapeutic efforts to treat mania since this drug is the option with the most available data on effectiveness and tolerability in this age group.[9] To date, the FDA has indicated risperidone, quetiapine and aripiprazole for use in children aged 10 or older and olanzapine for children aged 13 and older with bipolar disorder (i.e., mania and mixed mania); approved lithium for adolescents aged 12 and older; olanzapine for adolescents aged 13 and older; and aripiprazole and lithium as treatments to prevent the recurrence of bipolar symptoms in children and adolescents.[19, 21] There is currently insufficient evidence on treatment of bipolar depression in children and adolescents. Therefore, the AACAP *Practice Parameter for the Assessment and Treatment of Depression in Children and Adolescents* suggests avoiding the use of antidepressants based on research findings of their ineffectiveness on bipolar depression and danger of triggering manic episodes in the adult population.[15]

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%).[15] 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.[2, 8, 22] As well, the PPWG of the AACAP recommends fluoxetine as the first-line treatment for depression in preschoolers.[9] Other clinical trials have demonstrated the effectiveness of sertraline or citalopram against placebo for the treatment of MDD in youth.[23, 24] The Treatment for Adolescents With Depression Study (TADS) compared treatments for moderate to severely depressed youth and found that 70% of those who received fluoxetine combined with weekly cognitive-behavioral therapy (CBT) had response rates showing significant improvement at 12 weeks followed by 60.6% for those treated with fluoxetine alone, 43.2% treated with CBT alone and 34.4% for placebo.[2] Another important trial, the Treatment of Resistant Depression in Adolescent (TORDIA) study demonstrated that for adolescents with depression who do not response 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.[2, 23]

Anxiety Disorders

Obsessive-Compulsive Disorder (OCD): The AACAP Workgroup on Quality Issues that developed the *Practice Parameter for the Assessment and Treatment of Children and Adolescents With Obsessive-Compulsive Disorder* lauded rapid advances seen in the previous decade in the knowledge of the pharmacotherapy of OCD affecting children and adolescents. However, this parameter continues to recommend cognitive-behavioral therapy (CBT) as the first line of treatment for mild to moderate cases of OCD because CBT "presents a logically consistent and compelling relationship between the disorder, the treatment and the specified outcome." The AACAP parameter further specifies that for youth with moderate to severe OCD, medication is indicated in addition to CBT (p. 104).[25] At the present time, there are four medications that have FDA approval for use in OCD in children and adolescents: the tricyclic antidepressant, clomipramine, for children aged 10 and over, and the SSRIs: sertraline (6 and older), fluoxetine (7 and older) and fluvoxamine (8 and older).[26] A meta-analysis of all published randomized controlled medication trials in children and adolescents with OCD showed their moderate effect size and statistically significant difference against placebo with

differences in absolute response rates ranging from 16% (sertraline and fluvoxamine) to 24% for fluoxetine. Additionally, clomipramine was superior to each of the SSRIs, where they were comparably effective. However, professional consensus supports the use of newer SSRIs over clomipramine because of tolerability and safety in children and adolescents.[25] The *PPWG* of the AACAP recommends the newer SSRIs for use in preschoolers only when in accordance with professional consensus and FDA recommendations.[9] 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. [2, 25, 26, 27] 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.[28] 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.[26]

Generalized Anxiety Disorder (GAD)/Separation Anxiety Disorder (SAD)/Specific Phobia: Although the non-OCD disorders (i.e., GAD, SAD, 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.[26] One of the most important studies of pediatric anxiety cited by experts was the recent Child/Adolescent Anxiety Multimodal Study (CAMS) where patients (n=488; ages 7 – 17 yrs.) with non-OCD anxiety disorders showed the most improvement in combination CBT/sertraline (81%), followed by CBT alone (60%), sertraline alone (53%) compared with 24% response rate to pill placebo.[2, 26] An earlier clinical trial, the Research Unit on Pediatric Psychopharmacology (RUPP) Study of 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 (76%) versus 29% for placebo. [2, 9, 26, 29] The AACAP *Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders* also confirmed the efficacy of fluoxetine compared to placebo in treating non-OCD disorders but cautioned this treatment response was markedly less dramatic for social phobia.[26, 29] The *PPWG* of the AACAP recommended paroxetine only as the first-choice medication for preschoolers in the non-OCD cases because it has been used most extensively in older children and adolescents and has the strongest safety profile.[9] In the treatment of GAD specifically, the SNRI, venlafaxine extended-release (XR) demonstrated significant superiority to placebo in two randomized controlled studies. Overall, SSRIs and SNRIs have shown clear benefit in the treatment of GAD in children and adolescents, with an overall response rate almost double that of placebo, with SSRIs slightly more beneficial than venlafaxine XR.[26, 29] In addition, the aforementioned medication algorithm for pediatric anxiety proposed by Kodish et al. indicated that after two failed SSRI adequate trials, venlafaxine XR should be considered for non-OCD in children and adolescents. As recommended for OCD, and in cases of no response or familial preference, buspirone or mirtazapine alone or as an augmentation may be tried. In addition, prescribers may consider use of benzodiazepines for acute relief of severe symptoms or after no response is evident after multiple medication trials.[26]

