

An Introduction to Pediatric Psychopharmacology

Disclaimer

The information below is intended as general guidelines to the pediatrician. In no way is this information intended to guide specific practice with specific patients.

Some General Points:

DO NO HARM – As with all medications, psychotropic medications work best when the diagnosis is correct. In certain cases, they can make thoughts, feelings and behaviors worse, or cause physical problems. When in doubt regarding a diagnosis or treatment, an evaluation by a qualified mental health professional is advised.

MULTIMODAL TREATMENT – Medications alone are rarely the optimal treatment for a psychiatric problem. Other treatment modalities such as individual psychotherapy, family therapy, individual tutoring, school accommodations, group therapy, community supports such as social clubs, etc., are often warranted.

FDA APPROVAL – Until recently, the FDA did not require that psychiatric medications under development be studied in children. As a result, many medications that are increasingly used in children and adolescents have not been FDA approved. While in most cases there is some clinical evidence supporting the use of these medications for specific disorders, placebo-controlled randomized clinical trials with sufficient numbers of subjects are frequently lacking.

START LOW, GO SLOW – Psychotropic medications for children should be initiated at a careful dose, and dose increases should be cautious.

I will focus on:

- ADHD
- Depression

- Anxiety disorders
- Sleep problems

ADHD Medications

What's New?

- Stimulants still the first-line agent in those without tics, severe anxiety, glaucoma, mood instability, arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known sensitivity to sympathomimetics.
- FDA blackbox warnings on stimulants: “high potential for abuse...drug should be prescribed or dispensed sparingly;” and “Misuse...may cause sudden death and serious cardiovascular effects.” Personal and family cardiac history and an EKG (controversial) , are recommended before initiating treatment. Consider an echocardiogram in the setting of positive history or abnormal EKG, or consider nonstimulant treatment options.
- Isolated single active isomers
- Long-acting preparations
- Transdermal methylphenidate, “Daytrana,” approved by FDA in 2006 and now available
- New prodrug, “Vyvanse,” (converts to dextroamphetamine) now available.
- Modafinil (Provigil) **not** FDA-approved for an ADHD indication due to concerns regarding rash and psychiatric symptoms
- Atomoxetine (Strattera) – nonstimulant ADHD medication, now second in line after stimulants; inhibits norepinephrine reuptake; approved by FDA in 2002; Black Box warning imposed in 2005 due to 5 cases of suicidal ideation and one attempted suicide in 1300 clinical trial patients; additional concern re potential liver injury after 2 documented cases (monitoring for jaundice, dark urine, unexplained flu-like symptoms and abnormal LFTS recommended); may be preferable in context of stimulant side effects including tic exacerbation and insomnia.
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- Multimodal Treatment of ADHD Study (*Arch Gen Psychiatry*. 1999; 56:1073–1086) supports use of medications for ADHD; the Preschool ADHD Treatment Study (PATs) support the use of methylphenidate in preschoolers with ADHD (Abikoff HB et al. (2007) *Jl of Child and Adolesc Psychopharmacology*, 17(5): 581–592.

Medication Treatment for ADHD

STIMULANTS	Dosing	Side effects	Other
<i>Methylphenidates - Short acting</i>			
Methylphenidate(Ritalin)	Start 5mg qd–tid up to 60mg qd Peaks 1–3h Lasts 2–4h	Appetite suppression, sleep disturbance, tic exacerbation, stomachache, HA, emotional lability, rebound effect	Avoid late pm dosing Greater abuse potential than longer–acting stimulants.
Dextro–methylphenidate (Focalin)	Start 2.5mg qd Peaks 1–4h Lasts 2–5h	Same	Same
<i>Methylphenidates - Intermediate Acting</i>			
Sustained release methylphenidate (Ritalin SR, Metadate ER, Methylin ER)	Start 10mg qam Peaks 3h Lasts 5–8h	Same	
<i>Methylphenidates - Long-acting</i>			
Daytrana (methylphenidate transdermal patch)	10–30 mg daily Lasts 8–12 h	Same	Duration of action can be shortened by decreasing wear time

