PART 7 MEDICATIONS- PRACTICAL APPLICATIONS

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PRACTICAL PSYCHOPHARMACOLOGY IN CHILDREN AND ADOLESCENTS

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Basic points we' ll cover today:

- Pharmacokinetics in Children
- ADHD Medications
- Antidepressants and the Black Box
- Anxiety Disorders
- Other Topics
- Questions

Take Home Points

- 80% of Rx are not approved by the FDA for use in children [1]
- Fewer evidence-based studies in children than adult psychiatry
  - Often have to use your best judgment based on adult literature and clinical experience [1]
- Pharmacotherapy plus psychotherapy tends to have better results than pharmacotherapy alone [2,3]
- Strong stigma against using medications in treating pediatric mental illness

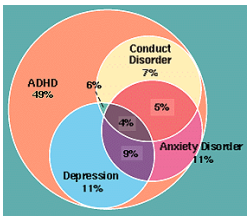
Pharmacokinetics in Pediatrics

- Lipophilic Medications:
  - Most psychotropic medications are highly lipophilic
  - The percentage of total body fat increases during the first year of life, then decreases gradually until puberty [4]
  - Children have different volumes of fat for drug storage at different ages.
- CYP/Metabolizing enzymes:
  - Both CYP450 and phase II drug metabolizing enzymes generally are absent in infancy, though rapidly develop over the first few years of life.
  - Toddlers and older children may have levels of these drug-metabolizing enzymes which exceed adult levels!
  - These decline until puberty, where they generally remain the same until adulthood.

Pharmacokinetics in Pediatrics

- Liver mass effects:
  - Relative to body weight, the liver mass of a toddler is 40-50% greater than an adult. A 6 year old is 30% greater than an adult.
  - Children tend to clear drugs more rapidly than adults
  - Children may require higher mg/kg concentrations to achieve the same plasma levels.
- Renal filtration:
  - By age 1, GFR and renal tubular mechanisms for secretion have reached adult levels
  - However, fluid intake may be greater in children relative to adults
  - Therefore, medications have a more rapid renal clearance in children compared to adults

Stimulants and ADHD



- Affects 5-10% of children in the US [5]
- 7 Million Ambulatory visits in 2006
- >$31.1 Billion annual US cost
- 2:1 Male:Female ratio in general population but up to 9:1 in mental health clinics [6]
- 50% of clinical samples have ODD or CD [6]
- 25-30% have comorbid anxiety disorders [6]
- 20-25% have comorbid learning disorders [6]
- Why do we care?

ADHD Medications

- Can help greatly with quality of life by affecting the ability to focus, decrease physical hyperactivity
- Combination of medications and behavioral interventions have been shown as a superior treatment to either alone [7]
- The goal of medication is *symptom reduction*, which requires careful assessment and ongoing monitoring of mental status/psychosocial functioning
- Use of Subscales can be helpful (Vanderbilt, Connors, etc) but not diagnostic – clinical judgment remains most important
- Stimulants
  - Most widely used
  - 65-75% efficacy in treating ADHD symptoms vs 4-30% placebo response
  - Only 55% of patients with ADHD get medication treatment
- Non-stimulants
  - May have fewer (or different) side effects
  - Typically considered second line treatment

The Stimulants

- Methylphenidate vs. Amphetamine
  - Methylphenidate blocks the reuptake of DA and NE but has little effect on presynaptic release of dopamine [8]
  - Amp blocks reuptake of DA and NE and increases release of DA and NE [8]
- Long Acting Forms - 3 delivery options:
  - SODAS/DIFFUCAPS: combination of immediate and extended release beads
  - OROS: capsule with H2O permeable holes which release medication depending on osmotic pressure
  - 3rd option: Lisdexamfetamine, a prodrug bound to L-lysine which uses GI tract to metabolize → dextroamphetamine