Post Traumatic Stress Disorder (PTSD): The diagnostic entity, PTSD, is generally disaggregated from other anxiety disorders research studies because of the uniqueness of its etiology and treatment. It is widely acknowledged that there is scant evidence to guide the pharmacological treatment of PTSD in children and adolescents.[30, 31] The AACAP *Practice Parameter for the Assessment and Treatment of Children and Adolescents With Posttraumatic Stress Disorder* recommends the use of trauma-focused cognitive-behavioral therapy (TF-CBT) alone as the first line treatment for PTSD in school-aged children and adolescents with the addition of an SSRI only if the child's symptom severity or lack of response suggested a need for additional interventions.[30] Two randomized trials have been conducted on sertraline in this population. These findings were equivocal because the effectiveness of sertraline comparable to placebo or CBT alone or combined with sertraline resulted in similar improvements.[31] The AACAP practice parameter does stress that school-aged children and adolescents suffering from PTSD who have co-morbid depressive disorder, GAD, OCD or other disorders known to respond to SSRIs should be treated with these agents earlier in treatment.[30] In contrast, the PPWG of the AACAP asserted that they "cannot recommend the use of psychopharmacological interventions for PTSD in preschoolers" in their

medication algorithms since the only randomized drug trials for this disorder have been performed on adults and the "clinical evidence supporting psychotherapeutic interventions for PTSD is quite strong" (p. 1558).[9] More recent open-label studies of α and β-adrenergic blocking agents (i.e., clonidine, propranolol) have shown promise in decreasing PTSD symptoms such as basal heart rate, anxiety, impulsivity and hyperarousal in children and youth.[30, 31]

Disruptive Behavioral Disorders/Aggression

Maladaptive aggression has been defined as a nonspecific, serious symptom accompanying many childhood disorders—i.e., oppositional defiant disorder (ODD), conduct disorder, ADHD and bipolar disorder. Severe problems with aggression have significant consequences in both social and academic functioning. Experts have termed maladaptive aggression the "fever" of child psychiatry because it is common, nonspecific, and as a phenomenon described it as "the language of the inarticulate" involving behavior that is unplanned, unprofitable and poorly controlled. It is differentiated from predatory aggression that is planned, sometimes profitable and highly controlled. The consensus development initiative, Treatment of Maladaptive Aggression in Youth (T-MAY), sponsored by Rutgers Center for Education and Research on Mental Health Therapeutics (CERT), provides recommendations for a standardized approach in dealing with maladaptive aggression seen in outpatient settings. CERT Guidelines indicate antipsychotics are the most studied class of drugs and have demonstrated the largest efficacy for disruptive/aggressive conditions, particularly risperidone versus placebo. In addition, the first-generation antipsychotic, haloperidol, demonstrated effectiveness in the treatment of aggression in hospitalized patients.[33] In a clinical review of studies, Correll et al. also noted that thioridazine was found to be an effective first generation antipsychotic agent for aggressive behavior in conduct disordered youth.[2] Other results from controlled clinical trials using conduct disorder as the principal diagnosis for inclusion, showed promise for mood stabilizers (e.g., divalproex, lithium), antipsychotics and stimulants.[9, 34, 35] Both the CERT Guidelines and the AACAP *Practice Parameter for the Assessment and Treatment of Child and Adolescents with Oppositional Defiant Disorder* recommend considering psychosocial interventions (i.e., evidenced-based parent and child skills training) as the first-line treatments since medications are to be considered "adjunctive, palliative and noncurative" (p. 137).[34] These guidelines also underscore the need for prescribers to target initial psychopharmacological treatment to the underlying primary psychiatric or co-morbid diagnosis(es) as this may ameliorate impulsive aggressive behavior.[33] In addition, the AACAP practice parameter indicates that many children who have an early onset of ODD, later progress to develop conduct disorder or antisocial personality disorders. The *PPWG* of the AACAP recommends a trial of risperidone for preschoolers with disruptive behavior disorders with severe aggression but without co-occurring ADHD. Although the *PPWG* notes the effectiveness and tolerability of risperidone in this age group, they recommend it should be discontinued after 6 months in order to reassess underlying symptoms and further validate diagnosis.[9]

Attention-deficit/Hyperactivity Disorder (ADHD)

The amphetamines and methylphenidate are stimulant drugs that remain first line treatments for ADHD with strong demonstrated efficacy in treating the core symptoms of hyperactivity, impulsivity, inattentiveness and associated aggressiveness. Higher stimulant doses generally are associated with better reduction in symptoms where it is estimated that at least 70% of school aged children respond favorably to stimulant medication.[18] The non-stimulant SNRI drug, atomoxetine, was approved by the FDA to treat ADHD and since it is not a controlled substance, it is more convenient for patients and physicians while reducing abuse potential. Atomoxetine does not offer the option for a drug holiday unlike stimulants and should be taken daily.[18] Meta-analytic findings of clinical trials for atomoxetine and stimulants yielded a moderate effective size for atomoxetine of 0.63 and large effect sizes of 0.99 and 0.95 for immediate and extended-release stimulants, respectively.[2] More recently, 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. None of these medications have FDA approval for use in preschool aged children. Nevertheless, current clinical guidelines now stipulate that children as young as four years of age may be diagnosed and treated for ADHD when academic/behavioral problems and core symptoms suggest the disorder and since ADHD does show diagnostic homotypic continuity throughout childhood and adolescence.[18] The *PPWG* of the AACAP recommends methylphenidate as the first-line psychopharmacological treatment for preschool ADHD and if ineffective, a switch to an amphetamine formulation. The *PPWG* algorithm

further allows clinicians to use individual clinical factors to choose between atomoxetine and α-agonists at this juncture, since the existing evidence does not support the superiority of agents to the other.[9] 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.[9] Additionally, the off-label use of SGA drug, risperidone, has shown promise in study results of children with aggressive behavior in ADHD. These findings need to be corroborated with supporting evidence from future clinical studies comparing antipsychotics with behavioral intervention, combination treatments and placebo.[2, 18]