Extended-release methylphenidate (Concerta)	Start 18mg qam up to 54mg daily Peaks 8h Lasts 12h	Same, but generally less rebound, less emotional lability	Capsule with osmotic release mechanism; capsule must remain intact
Metadate CD	Start 10mg qam Peaks 5h Lasts 8h		"Diffucap" bead release mechanism; can open and sprinkle beads. Mimics BID dosing.
Focalin XR	Start 5mg qam, or half the currently prescribed racemic dose of MPH up to max of 20mg daily. Lasts approx 8h	Same	Capsule can be opened and beads sprinkled. Mimics BID dosing.
Ritalin LA	20-60 mg qam; lasts 8-12h		Beads. Mimics BID dosing.
<i>Amphetamines - Short acting</i>			
Dextroamphetamine (Dexedrine)	Start 2.5mg qam-bid up to 40mg qd Peaks 1-3h Lasts 3-5h	Same	Greater abuse potential than longer acting stimulants.
Dextrostat	2.5-20mg	Same	"Branded

	qam-BID Lasts 3-5h		generic" of Dexedrine
<i>Amphetamines - Intermediate Acting</i>			
Amphetamine mixed salts (Adderall)	Start 2.5mg qd-bid; upperlimit 60mg/day Peaks 1-3h Lasts 4-8h	Same	Intermediate half-life; less rebound. Greater abuse potential than longer acting capsules.

<i>Amphetamines - Long- acting</i>			
Adderall XR	Start 10mg qam. Peaks 1-4h Lasts 8-12h	Same	Can open and sprinkle beads. Mimics BID dosing
Dexedrine spansules	Start 5mg qam. Peaks 1-4h Lasts 6-9h, perhaps longer	Same	Beads. Initial release, then continuous.
Vyvanse (dextroamphetamine prodrug)	15-30mg qam	Same	Possibly smoother time-release mechanism
NOREPINEPHRINE REUPTAKE INHIBITOR			
Atomoxetine (Strattera)	0.5 mg/kg - 1.2 mg/kg Lasts 24 h	CYP2D6 inhibitor; GI side effects, appetite	Monitor for liver injury, suicidal

		suppression	ideation. 24/7 coverage. No tic exacerbation. Less risk of worsening anxiety & mood
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ANTI-DEPRESSANTS			
Imipramine (Tofranil))	Start 10–20mg bid up to 150 mg/day, increasing q2w	Sleepiness, anticholinergic side effects, lower seizure threshold, EKG changes, blood pressure changes	Taper if stopping. Don't use if hx of conduction problems. Consider baseline EKG
Nortriptyline (Pamelor)	Start 10–25mg, target dose 10–150mg/day in div doses	Same	Not helpful with comorbid depression

Juvenile–Onset Depression

Symptoms of Depression: "SIGECAPS" DEPRESSED MOOD +

- SLEEP disturbance
- Loss of INTEREST/pleasure
- GUILT/worthlessness
- Decreased ENERGY
- Decreased CONCENTRATION
- Change in APPETITE
- PSYCHOMOTOR retardation or agitation

- SUICIDALITY

Features often unique to adolescents

- Increased sleep
- Irritability; negativistic or mixed mood state
- Increased po intake and weight gain
- Social withdrawal
- Decline in academic performance
- Masking by comorbid disorders (e.g. substance abuse, conduct disorder)

How to distinguish from juvenile-onset bipolar disorder

- JBPD is not like stereotype of adult "manic-depression," but phenomenology is controversial and under active study
- More chronic, continuous with long episodes
- Frequently mixed depressed/irritable/manic
- Mania characterized by hyperactivity, agitation, developmentally-dependent grandiosity (not euphoria)
- A complicated disorder that requires child psychiatry

How to approach depression in the pediatric office

- Identify depression and any comorbidities
- Ask about family history of mood disorders and suicide
- Assess stressors, family's dysfunction, other supports including school
- Provide psychoeducation and support, including re safety issues (e.g. lock up Tylenol, store gun with local police)
- Consider possible medical causes, e.g. anemia, hypothyroidism, lead, substance abuse, infectious mononucleosis
- Consider psychotherapy referral, SSRI and/or atypical antidepressant trial

Examples of questions to ask the patient

- Do you feel bad (sad, grumpy, mad) inside most days?
- Are you acting differently because of how bad you're feeling?
- Do you feel so bad that life doesn't seem worth living?

- Have you actually thought of ways you might hurt yourself, or even kill yourself?

