



Pediatric Psychopharmacology

Evidence-Based Care for Depression, Anxiety, and ADHD

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Disclosure

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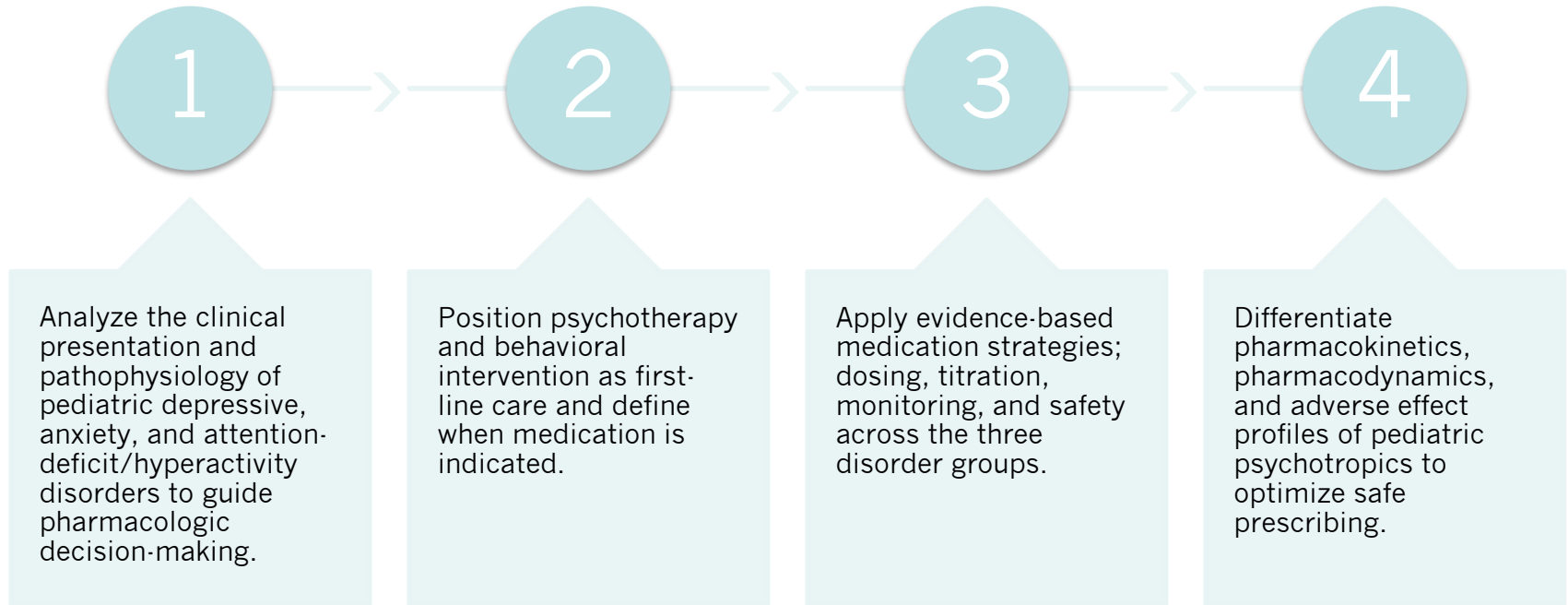
Any discussion of off-label medication use will be identified as such during the presentation.



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Learning Objectives





Therapy First: A Stepped-Care Framework

Psychotherapy is first-line for mild to moderate depression and anxiety; behavioral parent training is first-line for preschool ADHD when available.

- CBT, exposure therapy, interpersonal therapy, and parent management training carry strong pediatric evidence.

Medication is added to therapy, not substituted, when symptoms are severe or safety is at risk.

Screen for substance use, trauma, and bipolarity; address sleep and school supports first.

Combination treatment outperforms either modality alone in landmark pediatric trials for anxiety and depression (TADS, 2004; CAMS, 2008). In ADHD, medication outperforms all other modalities (MTA, 1999).

Shared decision-making with youth and caregiver drives adherence and realistic expectations.