Practical Steps in Stimulant Treatment

- Refer to handouts for dosing information
- Can titrate with short acting as needed on top of long acting
- Base your clinical decisions on the *best interests of the child*
- Adverse effects:
  - Common (10-50%): nausea, stomach upset, decreased appetite, insomnia, headache
  - Uncommon: motor tics (9%), dysphoria, irritability, hallucinations, "zombie"
  - Cardiac: 25 cases of sudden death; risk is 0.7-1.5/100K children <16
  - Growth: MTA – 1cm/year decrease in height over 1-3 yrs. of continuous treatment, but other studies show no difference

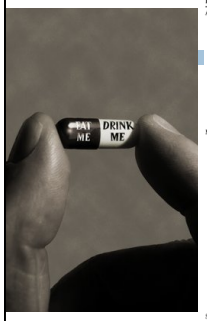


TABLE 2
Medications Approved by the FDA for ADHD (Alphabetical by Class)

Generic Class/ Brand Name	Dose Form	Typical Starting Dose	FDA Max/Day	Off-Label Max/Day	Comments
Amphetamine preparations					
Short-acting					
Adderall[a]	5, 7.5, 10, 12.5, 15, 20, 30 mg tab	3–5 y: 2.5 mg q.d.; ≥6 y: 5 mg q.d.–b.i.d.	40 mg	>50 kg: 60 mg	Short-acting stimulants often used as initial treatment in small children (<16 kg), but have disadvantage of b.i.d.–t.i.d. dosing to control symptoms throughout day
Dexedrine[a]	5 mg cap	3–5 y: 2.5 mg q.d.			
Dexedrine[a]	5, 10 mg cap	≥6 y: 5 mg q.d.–b.i.d.			
Long-acting					
Dexedrine Spansule	5, 10, 15 mg cap	≥6 y: 5–10 mg q.d.–b.i.d.	40 mg	>50 kg: 60 mg	Longer acting stimulants offer greater convenience, confidentiality, and compliance with single daily dosing but may have greater problematic effects on evening appetite and sleep. Adderall XR cap may be opened and sprinkled on soft foods
Adderall XR	5, 10, 15, 20, 25, 30 mg cap	≥6 y: 10 mg q.d.	30 mg	>50 kg: 60 mg	
Lisdexamfetamine	30, 50, 70 mg cap	30 mg q.d.	70 mg	Not yet known	
Methylphenidate preparations					
Short-acting					Short-acting stimulants often used as initial treatment in small children (<16 kg) but have disadvantage of b.i.d.–t.i.d. dosing to control symptoms throughout day
Focalin	2.5, 5, 10 mg cap	2.5 mg b.i.d.	20 mg	50 mg	
Methylin[a]	5, 10, 20 mg tab	5 mg b.i.d.	60 mg	>50 kg: 100 mg	
Ritalin[a]	5, 10, 20 mg	5 mg b.i.d.	60 mg	>50 kg: 100 mg	
Intermediate-acting					Longer acting stimulants offer greater convenience, confidentiality, and compliance with single daily dosing but may have greater problematic effects on evening appetite and sleep. Metadate CD and Ritalin LA caps may be opened and sprinkled on soft food
Metadate ER	10, 20 mg cap	10 mg q.a.m.	60 mg	>50 kg: 100 mg	
Methylin ER	10, 20 mg cap	10 mg q.a.m.	60 mg	>50 kg: 100 mg	
Ritalin SR[a]	20 mg	10 mg q.a.m.	60 mg	>50 kg: 100 mg	
Metadate CD	10, 20, 30, 40, 50, 60 mg	20 mg q.a.m.	60 mg	>50 kg: 100 mg	
Ritalin LA	10, 20, 30, 40 mg	20 mg q.a.m.	60 mg	>50 kg: 100 mg	
Long-acting					
Concerta	18, 27, 36, 54 mg cap	18 mg q.a.m.	72 mg	108 mg	Swallow whole with liquids. Nonabsorbable tablet shell may be seen in stool.
Daytrana patch	10, 15, 20, 30 mg patches	Begin with 10 mg patch q.d., then titrate up by patch strength	30 mg	Not yet known	
Focalin XR	5, 10, 15, 20 mg cap	5 mg q.a.m.	30 mg	50 mg	
Selective norepinephrine reuptake inhibitor					
Atomoxetine Strattera	10, 18, 25, 40, 60, 80, 100 mg cap	Children and adolescents <70 kg: 0.5 mg/kg/day for 4 days, then 1 mg/kg/day for 4 days, then 1.2 mg/kg/day	Lesser of 1.4 mg/kg or 100 mg	Lesser of 1.8 mg/kg or 100 mg	Not a schedule II medication. Consider if active substance abuse or severe side effects of stimulants (mood lability, sad) give q.a.m. or divided doses b.i.d. (effects on late evening behavior); do not open capsule; monitor closely for suicidal thinking and behavior, clinical worsening, or unusual changes in behavior