The American Academy of Pediatrics (AAP) *Clinical Practice Guideline for the Diagnosis, Evaluation , and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents* makes distinctions by the age cohort of children with ADHD regarding the recommended order in which drug treatments should be instituted. Specifically, the AAP recommends: (1) evidence-based parent- or teacher-administered behavioral treatment should be instituted before a medication trial in preschoolers where drug therapy should be introduced only if there is no improvement; (2) combined behavioral and pharmacological interventions should be considered first-line approaches for school-aged children; and (3) medications should initially be prescribed for adolescents and behavioral treatments are optional, although preferable.[17, 18]

Autistic Spectrum Disorders (ASDs)

There is currently no pharmacologic agent that is effective in treating the core behavioral manifestations of autism.[36, 37] Nevertheless, certain drugs may be effective in treating the associated maladaptive behavior problems and co-morbid psychiatric disorders—e.g., OCD, depressive disorders, GAD and ADHD.[36, 38] In cases where a DSM-IV-TR comorbid disorder has been made, the patient can be treated with medications that are used in treating these conditions in typically developing children. In the absence of a clear comorbid psychiatric diagnosis, and in cases where behavioral interventions and environmental modifications have proven suboptimal, the AAP guideline recommends a "target- symptom cluster approach" with the use of an appropriate psychotropic agent (pp. 1169, 1170) with likely efficacy as follows: [38, 39]

1. Repetitive behavior, rigidity, obsessive-compulsive symptoms—Selective serotonin reuptake inhibitors (SSRIs) i.e., fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine, sertraline
2. Hyperactivity, impulsivity, inattention symptoms—Atypical antipsychotic agents (i.e., risperidone, aripiprazole, olanzapine, quetiapine, ziprasidone), valproic acid, stimulants (i.e., methylphenidate, dextroamphetamine, mixed amphetamine salts) and alpha agonists (i.e., clonidine, guanfacine)
3. Aggression, explosive outburst, self-injury—Atomoxetine, atypical antipsychotic agents (i.e., risperidone, aripiprazole, olanzapine, quetiapine, ziprasidone), alpha agonists (i.e., clonidine, guanfacine), anticonvulsant mood stabilizers (i.e., levetiracetam, topiramate, valproic acid), SSRIs (i.e., fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine, sertraline), beta-blockers (i.e., propranolol, nadolol, metoprolol, pindolol)
4. Sleep dysfunction—Melatonin, ramelteon, alpha agonists (i.e., clonidine, guanfacine) and antihistamines (i.e., diphenhydramine, hydroxyzine)
5. Anxiety—Mirtazapine, SSRIs (i.e., fluvoxamine, citalopram, escitalopram, paroxetine, sertraline), buspirone
6. Depressive phenotype—SSRIs (i.e., fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine, sertraline), mirtazapine
7. Bipolar phenotype—Anticonvulsant mood stabilizers (i.e., carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate, valproic acid), atypical antipsychotic agents (i.e., risperidone, aripiprazole, olanzapine, quetiapine, ziprasidone) and lithium.

While SSRIs are commonly prescribed in the treatment of autism, their usage has been largely extrapolated from research on adults. In addition, results of more recent large studies of their usage in children and autism have been disappointing.[40, 41] Meta-analytic findings on the efficacy of SSRIs for repetitive behaviors in ASDs showed that current published literature overstates SSRI effectiveness when also examining their treatment effects as demonstrated in unpublished literature. Similarly, other meta-analytic findings on the use of SSRIs for core symptoms of autism (i.e., communications, social interaction and behavior problems) showed lack of efficacy in the treatment of autism. These findings have lead to a diminution in their usage because of drug side effects and the possible emergence of suicide-related behaviors.[40, 41] Atypical antipsychotics, risperidone and aripiprazole, are the two best-studied medications to treat

the challenging or repetitive behaviors manifested in ASD. Since strength of evidence of treatment efficacy is high for aripiprazole and moderate for risperidone, investigators have concluded that future research is unlikely to change the assessment of benefits of these agents. Because marked weight gain and risk of extrapyramidal symptoms are significant in these agents, their usage is typically reserved for cases of severe impairment or risk of injury due to their adverse-effect profiles.[42, 43]

Childhood Schizophrenia

Until recently, the treatment of childhood schizophrenia was of necessity based on evidence from clinical pharmacological studies conducted with adults. The FDA approved several SGA agents for use in children and adolescents (aged 13 – 17) with schizophrenia after a wave of new placebo-controlled clinical trials were conducted and demonstrated efficacy in this population.[2, 44] Findings from one international multi-site 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).[2] 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.[45]

Cautionary Guidelines for Broadened Usage of Drugs

The broadened use of psychotropic medications used in children and adolescents today is fueled by a number of concerns regarding not only the number of agents prescribed but also the appropriateness of the diagnoses used to justify such use. While unsuitability of diagnosis applies across the board, Correll et al. have specified that this problem is most applicable to the improper assignment of bipolar disorder in childhood.[2] Even though SGAs were developed and initially studied as treatments for psychotic illnesses in adults, psychopharmacology experts report that aggression, and not psychosis, is the most common target symptom for which SGAs are prescribed to children and adolescents. [2, 44] 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. [2, 3, 9]