Ruling Out Medical Mimics Before Prescribing

- **Baseline for everyone:** focused history, physical exam, vital signs, growth parameters, and a medication, supplement, and substance review.
- **Thyroid:** TSH with reflex free T4; hyper- and hypothyroidism mimic anxiety, depression.
- **CBC and ferritin:** anemia and low iron stores cause fatigue, poor concentration, and restless legs that disrupt sleep.
- **Metabolic panel and vitamin D or B12:** screen fatigue, mood change, and cognitive complaints; add hepatic and renal function when baseline data guide dosing.
- **Targeted testing by presentation:** urine toxicology, pregnancy test before prescribing, mononucleosis or infectious workup, sleep study for suspected apnea, and lead level in young children.
 - ECG only with cardiac history, syncope, or a concerning family history; not routine before stimulants.
- **Do not delay treatment for an exhaustive workup** - test what the history and exam suggest.





Pediatric Depressive Disorders

Presentation, pathophysiology, and pharmacologic management



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Depression: Clinical Presentation and Pathophysiology

- Presentation is age-dependent: irritability rather than sadness, isolation, somatic complaints, school refusal, and falling grades.
- DSM-5-TR still requires two weeks of depressed or irritable mood or anhedonia, plus neurovegetative change and impairment.
- Screen every visit for suicidal ideation, self-harm, substance use, trauma, and past hypomania before prescribing.
- Pathophysiology is multisystem: monoamine theory, reduced neuroplasticity, HPA-axis dysregulation, and gene-environment interaction.
 - Immature prefrontal control over an early-maturing limbic system drives emotional reactivity and impulsive risk.
- Comorbid anxiety, ADHD, and learning disorders shape the medication plan.





Depression: Therapy First, Then Medication

- **Mild:** active support, behavioral activation, and CBT; reassess at six to eight weeks.
- **Moderate to severe:** combine an SSRI with CBT; the highest response rates and fastest functional recovery (TADS; March et al., 2004).
- Medication alone is acceptable when therapy is inaccessible but arrange behavioral care in parallel.
- Expect partial response by weeks two to four; a full trial takes six to eight weeks at an adequate dose.
- Continue six to twelve months past remission, then taper slowly during a low-stress period.
- Refer to psychiatry for psychosis, bipolar features, persistent suicidality, or two failed trials.





Depression: Antidepressant Selection and Dosing

First-Line Agents

- **Fluoxetine:** FDA-approved age 8+ for MDD. Start 10 mg daily, usual 20 mg, range 10-60 mg. Longest half-life, most robust pediatric evidence, forgiving of missed doses. Strong CYP2D6 Inhibitor
- **Escitalopram:** FDA-approved age 12+ for MDD. Start 5 mg daily, usual 10 mg, range 5-20 mg. Clean interaction profile.
- **Sertraline:** widely used off-label for MDD. Start 25 mg daily, usual 50-100 mg, range 25-200 mg. Take with food to limit GI upset.

Titration and Second-Line Options

- Titrate every two to four weeks if response is partial and tolerability is good; an adequate trial is six to eight weeks at a therapeutic dose.
- **Second-line:** switch to a different SSRI before changing class; roughly half of SSRI non-responders respond to a second SSRI (TORDIA; Brent et al., 2008).
- **Third-line or comorbidity-driven:** duloxetine, venlafaxine XR, or bupropion for comorbid ADHD; mirtazapine when insomnia and low appetite dominate.
- Avoid paroxetine (Paxil) in youth due to short half-life, anticholinergic burden, and the weakest efficacy data.





Depression: Safety, Monitoring, and Adverse Effects

- **Boxed warning:** increased suicidal ideation under age 25. Absolute risk is small and untreated depression carries greater risk.
 - Any change in baseline SI should be reported to provider immediately.
- Early effects: GI upset, headache, sleep disruption, jitteriness are usually transient and dose-related.
- Activation, disinhibition, or emerging mania warrants reassessment for bipolar disorder, not a dose increase.
- Longer term: sexual side effects, emotional blunting, loss of efficacy- “poop out.”
- Serotonin syndrome risk rises with triptans, tramadol, fentanyl, linezolid, St. John’s wort, or dextromethorphan; counsel families on symptoms- confusion, tachycardia, hypertension, muscle rigidity, fever, diarrhea. Medical emergency requiring evaluation.
- Taper on discontinuation except fluoxetine; document a safety plan and means restriction at every visit.