Non-Stimulant Treatment of ADHD

- Atomoxetine:
  - Selective NE reuptake inhibitor
  - Advantages: low abuse potential, less insomnia/growth problems
  - Disadvantages: delayed onset of effect (2-4 wks), lower efficacy than stimulants
  - Dose based on weight: 0.5mg/kg/day, up to 1.2mg/kg/day as tolerated
  - Adverse effects: nausea, stomach pain, moodiness, increased heart rate, Black Box – suicidality

Other Non-stimulant Meds for ADHD

- Buproprion:
  - NE reuptake and DA reuptake inhibitor
  - Dosing is somewhat unclear in children; adults = mean 393mg/day of Wellbutrin XR
- α_2 Adrenergic Agonists:
  - May strengthen working memory by improving functional connectivity in prefrontal cortex
    - Clonidine: less effective than stimulants, used as adjunct to manage tics, sleep problems and aggression
      - Adverse Effects include bradycardia and sedation
    - Guanfacine: more selective for α_{2a} receptor
      - less sedation/dizziness than clonidine
      - 2-4 mg with effect between 2-4 weeks

Major Studies in ADHD Tx

- MTA study [7]
  - 14 month RCT with 579 children
  - Behavioral modification + medication > meds alone > BM alone > community care
- PATS study [13]
  - 303 Preschool children (3 – 5½)
  - Lower efficacy than older children (MTA) but still better than placebo
  - More adverse effects than seen with MTA

Mood Disorders in Children

- Major Depressive Disorder
  - Criteria are same for children, but clinically children often appear irritable
  - 1 in 20 teens suffer from depression [9]
    - Of these, only 1/3 receive treatment of any kind
    - Depression is a chronic illness
  - Can use screening tools (PHQ-9, Columbia Dep. Scale), but gold standard is clinical examination
  - Frequent monitoring, psycho-education, social support, and psychotherapy (CBT, IPT, supportive Tx) is standard of care [9]

Suicidality in Children/Adolescents

- Suicide is the 3rd leading cause of death in children ages 10-19 [10]
- 90% of suicides in youth are associated with psychiatric illness [10]
- Only 2% of youths who have committed suicide are actually taking any kind of psychiatric medications [10]
- Most of these children who committed suicide sought out treatment only 1 month prior to the event [10]
- 35-50% of depressed children receiving care have made or will make a suicide attempt [10]
  - 2-8% completing within a 10 year period in adults
- In 2003, early warnings from the UK appeared
  - "3.2% risk of self-harm and potentially suicidal behavior in paroxetine-treated patients vs. 1.5% in placebo"
- Warnings expanded over the next year, encompassing more antidepressants, until…

The Black Box Warning

- October 2004: Black Box warning for suicidality in adolescents and children
  - 24 Trials examined, containing 4400 children and adolescents
  - 9 Antidepressants included
  - No completed suicides in these trials
  - **More youth on a med spontaneously reported suicidality vs. youth on placebo (4/100 vs. 2/100)** [11]
    - **This included suicidal thoughts and behaviors but again, none of these studies had any completed suicides.** [11]
- A more recent trial has shown that a decrease in the amount of SSRI use has led to an increase in the suicide rates in children and adolescents. [10]

