

## **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 usually 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. Informed consent with patients regarding use of off-label medications should also include acknowledgment of their off-label status and an explanation of why an off-label medication is preferable to an FDA approved alternative.

**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, narrow-angle glaucoma, mood instability

- Blackbox warnings on stimulants likely by FDA due to sudden death risk and cardiovascular problems; Most recent American Heart Association [guidelines](#) recommend screening for personal and family cardiac history; an EKG maybe ordered at the discretion of the prescriber. Consider an echocardiogram or pediatric cardiology referral in the setting of positive history or abnormal EKG, or consider [nonstimulant](#) treatment options.
- Isolated single active isomers
- Long-acting preparations
- Transdermal methylphenidate
- Prodrug (Vyvanse)
- Atomoxetine (Strattera) - nonstimulant ADHD medication, now second in line after stimulants; inhibits norepinephrine reuptake; approved by FDA in 12/02; 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.
- Multimodal Treatment of ADHD Study (Arch Gen Psychiatry. 1999; 56:1073-1086) clearly supports use of medications for ADHD, although follow-up studies underscore these children continue to have areas of difficulty.

#### Medication Treatment for ADHD

STIMULANTS	Dosing/Peak/Duration	Side effects	Other
<i>Methylphenidates – Short acting</i>			
Methylphenidate(Ritalin)	Start 5mg qd-tid up to 60mg qd. Peaks 1-3hLasts 2-4h	Appetite suppression, sleep disturbance, tic exacerbation, stomachache, HA, emotional lability, rebound effect	Avoid late pm dosing
Dextro-methylphenidate (Focalin)	Start 2.5mg qd Peaks 1-4h Lasts 2-5h	Same	Same
<u>Methyline</u> CT	Start 5 mg BID up to 20 mg TID. Lasts 3-4h	Same	Chewable tablet

Methylin Oral Solution	Start 5 mg BID up to 30 mg BID	Same	Grape-flavored clear liquid
<i>Methylphenidates – Intermediate Acting</i>			
Ritalin SR	Start 10mg qam up to 60 mg qam Peaks at 3 hours. Lasts 4-8 hours	Same	Continuous release tablet; individual variability in duration of action due to wax matrix
Metadate ER	Start 10 mg qam up to 30 mg BID Lasts 6-8 hours	Same	Brand-name generic of Ritalin SR
Methylin ER	Start 20mg qam up to 60 mg qam Lasts 4-8 hours	Same	Brand-name generic of Ritalin SR
<i>Methylphenidates – Long-acting</i>			
Extended-release methylphenidate (Concerta)	Start 18mg qam up to 54mg qd Peaks 8h Lasts 12h	Same, but generally less rebound, less emotional lability. Possibly less potential for abuse.	Capsule with osmotic release mechanism; capsule must remain intact
Metadate CD	Start 10mg qam Peaks 5h Lasts 8h	Same	"Diffucap" bead release mechanism; can open and sprinkle beads. 30% released immediately, 70% delayed release.
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 2 equal doses of regular Focalin.
Ritalin LA	10-60 mg qam	Same	Capsule can be opened and beads sprinkled. Mimics 2

			equal doses of regular Ritalin
Daytrana (MPH transdermal system)	10-30mg po qam. Remove after 9 hours. Lasts 8-12 hours.	Same	Continuous release patch. Can remove patch earlier to decrease duration.
<i>Amphetamines – Short acting</i>			
Dextrostat (dextroamphetamine)	Preschoolers: 2.5 mg qam up to 20 mg BID School-aged and adolescents: 5mg qam up to 20 mg BID Lasts 3-5 hours	Same	Brand-name generic of Dexedrine
Liquadd (dextroamphetamine)	Start 5 mg qam up to 20 mg BID Lasts 3-5 hours	Same	Bubble-gum flavored liquid
Desoxyn (metamphetamine)	Start 2.5-5 mg qam up to 10 mg BID Lasts 3-5 hours	Same	Tablet
Amphetamine mixed salts (Adderall)	Start 2.5mg qd-bid; upper limit 60mg/day Peaks 1-3h Lasts 5h	Same	Intermediate half-life; less rebound
Dextroamphetamine (Dexedrine)	Start 2.5mg qd-bid up to 40mg qd Peaks 1-3h Lasts 5h	Same	Tablet
<i>Amphetamines-Intermediate-acting</i>			
Adderall	Start 2-5-5mg qam up to 60 mg qam Lasts 4-8 hours	Same	Tablet. Can be crushed. Available in smaller dosing increments (5, 7.5, 10, 12.5, 15, 20, 30)