The AACAP *Practice Parameter for the Use of Atypical Antipsychotic Medication in Children and Adolescents* was developed in order to provide specific recommendations for baseline assessment and routine ongoing medical monitoring of the following significant safety issues/ concerns that are associated with the SGA side effects that can develop at treatment initiation and even with sustained use: (1) weight gain, diabetes and hyperlipidemia; (2) cardiovascular problems such as prolongation of QTc interval, orthostatic hypotension, tachycardia and pericarditis and coronary artery disease associated with weight gain; (3) neutropenia and potential agranulocytosis; (4) hepatic dysfunction; (5) elevation of prolactin levels; (6) electroencephalogram (EEG) abnormalities and possible seizure activity; (7) potential for the development of extrapyramidal symptoms, tardive dyskinesia and withdrawal dyskinesias; (8) neuroleptic malignant syndrome; and (9) formation of cataracts.[44]

The AACAP practice parameter summarized above also underscores the importance of prescribers in consulting the existing scientific literature before selecting the SGA agent. At the present time, SGAs clozapine, risperidone, olanzapine, quetiapine, ziprasidone, paliperidone and aripiprazole have published pediatric clinical trial data, but the more recently FDA approved SGA, asenapine, has no data pertaining to its use in the young population.[44, 45] Since the current FDA-approved indication for SGA use in children and adolescents includes only schizophrenia, bipolar disorder and specific symptoms of autism, the clinician is strongly urged to consider alternative pharmacological or psychosocial treatments for these other specific problems (i.e., disruptive behavior disorders and aggression).[44]

Drug Treatment Effects on Nervous System Development

The unknown long-term safety effects of psychiatric drugs taken by children and adolescents also includes their potential impact on developing organs, skeletal system, brain and central nervous system of a fetus in utero and throughout child's entire growth period.[47] Developmental effects of drugs may include minor and major malformations (i.e. somatic teratogenesis) in the

embryonic phase or effects on the fetus and breastfeeding infant which can affect the child's subsequent behavior, cognitive abilities and/or emotional regulation (i.e., neurobehavioral teratogenesis).[48] The FDA recently issued warnings against the use of the following drugs during pregnancy: (1) FGA/SGA antipsychotic drugs due to the risk of abnormal muscle movements and withdrawal symptoms in newborns, (2) valproic acid for risk of neural tube birth defects, (3) topiramate for risk of cleft lip/palate defects, (4) SSRIs for increased risk (i.e., up to 6 times more) of neonatal persistent pulmonary hypertension (PPHN) after the 20th week of gestation and (5) changing paroxetine assigned pregnancy category from C (i.e., risk cannot be ruled out) to D (i.e., positive evidence or risk to humans, risk may outweigh benefit) due to an increased risk of congenital malformations, particularly cardiovascular, in the first trimester of pregnancy (refer to table in appendix on page 21).[48,49, 50, 51, 52, 53]

Psychotropic drug use among pregnant women was quantified in a large retrospective cohort study conducted by investigators at Vanderbilt University using women (n=296, 817) enrolled in Tennessee Medicaid through pregnancy who had a live birth or fetal death from 1985 to 2005.[50] These women were treated with one or a combination of antipsychotics, lithium and anticonvulsants for a variety of disorders (i.e., pain, epilepsy, schizophrenia, bipolar disorders, unipolar depression and others). Overall, the adjusted use of study medications during pregnancy for these agents increased from nearly 14 to 31 per 1000 pregnancies in the twenty year span reviewed. In addition, the study revealed there were significant increases in the use of atypical antipsychotics (1.73 to 16.5 per 1000) and anticonvulsants (i.e., 4.12 to 13.2 per 1000) during pregnancy but decreases in the use of typical antipsychotics (7.77 to 0.99 per 1000) and lithium (2.11 to 0.46 per 1000).[50]

The marked increase in trend of psychotropic drug use in pregnant women, children and adolescents has provoked heightened research within the field of developmental neuroscience. In a published systematic review of the literature, Gentile argued that inherent potential neurobehavioral toxicity deserves attention since reproductive safety of psychotropic drugs has typically assessed the risk of congenital malformations and perinatal complications. Author 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.[54] In addition, Gentile acknowledged that preliminary data on SSRIs seems to exclude neurocognitive effects of prenatal exposure to these agents on infant development. However, other studies have pointed toward premature delivery and its association with depression itself.[48, 51] Gentile also emphasized that the neurobehavioral safety of SGAs is unknown due to a paucity of data, whereas the presumed safety of FGAs, tricyclic antidepressants (TCAs) and benzodiazepines remains preliminary for informing the decision making process.[54]

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 preventative 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.[55] 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" (p. 423).[56] Author proposed the concept that "drug effects incubate" and noted emerging evidence suggest "long-term effects of drug exposure are delayed and expressed once the vulnerable system reaches maturation" (p. 423).[56] In a more recent discussion of neurodevelopment, Andersen et al. further stipulated that the "adult system *accommodates* the drug only temporarily"... whereas the "drug *assimilates* into the juvenile brain by producing permanent alteration of the system" so that the "immature brain reprograms its developmental trajectory as if the drug was part of its local environment." It is, therefore, theorized by neuroscientists that "chronic exposure to commonly used therapeutic agents during a sensitive period has the potential to either prevent or exacerbate symptoms later in life." Based on this theoretical framework, Andersen also speculated that future research will focus on development of novel therapeutic agents designed to "challenge deficit states and reprogram development rather than attempt to merely treat them" (p. 11 – 12).[55]