Pediatric Anxiety Disorders

Presentation, pathophysiology, and pharmacologic management



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Anxiety: Clinical Presentation and Pathophysiology

- Anxiety disorders are the most common pediatric psychiatric conditions
- DSM-5-TR pediatrics: GAD- Excessive anxiety and worry occurring more days than not for 6 months, which the child finds difficult to control. Accompanied with 1 of 6 symptoms restlessness, fatigue irritability, sleep disturbance, concentration issues. Must cause impairment. Not explained by another issue.
- DSM-5-TR pediatrics: Social Anxiety- Marked fear or anxiety in context of peers, not just adults lasting 6 months or longer. Intense fear of negative evaluation. Social situations provoke the fear. Active avoidance. Fear or anxiety is out of proportion.
- Presentation is behavioral, not verbal: school refusal, somatic complaints, reassurance-seeking, separation tantrums, selective mutism.
 - Separation anxiety predominates in younger children; generalized and social anxiety emerge later.
- Pathophysiology: overactive amygdala (threat detection, emotions, emotional memory) threat response with weak prefrontal control, plus GABAergic (inhibitory neurotransmitter) and serotonergic dysregulation.
- Behavioral inhibition temperament (shyness,) parental anxiety, and caregiver accommodation maintain avoidance.
- Distinguish from ADHD, autistic rigidity, trauma, and medical mimics: thyroid disease, arrhythmia, caffeine excess, substance use.





Anxiety: CBT and Exposure Come First

- Exposure-based CBT is first-line for mild to moderate anxiety and is as effective as medication alone, with durable gains after treatment ends.
- Combination of CBT plus sertraline produced the highest response rate in the landmark pediatric anxiety comparative trial; roughly 80 percent versus about 55 to 60 percent for either alone (CAMS; Walkup et al., 2008).
- **Parent-directed work matters:** reducing family accommodation improves outcomes even when the child resists treatment.
- Add medication when anxiety is severe, when school attendance or development is derailed, when CBT cannot be accessed, or after an inadequate therapy response.
 - Medication can be the bridge that makes exposure work tolerable, frame it that way with families.





Anxiety: Medication Strategies and Dosing

First-Line SSRIs

- Sertraline: Off-label start 12.5-25 mg daily, usual 50-100 mg, max 200 mg. Strongest pediatric anxiety trial evidence.
- Fluoxetine: Off-label- start 10 mg daily, usual 20 mg, max 60 mg. Long half-life smooths adherence gaps.
- Escitalopram: FDA-approved age 7+ for generalized anxiety. Start 5 mg, usual 10 mg, max 20 mg. Clean interaction profile.
- Fluvoxamine: effective in anxiety (off-label) and OCD; more sedation and more CYP1A2 interactions.

Titration and Alternatives

- Start at half the depression starting dose; anxious kids are sensitive to activation and may abandon treatment after one “bad” week.
- Titrate every two to four weeks; anxiety often needs higher final doses and longer trials than depression.
- Second-line: switch SSRI, or use an SNRI such as duloxetine, which is FDA-approved age 7+ for generalized anxiety.
- Buspirone and hydroxyzine (excellent PRN) are adjuncts with modest evidence; beta blockers help performance anxiety only.
- No evidence for efficacy of Benzodiazepines in pediatric anxiety. Worsens anxiety overtime, decreased therapy efficacy.





Anxiety: Monitoring, Risks, and Benefits

- **Benefits:** rapid reduction in avoidance, return to school and peer activity, and readiness for exposure therapy.
- **Boxed warning:** increased suicidal ideation under age 25.
- Activation: restlessness, insomnia, irritability, impulsivity is common in younger anxious children.
 - Reduce the dose and re-titrate slowly rather than abandoning the class.
- Track response with SCARED or GAD-7 at baseline and follow-up, not global impression.
- Continue effective treatment 6–12 months past remission, then taper slowly.