STIMULANTS (continued)	Dosing	Side effects	Other
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<i>Amphetamines – Long-acting</i>			
Adderall XR	Start 10mg qam Peaks 1-4h Lasts 9h	Same	Can open capsule and sprinkle beads.
Dexedrine spansules	Start 5mg qam Peaks 1-4h Lasts 6-9h	Same	
Vyvanse			
<b>NOREPINEPHRINE REUPTAKE INHIBITOR</b>			
Atomoxetine (Strattera)	Start 10-25 mg (weight dependent) up to 80 mg qd	CYP2D6 inhibitor; GI side effects, appetite suppression	Monitor for liver injury, suicidal ideation (black box warning); 24/7 coverage; no insomnia

<b>ANTI-DEPRESSANTS</b>			
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 (TADS study supports combined fluoxetine and cognitive-behavioral therapy)
- 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.**

**A recent meta-analysis found a favorable benefit-risk ratio in treating depressed youth with antidepressants (Bridge JA et al 2007: Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA 297:1683-1696).**

**Pediatricians should conduct and document *an informed consent process with parents before prescribing antidepressants for juveniles.***

## Classes of Antidepressants

- Selective Serotonin Reuptake Inhibitors
- Other 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 other type of 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 and levo-citalopram FDA approved for use in juveniles; controlled data support the use of fluoxetine (most recently the NIMH-funded 2004 Treatment of Adolescent Depression Study TADS), sertraline and citalopram in children; paroxetine is also supported by one controlled study but see FDA warning below.
- The TORDIA study (Treatment of Resistance Depression in Adolescents, **Brent D et al. (2008) Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. JAMA. Feb 27;299(8):901-13**) supports the use of a 2<sup>nd</sup> SSRI if 1<sup>st</sup> is ineffective. Contrary to previous thinking, no evidence that venlafaxine is superior, and it may be associated with increased risk of suicidality
- Most common side effects 1) Sexual dysfunction 2) Nausea 3) Sleep disturbance
- 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
- Newer 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 (particularly when combined with non-steroidal anti-inflammatories)

### **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), 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)
- 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
- Usually clinically inconsequential medication interactions
- May be associated with increase in spontaneous suicidality (Hammad et al, 2006, Arch Gen Psychiatry 63:332-333).

### **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)**

- One controlled study does not support its use in children/adolescents
- 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; one controlled study supports use of fluoxetine in juveniles; one open study supports use of fluvoxamine
- 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

### **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 (CBT), family work, stress reduction, etc.

Consider meds if important functional impairment (e.g. not able to go on playdates, not going to school).

The CAMS Study (Child/Adolescent Anxiety Multimodal Treatment Study) supports combined use of SSRI and CBT as first-line treatment (Walkup JT et al. Cognitive Behavioral Therapy, Sertraline, or a Combination in Childhood Anxiety. *NEJM* 359:2753-2766, Dec 25, 2008.)

### **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
- Separation anxiety disorder

## **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 (one controlled study in adolescents)

Always begin by emphasizing sleep hygiene.

**For additional information please consult:**

[www.parentsmedguide.org/parentsmedguide.htm](http://www.parentsmedguide.org/parentsmedguide.htm)  
[www.parentsmedguide.org/physiciansmedguide.htm](http://www.parentsmedguide.org/physiciansmedguide.htm)