Conclusion

The increase in dissemination of pediatric practice parameters and the considerable progress made in implementation of pediatric psychopharmacological clinical trials may help to abate the crisis of over-medicating children and adolescents with mental health disorders in the US today.[2] 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.[57]

Since most of mental health treatment is currently provided in primary care practices, there is a need for primary care clinicians and behavioral health specialists to forge new collaborative relationships that enhance the delivery of evidence-based care to affected children and their families. Well-designed pilot projects where primary care providers and child psychiatrist have used consultation, collaboration and comanagement employing telephonic, video conferencing and on-site educational case reviews/training sessions have been lauded as model programs. Professional and consumer advocacy groups along with managed care organizations have urged state governments and health care systems to consider them as viable alternative approaches.[5]

In addition, the quest for more scientifically-validated clinical information on the pharmacological treatment of children and adolescents remains urgent and is of paramount importance. The future direction for pediatric psychopharmacological research must provide a platform to: (1) identify clinical and biological response predictors of treatment; (2) generate precise benefit and risk estimates of treatment in patient subgroups; (3) increase understanding of psychotropic drug exposure on the developing brain; (4) study the moderators, mediators, biomarkers and biosignatures of treatment outcome; and (5) test multi-stage treatment strategies utilizing dynamic/multimodal treatment regimes. This clinical research agenda is necessary if the ideal goal of increased personalized treatment of our young population is to be accomplished.[2]

Note: Medication Charts to follow 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.

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

Drug Generic Name	FDA Approval Age/Indication	Pediatric Dosage/ Serum Level when applicable	Warnings and Precautions/Black Box Warnings
Combination Antipsychotic/Antidepressant			
fluoxetine & olanzapine	18 and older	N/A: Pediatric dosing is currently unavailable or not applicable for this drug.	*Black Box Warning for fluoxetine/olanzapine combination formula (marketed as Symbyax):* Usage increased the risk of suicidal thinking and behaviors in children and adolescents with major depressive disorder and other psychiatric disorders. *Other precautions for fluoxetine/olanzapine combination:* Possibly unsafe during lactation. Avoid abrupt withdrawal.
Antipsychotic Medications			
**Precautions which apply to <u>all</u> atypical or second generation antipsychotics (SGA):* Neuroleptic Malignant Syndrome/Tardive Dyskinesia/ Hyperglycemia/ Diabetes Mellitus/ Weight Gain/ Akathisia/Dyslipidemia *†Precautions which apply to <u>all</u> typical or first generation antipsychotics (FGA):* Extrapyramidal symptoms/Tardive Dyskinesia			
aripiprazole * (SGA)	10 and older for bipolar disorder, manic, or mixed episodes; 13 to 17 for schizophrenia and bipolar; 6 to 17 for irritability associated with autistic disorder	2-10 mg/kg/day	*Black Box Warning for aripiprazole:* Not approved for depression in under age 18. Increased risk of suicidal thinking and behavior in short-term studies in children and adolescents with major depressive disorder and other psychiatric conditions.
asenapine*	18 and older	N/A	*Black Box Warning for asenapine:* Not approved for dementia-related psychosis. Increased mortality risk for elderly dementia patients due to cardiovascular or infectious events.
chlorpromazine† (FGA)	18 and older	0.25 mg/kg tid	*Other precautions for chlorpromazine:* May alter cardiac conduction; sedation; Neuroleptic Malignant Syndrome; weight gain. Use caution with renal disease, seizure disorders, and respiratory disease and in acute illness.
clozapine* (SGA)	18 and older	Children: 150-300 mg/day Adolescents: 200-600mg/day	*Black Box Warning for clozapine:* Agranulocytosis; seizures; myocarditis; other adverse cardiovascular and respiratory effects. (<u>Note</u>: Clozapine is considered a treatment of last resort in children in whom trials of both FGA and SGA agents have failed).
haloperidol† (FGA)	3 and older	0.15-0.5 mg/kg/ day	*Other precautions for haloperidol:* May cause sedation, orthostatic hypotension, photosensitivity, constipation, dry mouth, prolactin elevation.
iloperidone* (SGA)	18 and older	Insufficient evidence	*Other precautions for iloperidone:* Prolonged QTc interval
loxapine† (FGA)	18 and older	N/A: Pediatric dosing is currently unavailable or not applicable for this drug.	*Other precautions for loxapine:* Safety unknown in lactation