Attention-Deficit/Hyperactivity Disorder

Presentation, pathophysiology, and pharmacologic management



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ADHD: Clinical Presentation and Pathophysiology

- DSM-5-TR requires symptoms before age 12, in two or more settings, for at least six months, with clear functional impairment: six symptoms for children, five for those 17 and older.
- Diagnosis is cross-informant: parent and teacher rating scales such as Vanderbilt or Conners are useful; clinical judgement is crucial.
- Core deficit is executive dysfunction: working memory, inhibition, sustained attention, and delay aversion. It is not a deficit of intelligence or effort.
- Pathophysiology involves hypo-functioning dopamine and norepinephrine signaling in prefrontal-striatal circuits and delayed cortical maturation.
 - Heritability is high, near 75 to 80 percent, with prematurity, lead, and prenatal exposures as contributors.
- Always screen for sleep disorder, learning disability, anxiety, depression, trauma, and substance use; each mimics or magnifies inattention.





ADHD: Behavioral Intervention First

- **Ages 3 to 5:** parent training in behavior management is first-line; reserve Adderall or methylphenidate, off-label, for persistent moderate to severe impairment after a behavioral trial or lack of access (PATs; Greenhill et al., 2006). Mixed Amphetamine Salts (Adderall) and Dextroamphetamine (ProCentra, Dexedrine, Zenzedi) FDA approved ages 3-5.
- **Ages 6 and older:** FDA-approved medication plus behavioral therapy and school supports together; medication alone treats symptoms, behavioral work builds skills (MTA Cooperative Group, 1999).
 - Classroom accommodations, a 504 plan or IEP, and daily/weekly report cards are part of the prescription.
- Behavioral intervention targets what medication does not: organization, homework routines, peer skills, and parent-child conflict resolution.
- Medication produces the larger effect size on core symptoms, so do not withhold it when impairment is significant, but pair it with skills.
- **Adolescents:** add organizational skills coaching, driving safety counseling, and an explicit diversion and misuse discussion.





ADHD: Stimulants — Formulations and Dosing

Methylphenidate Class (1st Choice)

- First-line; off-label under age 6, better tolerated in young children.
- IR: start 5 mg once or twice daily, titrate 5-10 mg weekly; 3-4 hours, up to 3-4 doses daily.
- ER (Concerta, Metadate CD, Ritalin LA): start 18-20 mg each morning; 8-12 hours.
- Typical range 0.3-1 mg/kg/day; titrate to effect.
- Children's Health Council guide: free stimulant chart.
- Liquid and chewable forms available.
- IR dose as an afternoon "booster."

Amphetamine Class (Second Line)

- Mixed amphetamine salts (Adderall): start 5-10 mg each morning, titrate weekly, max 30 mg in children.
- Lisdexamfetamine (Vyvanse): prodrug, start 20-30 mg each morning, range 30-70 mg; lower abuse liability.
- Roughly twice as potent mg for mg, with more appetite suppression and irritability.

Practice Points

- Response is idiosyncratic: ~70% respond to the first class, 85-90% to one of the two - cross-trial before declaring failure.
- Match duration to the day the family needs covered, including homework.





ADHD: Nonstimulants

- **When to choose a nonstimulant:** stimulant intolerance or non-response, significant tic or anxiety comorbidity, substance misuse or diversion risk, or family preference.
- **Atomoxetine:** norepinephrine reuptake inhibitor. Start 0.5 mg/kg/day for 7 to 14 days, then 1.2 mg/kg/day; allow four to six weeks for full effect.
- Atomoxetine carries a suicidality boxed warning, is metabolized by CYP2D6, and may help comorbid anxiety.
- **Guanfacine ER:** alpha-2A agonist. Start 1 mg at bedtime, titrate weekly by 1 mg to 1 to 4 mg daily; helps hyperactivity, impulsivity, and tics.
- **Clonidine ER:** start 0.1 mg at bedtime; more sedating than guanfacine and useful when sleep onset is a problem. Onyda XR is extended-release oral suspension.
- **Viloxazine ER:** a newer option for ages 6 and older; both alpha-2 agonists are FDA-approved as stimulant adjuncts as well as monotherapy.