Treatment of Depression

- Multimodal approach (Treatment of Adolescent Depression Study [TADS] supports combined fluoxetine and cognitive-behavioral therapy: March J et al (2004) JAMA 292: 807-820.
- If first SSRI trial (usually fluoxetine) unsuccessful, try a second SSRI (see Brent et al (2008) "Switching to another SSRI or venlafaxine with or without CBT for adolescents with SSRI-resistant depression; the TORDIA randomized controlled trial. JAMA 299 (8): 901-913.
- Manage psychosocial stressors
- Include parents
- Address school issues
- Psychoeducation of child and family

BLACK BOX WARNING

On October 15, 2004, the Food and Drug Administration issued a requirement that all antidepressants prescribed for children and adolescents carry a black box warning in their package insert. The warning concerns increased suicidal thinking and behavior that may occur in children and adolescents during the early phase of treatment. The warning is based on pooled analyses of short-term (4-16 weeks) placebo-controlled trials of SSRIs and other antidepressants in a variety of diagnoses in over 4400 patients. The FDA reported an increased risk of suicidal thinking or behavior during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

In light of these findings, the FDA recommends that observation for clinical worsening, suicidality or unusual changes in behavior during the first few months of antidepressant medication therapy *include weekly visits during the*

first four weeks, biweekly visits for the next eight weeks, then visits as clinically indicated.

Organizations of psychiatrists such as the American Psychiatric Association and the American Academy of Child and Adolescent Psychiatrists have expressed their protest to this warning, focusing on the potential for antidepressants to save lives and the deterrence to treatment that the black box may represent. (One study reported in Psychiatric News 9/02/05 reported 20% decline in antidepressant prescribing to youth since 10/04.) They also point out the lack of any research basis for the monitoring recommendations. Finally, they raise concerns re the mixed nature of the evidence. Nonetheless, it is recommended that practitioners do their best to follow the FDA recommendations, and that *they complete an informed consent process with parents before prescribing antidepressants for juveniles.*

Classes of Antidepressants

- Selective Serotonin Reuptake Inhibitors
- Atypical antidepressants (bupropion, venlafaxine, nefazodone, mirtazapine)
- Tricyclic antidepressants
- Monoamine Oxidase Inhibitors (MAOIs) (phenelzine, tranylcypromine, selegiline)

Antidepressants and the Pediatrician: Suggestions

- Consider becoming familiar with ONE SSRI and ONE atypical antidepressant
- Prioritize your treatment: Start with a safety evaluation; arrange for a next visit for further evaluation and assessment of treatment needs, including medication
- Discuss with your practice group what billing codes you may use for further visits
- PROVIDE AND DOCUMENT AN INFORMED CONSENT PROCESS BEFORE STARTING ANY MEDICATION

- REMEMBER: No treatment can be less safe than treatment; consider a referral to a child psychiatrist if in doubt

Issues with SSRIs

- Delayed efficacy (3–6 weeks)
- Annoying but not life-threatening side effects
- Generally safe in overdose
- Fluoxetine approved for use in juveniles; controlled data support the use of fluoxetine , sertraline and citalopram in children; paroxetine is also supported by one controlled study but see FDA warning below.
- Most common side effects 1) Sexual dysfunction 2) Nausea 3) Sleep disturbance or sedation 4) Headaches. Weight gain possible.
- Beware of activation, precipitating a mania. A child who is activated on an antidepressant, or who has an underlying bipolar disorder and has been precipitated into a manic phase by the antidepressant, may be agitated, hyperactive, unable to sleep. Treatment is to stop the medication.
- Discuss sexual dysfunction, change in appetite.
- MAY NOT BE SAFE IN PREGNANCY, ACCORDING TO RECENT EVIDENCE; FEMALE PATIENTS SHOULD HAVE A PREGNANCY TEST PRIOR TO INITIATING TREATMENT AND SHOULD TAKE APPROPRIATE PRECAUTIONS TO PREVENT PREGNANCY WHILE ON AN SSRI
- New SSNRI Duloxetine HCl (Cymbalta) associated with hepatic injury in postmarketing reports

SSRI Side-Effects (Kutcher, 1997): *Relatively common*

- Sexual dysfunction
- Dizziness
- Sweating
- Diarrhea
- GI distress
- Sexual disturbances
- Headaches
- Fatigue
- Restlessness

- Initial insomnia
- Weight gain

SSRI Side-Effects (Kutcher, 1997): *Relatively uncommon*

- Delayed micturition
- Blurred vision
- Hypomanic symptoms
- Tachycardia
- Seizures
- Skin rashes
- Hypersomnia
- Sexual dysfunction
- Dry mouth
- Tremor
- Constipation
- Bleeding/bruising

A clinical approach to side effects

- Side-effects are very idiosyncratic in children; if a child develops a symptom on the SSRI, it may well be the SSRI.
- Determine with the child and family how impairing the side effect(s) is (are) and make a risk-benefit analysis re continuing the medication.