Drug Generic Name	FDA Approval Age/Indication	Pediatric Dosage/ Serum Level when applicable	Warnings and Precautions/Black Box Warnings
Antipsychotic Medications *continued*			
molindone† (FGA)	18 and older	N/A	*Note:* Molindone was discontinued by its sole supplier, Endo Pharmaceuticals, on January 13, 2010.
olanzapine* (SGA)	18 and older; ages 13 to 17 as second line treatment for manic or mixed episodes of bipolar disorder and schizophrenia 18 and older	2.5-5mg qhs	
paliperidone* (SGA)	12 and older	N/A	*Other precautions for paliperidone:* Prolonged QTc interval
perphenazine† (FGA)	12 and older for psychotic disorders	6-12 yrs: 6mg/day ≥ 12yrs: 64mg/day	*Other precautions for perphenazine:* May cause dystonia, Neuroleptic Malignant Syndrome, orthostatic hypotension, weight gain, endocrine changes and alterations in cardiac condition.
pimozide (for Tourette's disorder) † (FGA)	12 and older	≤ 12 yrs: 0.2mg/ kg/d › 12 yrs: 1-10 mg/ day	*Other precautions for pimozide:* Dyskinesias, dry mouth, constipation, prolactin elevation, prolonged QTc interval. Possibly unsafe during lactation. Avoid abrupt withdrawal.
quetiapine*(SGA)	13 and older for schizophrenia; 18 and older for bipolar; 10 to 17 for treatment of manic and mixed episodes of bipolar disorder	25-300mg/day	
risperidone* (SGA)	13 and older for schizophrenia; 10 and older for bipolar mania and mixed episodes; 5 to 16 for irritability associated with autism	Usually 1-2mg/ day; other recommended doses: 3mg/day - children; 6mg/day - adolescents	
thioridazine† (FGA)	2 and older	3mg/kg/day	*Black Box Warning for thioridazine:* Dose-related prolongation of QTc interval may cause torsade de pointes-type arrhythmias and sudden death. Use restricted to schizophrenia resistant to standard antipsychotic drugs.
thiothixene† (FGA)	18 and older	N/A	*Other precautions for thiothixene:* CNS collapse, CNS depression, blood dyscrasias. Safety in lactation is unknown.

Drug Generic Name	FDA Approval Age/Indication	Pediatric Dosage/ Serum Level when applicable	Warnings and Precautions/Black Box Warnings
Antipsychotic Medications *continued*			
trifluoperazine* (FGA)	18 and older	0.5-10mg/day	*Other precautions for trifluoperazine:* CNS collapse, CNS depression, blood dyscrasias, bone marrow depression, hepatic impairment. Safety in lactation is unknown.
ziprasidone* (SGA)	18 and older	Children: 10mg/ day initial dose, maximum dose not established; 160mg/day – adolescents.	*Black Box Warning for ziprasidone:* Not approved for depression in under age 18. Increased risk of suicidal thinking and behavior in short-term studies in children and adolescents with major depressive disorder and other psychiatric conditions. *Other precautions for ziprasidone:* Prolonged QTc interval.
Antidepressant Medications (also used for anxiety disorders)			
◊ ∞ *Precautions which apply to all Selective Serotonin-Reuptake Inhibitors (SSRI) and <u>all</u> Serotonin and Norepinephrine Re-uptake Inhibitors (SNRI) antidepressants:* Activation of mania/hypomania, Discontinuation syndrome, increased risk of bleeding and use in combination with Monoamine oxidase inhibitors (MAOIs). ◊ ∞ ǂ *Black Box Warning which applies to <u>all</u> Selective Serotonin-Reuptake Inhibitors (SSRI), Selective Serotonin-Reuptake Inhibitors (SNRI) and tricyclic (TCA) antidepressants:* Usage increased the risk of suicidal thinking and behaviors in children and adolescents with major depressive disorder and other psychiatric disorders. ǂ *Monitoring of cardiac function is wise when TCAs are used in children.* EKG indicated prior to treatment, when dose exceeds 3mg/kg and every 2 weeks if dose is increased.			
amitriptyline ǂ (tricyclic [TCA])	18 and older	9-12 yrs: 1-3 mg/ kg/day ›12 yrs: 50-100 mg/ day	*Precautions for amitriptyline and other TCAs:* General caution for use in patients ‹ 25 yrs; those with bipolar disorder or comorbid schizophrenia or cardiovascular diagnosis. Avoid abrupt withdrawal. Do not take if an MAOI was used within the past 14 days.
amoxapine ǂ (TCA)	18 and older	N/A	
bupropion (aminoketone class)	18 and older	1-7 mg/kg/day	*Precautions for bupropion:* Anorexia and risk of seizures
citalopram* (SSRI)	18 and older	10-20 mg/day	
clomipramine ǂ (TCA)	10 and older (for OCD only)	Used for OCD ›10 yrs: Max: 3 mg/kg/ day up to 100 mg/ day in first 2wk; up to 200 mg/day	
desipramine ǂ (TCA)	18 and older	1-5 mg/kg/day 150-250 ng/mL (serum level)	
desvenlafaxine ∞ (SNRI)	18 and older	N/A	*Precautions for desvenlafaxine and other SNRIs:* Use in combination with MAOIs, activation of mania/ hypomania, Discontinuation syndrome, increased risk of bleeding.
doxepin ǂ (TCA)	12 and older	N/A	*Safety information for doxepin:* Unsafe in lactation. Significant adverse effects to infant/breast milk production - contraindicated or requires cessation of breastfeeding.