ADHD: Safety and Monitoring

- **Every visit:** height, weight, blood pressure, and pulse, plus a review of appetite, sleep, mood, and tics. OARRS report.
- **Growth:** plot on the growth chart at least every six months; modest slowing is expected, but persistent deceleration warrants a dose/medication review. Research shows kids catch up eventually, but growth may be delayed.
- **Appetite suppression:** shift calories to breakfast and evening and add high-density snacks before reflexively lowering the dose. Calorie drinks like Ensure to supplement. Periactin available if medication benefit is significant.
- **Cardiovascular:** small increases in heart rate and blood pressure are expected. Screen by personal and family cardiac history, routine ECG is not required in healthy children.
 - Refer to cardiology for syncope, exertional chest pain, palpitations, or a family history of sudden death under age 40.
- **Neuropsychiatric:** watch for late-day rebound irritability, emerging tics, anxiety, personality changes, and rare psychosis or hallucinations; reassess rather than escalating the dose.
- **Nonstimulants and controlled substances:** taper alpha-2 agonists to avoid rebound hypertension, monitor sedation, and discuss diversion and misuse plan with adolescents.
- **Substance use:** Increased risk of SUD (alcohol, drugs) in untreated ADHD is 2-3x peers. Nicotine 5x.





Developmental Pharmacokinetics and Pharmacodynamics

Pharmacokinetics- what the body does to the drug

- Higher hepatic mass per kilogram means faster CYP-mediated clearance; children often need higher weight-based mg/kg doses than adults.
- Shorter half-lives can produce inter-dose withdrawal or end-of-day rebound, favoring divided or **extended-release** dosing.
- CYP2D6 and CYP2C19 polymorphisms alter exposure to many SSRIs and atomoxetine. (Rapid/Slow metabolizer.) Genesight testing is not valid or recommended in pediatrics per AACAP.
- Larger total body water and lower fat mass shift volume of distribution.

Pharmacodynamics- what the drug does to the body

- Prefrontal maturation runs into the mid-twenties while limbic circuits mature early; all gas, no brakes.
- Immature serotonergic and dopaminergic signaling raises risk of activation, disinhibition, and irritability.
- Youth are more sensitive than adults to weight gain, metabolic effects, prolactin elevation, and EPS.
- Start low, go slow, but titrate to an adequate dose; undertreatment is the more common error. Increase until effective, limited by side effects, or at maximum dose.





Comparing Classes: PK, PD, and Adverse Effects

Antidepressants

- Mechanism: serotonin, and for SNRIs norepinephrine, reuptake blockade with downstream receptor adaptation.
- Onset is slow. two to four weeks for early change, six to eight weeks for full trial.
- Hepatic metabolism via CYP2D6 and CYP2C19; fluoxetine and paroxetine are strong 2D6 inhibitors.
- Key risks: activation, suicidality warning, GI upset, bleeding risk, discontinuation symptoms, rare serotonin syndrome.

ADHD Agents

- Mechanism: stimulants increase synaptic dopamine and norepinephrine within hours; nonstimulants act indirectly over weeks through norepinephrine modulation.
- Onset differs significantly- stimulants work the first dosed day, atomoxetine, viloxazine, and guanfacine take four to six weeks.
- Stimulant duration is formulation-driven, so Pharmacokinetics, not potency, determines afternoon coverage and rebound.
- Key risks: appetite suppression, insomnia, irritability and rebound, small blood pressure and pulse rise, tic exacerbation (short term,) growth monitoring, and diversion.
- Nonstimulants add sedation, hypotension, and rebound hypertension on abrupt stop.





Key Takeaways

- Therapy first: psychotherapy and behavioral intervention are the foundation, and combination treatment consistently outperforms medication alone.
- Diagnose before prescribing. Screen for bipolarity, trauma, substance use, sleep disorder, and medical mimics.
- Start low and go slow but titrate to an adequate dose for an adequate duration; undertreatment is the more common failure.
- Side effects... Wait, wait, wait! They usually go away.
- Match monitoring to the class: suicidality and activation for antidepressants, growth, vitals, sleep, and diversion (parents too) for stimulants.
- Developmental pharmacokinetics and pharmacodynamics mean children are not small adults; clearance is faster and sensitivity is higher.
- Measure outcomes with standardized rating scales, and partner with families, schools, and therapists at every step.





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