SSRI Discontinuation Syndrome Most documented with paroxetine (Paxil) and fluvoxamine (Luvox), probably because they have shorter half-lives and no active metabolite

- Dizziness, paresthesias, asthenia, nausea, visual disturbance and headache
- Taper all SSRIs except possibly fluoxetine (Prozac) because of its long half-life

SSRIs: Dosing

- Start at $\frac{1}{4}$ to $\frac{1}{2}$ of adult starting dose

- For young children, if well tolerated go up to half of adult starting dose after 1–2 weeks and wait 3–4 weeks.
- For adolescents, if well tolerated go up to adult starting dose after 1–2 weeks and wait 3–4 weeks.
- If some evidence of response, consider more time OR slow dose increase.
- If no evidence of response, consider slow dose increase, augmentation with lithium, or switching to another SSRI; if prohibitive side effects, switch to another SSRI.

SSRIs: Drug–Drug Interactions

The SSRIs are known to inhibit metabolism of various cytochrome P450 isoenzymes. The effect is to raise the level of any co-administered medication which may be metabolized by the same isoenzyme.

For example, sertraline (Zoloft), citalopram (Celexa, Lexapro), fluoxetine (Prozac) and fluvoxamine (Luvox) are all metabolized by the P450 IIIA4 isoenzymes. So is erythromycin. Thus, coadministration of, say, sertraline and erythromycin may actually increase erythromycin levels, thus increasing the risk of side effects from erythromycin.

Serotonin Syndrome

- Usually occurs with the addition of a serotonergic agent to other meds
- Characterized by mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, fever
- Need to rule out sepsis, neuroleptic malignant syndrome

Tricyclic Antidepressants

Evidence suggests these are not significantly better than placebo in treating child/adolescent depression

Atypical antidepressants (second–line treatment for depression in children/adolescents)

- Venlafaxine (Effexor) (not effective in one placebo-controlled study of juveniles with depression; no more effective than SSRIs in TORDIA study)
- Nefazodone (Serzone) (not effective in one placebo-controlled study of juveniles with depression; brand name medication removed from market due to association with liver problems)
- Mirtazapine (Remeron)
- Bupropion (Wellbutrin)

Atypical antidepressants: Venlafaxine (Effexor)

- Can cause diastolic hypertension, discontinuation syndrome
- May cause anxiety, nausea, insomnia, sedation, dizziness, constipation, stomachaches, headaches

Atypical antidepressants: Nefazodone (Serzone brand removed from market)

- Serotonin and NE reuptake inhibition
- Indicated for depression; ? Also useful for anxiety
- New blackbox warning re liver failure; monitor liver function tests at baseline, with dose increases, and at regular intervals on stable dose
- May cause nausea, sedation (slow titration), agitation, dry mouth, constipation, confusion
- Few sexual side effects
- Less activating
- A metabolic inhibitor with med-med interactions like the SSRIs

Atypical antidepressants: Mirtazapine (Remeron)

- Controlled studies do not support its use for depression in children/adolescents; may be useful for anxiety
- Alpha-2 presynaptic autoreceptor inhibition (like yohimbine)
- Also stimulates serotonin and NE release
- Blocks post-synaptic serotonin receptors, so may cause sedation, weight gain, nausea

Atypical antidepressants: Bupropion (Wellbutrin)

- Affects both dopamine and NE systems
- Effective anti-ADHD agent
- Effective for depression in adults
- Anti-smoking (Zyban)
- No sexual dysfunction, ?less manicogenic
- Not to be used with seizures, bulimia
- May cause appetite suppression, sleep disturbance, tic exacerbation, irritability (esp at too-high dose)
- Caution in combining with other drugs that can lower seizure threshold
- Now available in one-a-day dosing (Wellbutrin XL)

Monoamine Oxidase Inhibitors

- Examples: Phenelzine (Nardil), Tranylcypromine (Parnate)
- Complicated to use (dietary restrictions and med interactions)
- BEWARE OF COMBINING WITH: Sympathomimetics, (e.g. Pseudoephedrine) (hypertensive crisis); Demerol, dextromethorphan, serotonergic agents (serotonin syndrome); TCAs (get symptoms like serotonin syndrome)
- Do not recommend use by pediatricians

Anxiety Disorders

- Generalized anxiety disorder
- Social phobia, selective mutism
- Panic disorder
- Obsessive-compulsive disorder
- Post-traumatic and acute stress disorders
- Separation anxiety
- Specific phobia
- Adjustment disorder with anxiety