Drug Generic Name	FDA Approval Age/Indication	Pediatric Dosage/ Serum Level when applicable	Warnings and Precautions/Black Box Warnings
Antidepressant Medications (also used for anxiety disorders) *continued*			
duloxetine∞ (SNRI)	18 and older	N/A	*Safety information for duloxetine:* Inadequate data to assess safety in lactation. Physicians should consider tapering dose in 3rd trimester pregnancy.
Antidepressant Medications (also used for anxiety disorders)			
escitalopram * (SSRI)	18 and older; 12-17 (for major depressive disorder)	12-17 yrs: Max: 20 mg/day Taper dose gradually to D/C	*Black Box Warning for escitalopram:* As noted above plus notes not to be used in children under 12 years of age.
fluoxetine* (SSRI)	8 and older; 18 and older (for premenstrual dysphoric disorder)	5-30 mg/day	
fluvoxamine* (SSRI)	8 and older (for OCD only)	Maximum doses -Children: 200mg/ day Adolescents: 300mg/day	
imipramine‡ (TCA)	6 and older (for bedwetting)	1-5 mg/kg/day; 150-250 ng/mL (serum level)	
isocarboxazid (MAOI)	18 and older	N/A	*General caution for isocarboxazid and other MAOIs:* Use in patients under 25 yrs. old. Patients must avoid foods that are high in tyramine and avoid alcohol. This medication should not be used if another MAOI has been previously prescribed. Serious, life-threatening side effects can occur if isocarboxazid is consumed before another MAOI has cleared from the body.
maprotiline‡ (TCA)	18 and older	N/A	
mirtazapine (tetracyclic)	18 and older	N/A	*General precaution for mirtazapine:* Do not take if an MAOI was used within the past 14 days.
nortriptyline‡ (TCA)	18 and older	0.5-2 mg/kg/day 75-150 ng/mL (serum level)	
paroxetine* (SSRI)	18 and older	Children: N/A Adolescents: 10-20 mg/day	*Note:* FDA changed classification of paroxetine from category C to D for scientific evidence of positive teratogenic effects. Paroxetine should be avoided in pregnancy if possible, or limited to first trimester.
phenelzine (MAOI)	18 and older	0.25-1 mg/kg/day	
protriptyline‡ (TCA)	18 and older	N/A	
selegiline (MAO-B inhibitor/ phenethylamine class)	18 and older	N/A	*Precautions for selegiline:* Same dietary restrictions as for the MAOIs – avoid foods high in tyramine.

Drug Generic Name	FDA Approval Age/Indication	Pediatric Dosage/ Serum Level when applicable	Warnings and Precautions/Black Box Warnings
Antidepressant Medications (also used for anxiety disorders) *continued*			
sertraline* (SSRI)	6 and older (for OCD only)	200 mg/day	
tranylcypromine (MAOI)	18 and older	N/A	
trazodone (serotonin antagonist and reuptake inhibitor [SARI] class)	18 and older	N/A	*Black Box Warning for trazodone:* As noted for other classes of antidepressants for increased suicide risk. *Other precautions:* Should not be used within 14 days of MAOI treatment, monitor for emergence of mania/ hypomania, prolongation of the QT/QTc interval, increased risk of bleeding, priapism and possible hyponatremia.
trimipramine‡ (TCA)	18 and older	>12 yrs: 100 mg/day	
venlafaxine∞ (SNRI)	18 and older	N/A	
vilazodone (SSRI and 5-HT1A receptor partial agonist)	18 and older	N/A	
Mood Stabilizing and Anticonvulsant Medications			
carbamazepine	any age (for seizures)	10-50 mg/kg/day 8-12 mcg/mL (serum level)	*Black Box Warning for carbamazepine:* Stevens-Johnson Syndrome (particularly among Asians), aplastic anemia, agranulocytosis. *Other warnings/precautions:* neutropenia, hyponatremia, induces metabolism of itself and some other drugs, decreased efficacy of oral contraceptives, teratogenicity, MAOI use within 14 days.
divalproex sodium (valproic acid)	2 and older (seizures) Efficacy not established for bipolar disorder in children (ages 10-17)	15-60mg/kg/day 50-100 mcg/mL (serum level)	*Black Box Warning for divalproex sodium:* Hepatoxicity, teratogenicity, pancreatitis. *Other warnings/precautions:* urea cycle disorders, multi-organ hypersensitivity reaction, thrombocytopenia, withdrawal seizures, suicidal ideation, polycystic ovaries.
gabapentin	18 and older	N/A	
lamotrigine	18 and older	0.15-5.0 mg/kg/ day (25-200 mg/ day)	*Black Box Warning for lamotrigine:* Serious rashes including Stevens-Johnson Syndrome and aseptic meningitis. *Other warnings/precautions:* acute-multi-organ failure, withdrawal seizures, blood dyscrasias, hypersensitivity, suicidal ideation.

Drug Generic Name	FDA Approval Age/Indication	Pediatric Dosage/ Serum Level when applicable	Warnings and Precautions/Black Box Warnings
Mood Stabilizing and Anticonvulsant Medications *continued*			
lithium carbonate/ citrate	12 and older	300-2,400 mg/day 0.5-1.2 mEq/L (serum level)	*Black Box Warning for lithium:* Toxicity above therapeutic serum levels. *Other warnings/precautions:* Renal function impairment, polyuria, tremor, diarrhea, nausea, hypothyroid, teratogenic effects. Special risk patients include those with significant renal or cardiovascular disease, severe debilitation, dehydration, sodium depletion.
oxcarbazepine	4 and older	5-30 mg/kg/day (150-1,200 mg/ day)	*Warnings/precautions for oxcarbazepine:* hyponatremia, suicidal ideation.
topiramate	18 and older	N/A	
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:* Avoid abrupt withdrawal. These agents should be used for a limited time period and discontinuation of these drugs requires tapering.			
alprazolam	18 and older	N/A	
buspirone	18 and older	6-17 yrs: 60 mg/day (max)	
chlordiazepoxide	18 and older	> 6 yrs: 20-30 mg/ day	
clonazepam	18 and older	N/A	
clorazepate	18 and older	> 12 yrs. for partial seizures: 90 mg/ day (max)	
diazepam	18 and older	6 mo.-12 yrs: 0.12-0.8mg/kg/day	
lorazepam	8 and older	2 mg per dose, every 4-8 hours (max)	
oxazepam	18 and older	N/A	
ADHD Medications (Drugs below are *stimulants*, except atomoxetine, clonidine and guanfacine)			
Classification of non-stimulant drugs: (1) atomoxetine is a selective norepinephrine reuptake inhibitor or NRI; (2) clonidine and (3) guanfacine are classified as alpha-2 receptor agonists. *Black Box Warning for <u>all</u> stimulants:* Abuse potential. Risk of sudden death and serious cardiovascular events. *Warnings/precautions for <u>all</u> stimulants:* 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.			
amphetamine/ amphetamine extended release	3 and older/ 6 and older (XR)	40 mg/day max 30 mg/day max	