Anxiety Disorders: General

- Most common psychiatric condition in children and primary cause of inattention
- If child meets criteria for one anxiety disorder, frequently meets others
- Controversial diagnostically because of this and comorbidity with other psychiatric disorders, lack of biological markers
- Good evidence for cognitive-behavioral treatment
- Highly familial
- Relationship to temperament (Chess and Thomas, Kagan's "inhibited child" work)
- Course tends to be chronic, (remission/relapse)
- Medical conditions such as hyperthyroidism, hypoglycemia, pheochromocytoma, and substance-induced anxiety, need to be ruled out; an association has been demonstrated between asthma and anxiety

Obsessive Compulsive Disorder – PANDAS (controversial)

- Pediatric
- Autoimmune
- Neuropsychiatric
- Disorders
- Associated with
- Strep

When to check for Strep (throat culture, ASO titer, anti-Dnase-B titer)

Any patient with tics, chorea, Obsessive Compulsive Disorder, choreiform movements who has:

- Abrupt onset of symptoms
- Abrupt exacerbation of symptoms
- Loss of a medication response
- History of good behavior with sudden dramatic behavioral difficulties (Leonard, 1999)

Treatment of Anxiety Disorders

Consider first: Cognitive Behavioral Therapy, family work, stress reduction, etc.

Consider meds if important functional impairment (e.g. not able to go on playdates, not going to school) or significant distress (symptoms bother the child a great deal)

How to handle anxiety in the pediatric office

- Identify anxiety and functional impairment
- Identify comorbidities
- Take family history
- Rule out possible medical causes including substance abuse
- Provide psychoeducation, advice re relaxation techniques (exercise, pleasure activities, etc.)
- Ask patient to keep a journal of the A, B, Cs of his or her anxiety symptoms (antecedent, behavior, consequence, including any efforts to contain)

Medications for Anxiety

- SSRIs
- Tricyclics
- Buspirone
- Benzodiazapenes
- Beta-blockers
- Combination of the above

NOTE: SEE BLACK BOX WARNING RE ANTIDEPRESSANTS ABOVE

SSRIs for Childhood Anxiety Disorders increasing usage, although little data, for:

- Panic disorder
- Social phobia
- Generalized anxiety disorder (GAD)
- Separation anxiety disorder

Treatment for Obsessive Compulsive Disorder (OCD) appears to require higher doses and longer medication trials. Referral to a child psychiatrist may be warranted.

For parent support, refer to Ocfoundation.org

Buspirone (Buspar)

- 5HT-1A receptor agonist
- Clinical effects not uniform
- No pharmacokinetic studies in children
- May be helpful for GAD, ?with ADHD, in med-sensitive populations (e.g. brain-injured, PDD)
- Start 2.5–5 mg TID, up to 30–60 mg/d
- Delayed onset of anxiolytic action
- Advantages: mild side effects, no addictive potential
- Can cause hypertension

Benzodiazepines

Short half-life:

- Alprazolam (Xanax)
- Lorazepam (Ativan) Longer half-life:
- Clonazepam (Klonopin)
- Diazepam (Valium)

Concerns about benzodiazepines

- Sedation, cognitive impairment
- Disinhibition
- Dependence/tolerance
- Potentiate effects of other medications
- Withdrawal side effects (need to taper)

When to consider using benzodiazepines

- Short-term treatment of disabling symptoms, e.g. for school avoidance until an SSRI starts to "kick in"
- Recurrent panic disorder, as a prn or "security blanket" (NOTE: clonazepam and alprazolam most effective for panic in adults)
- RARELY for short-term sleep difficulties

Example of using a benzodiazepine

Problem: 9 yo with school avoidance secondary to social phobia and separation anxiety; develops panic symptoms when approaching school in parents' car

Solution: 0.25–0.5 mg of clonazepam (Klonopin) given 30–45 minutes before arrival at school to offset panic symptoms and allow desensitization therapy to occur; may need to adjust timing of dosing given wide range of time to onset

Sleep medications for children/adolescents

- Diphenhydramine (Benadryl) 25–50 mg
- Trazodone (Desyrel) 25–50 mg (Key potential side effect is priapism in males)
- Zolpidem (Ambien) 5–10 mg
- Clonidine (Catapres) 0.05–0.10
- Mirtazapine (Remeron) 7.5 mg
- Melatonin 0.5 up to max of 10mg qhs (controlled data accumulating)

Always begin by emphasizing sleep hygiene.

For additional information please consult:

www.parentsmedguide.org/parentsmedguide.htm

www.parentsmedguide.org/physiciansmedguide.htm