Drug Generic Name	FDA Approval Age/Indication	Pediatric Dosage/ Serum Level when applicable	Warnings and Precautions/Black Box Warnings
ADHD Medications (Drugs below are *stimulants*, except atomoxetine, clonidine and guanfacine) *continued*			
atomoxetine	6 and older	Children: 0.5 mg/ kg/day Adolescents: 40mg/da	*Black Box Warning for atomoxetine:* May cause serious cardiovascular events including sudden death, particularly in those with pre-existing structural cardiac abnormalities or serious heart problems; increase in blood pressure and heart rate; adverse psychiatric events and liver injury.
clonidine immediate release (IR)/clonidine extended release (ER)	IR- not approved for children ER - 6-17 years old	N/A Up to 0.4 mg/day	
dexmethylpheni-date/dexmethyl-phenidate extended release	6 and older	20 mg/day max 30 mg/day max	
dextroampheta-mine	3 and older	40 mg/day max	
guanfacine	6 and older	27-40.5 kg: 2mg/ day 40.5-45 kg: 3 mg/ day >45 kg: 4 mg/day	*Warnings/precautions for guanfacine:* May cause sedation and hypotension. Do not discontinue abruptly.
lisdexamfetamine dimesylate	6 and older	70 mg/day max	
methamphetamine	6 and older	60 mg/day max	
methylphenidate/ methylphenidate ER *and* ER suspension	6 and older	60 mg/day max	
methylphenidate long acting	6 and older	72 mg/day max	
methylphenidate patch	6 and older	30 mg/day max	
methylphenidate oral solution and chewable tablets	6 and older	60 mg/day max	

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

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

Class of Drugs	Typical Side Effects	Possible Teratogenic Risk	Risk Category*
Antipsychotic Medications	• 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, 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 be responsible for 4 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 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 bipolar disorder and greater suicide risk.	SSRIs: Perinatal and cardiovascular complications, spontaneous abortions. Potential premature delivery and neonatal persistent pulmonary hypertension (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

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

Class of Drugs	Typical Side Effects	Possible Teratogenic Risk	Risk Category*
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 anomaly) and behavioral effects.	D
	• Valproate: Children younger than 2 yrs. are at greatest risk for hepatotoxicity. Common reactions: headache, nausea/vomiting, loss of muscle strength, somnolence, thrombocytopenia, dyspepsia, dizziness, diarrhea, abdominal pain, tremor.	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, 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, 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, viral infection.	Gabapentin/ pregabalin: Unknown	C
	• Pregabalin: May cause dizziness, somnolence, xerostomia, peripheral edema, blurred vision, weight gain, abnormal thinking, constipation, impaired coordination, pain, decrease in 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. • Sedative antihistamines may have some antianxiety or hypnotic ability. Prolonged used 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.	BZDs: "Floppy baby", withdrawal, increased risk of cleft lip or palate. Hypnotic BZDs: Decreased intrauterine growth Buspirone: Unknown	D/ X(hypnotic BZDs) C

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

Recommended Clinical Monitoring of Children and Adolescents for Select Psychotropic Drugs

Class of Drugs	Monitoring Recommendation	Frequency Suggestion
Atypical Antipsychotic Medications	1. Height and weight 2. Labs: fasting blood sugar, fasting triglyceride/cholesterol 3. Screen for dyskinesia movements 4. Labs: 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 6 months) 2. At least every 6 months 3. At least every 6 months 4. Once, 2 – 3 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 4 – 6 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 2, weeks 4 – 6 and other visits 4. Screen for new irritability or agitation around week 2 and weeks 4 – 6 5. At least once after treatment begins 6. At baseline and each F/U visit, at least every 6 months 7. Repeat disorder-specific rating scales(s) until remission is achieved. Increase at 4 – 6 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 2, weeks 4- 6 and other visits 4. As clinically indicated
Tricyclic Antidepressant Medications	1. Electrocardiograms (ECGs) 2. Obtain outside consultation 3. Lower dosage with significant slowing of cardiac conduction 4. Monitor for emergence of suicidal ideation or behavior	1. Prior to staring TCA therapy, when dose exceeds 3mg/kg and then every 2 weeks if dose is being increased 2. When prescribing doses > 5 mg/kg 3. In cases with ECG findings: PR interval over 0.20 msec, QRS interval over 0.12 msec 4. Ongoing—usually around week 2, weeks 4-6 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 6 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 6 months 6. Repeat ADHD-specific rating scale(s) until remission is achieved. Increase at 2 to 4 weeks if insufficient response

Class of Drugs	Monitoring Recommendation	Frequency Suggestion
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. (a) Baseline monitoring (b) every 3-6 months 2. (a) Baseline monitoring (b) every 3-6 months 3. (a) Baseline monitoring (b) Routine monitoring in growing children to check for autoinduction of carbamazepine—usually occurring after one week and/or dosage changes

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

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