Suicide Prevention in Depressed Children and Adolescents

- Encourage home safety
  - Adolescents are much more likely to kill themselves with firearms [12]
  - Children are much more likely to kill themselves by strangulation [12]
- Ask about suicide and watch for suicidal behavior
- Monitor and ask about drug/alcohol use
- Monitoring after starting antidepressant:
  - Weeks 1-4: weekly
  - Weeks 5-12: every other week
  - After Week 12: as clinically indicated (Q4wks?)
  - Bottom line is any child on an SSRI, monitor carefully especially in the beginning.

Treatment of Depression

- All children with depression should have ongoing psychotherapy as this has been shown to reduce suicidal thoughts and behaviors. [2]
- If medications are indicated, begin with Fluoxetine
  - It is the only FDA approved SSRI for depression in children 8 and up.
- If this does not work, consider switching to another SSRI [2]. Citalopram, Escitalopram, Sertaline are all good options. Do not use Paroxetine. [14]
- If this still does not work, consider switching to venlafaxine. [12]

SSRI Treatment Choices for Depression

SSRI	Forms	Start Dose	+/- by	Max Dose	+RCT Evid.	FDA Approval
Fluoxetine	Tab, liquid	10 mg	5-10mg	60mg	Y	8-17
Sertraline	Tab, liquid	25mg	12.5-25 mg	200mg	Y	N
Citalopram	Tab, liquid	10mg	10mg	40mg	Y	N
Escitalopram	Tab, liquid	5mg	5mg	20mg	Y	12-17
Paroxetine	Tab, liquid	10mg	10mg	60mg	N	N
Fluvoxamine	Tab, liquid	25mg BID	25mg	300mg	N	N

Non-OCD Anxiety Disorders Treatment

- There are no FDA approved medications for children and adolescents for non-OCD anxiety disorders.
- Approximately 10-20% of children have an anxiety disorder such as GAD, Separation Anxiety Disorder, or Social Phobia. [3]
- Children and adolescents do best in combined therapy in which CBT and medications are prescribed.

Non- OCD Anxiety Disorders

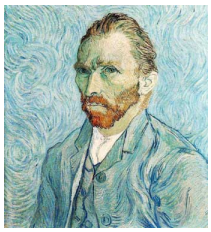
- While sertraline does not have FDA approval for treatment of anxiety disorders in children, there is good evidence for its efficacy.
- Medications should be dosed at rates done in clinical trials. [15]
- Typical dosages for sertraline based on CAMS study are 100-150 mg by week [15].
- Typical dosage for fluoxetine are based on TADS and TORDIA studies and show need to titrate up to 40 mg by week 12.

OCD

- DON'T FORGET THE POWER OF PSYCHOTHERAPY!!!
- FDA approved medications for treatment of OCD
  - Clomipramine $\geq$ 10 y/o
  - Fluvoxamine $\geq$ 8 y/o
  - Sertraline $\geq$ 6 y/o
  - Fluoxetine $\geq$ 7 y/o
- Medication Augmentation: Clomipramine, Clonazepam, Neuroleptics, Add second SSRI, Lithium [16]

Pediatric Bipolar Disorder

- Controversial diagnosis
- Psychosocial interventions are necessary in addition to medications
- Approved Medications by FDA for manic and mixed states in ages 10-17: Lithium, Quetiapine, Risperidone, Aripiprazole. Olanzapine has been approved to age 13 and up.
- Also used but not officially approved: Carbamazepine, Divalproex in monotherapy and as augmentation to above agents, as well as Ziprasidone, Clozapine, and ECT (in adolescents).
- topiramate and oxcarbazepine only have negative studies in children under age 18, so DON"T USE THEM!!



Oppositional Defiant Disorder Tx

- No official medications approved by FDA for treatment
- Best evidence is for psychotherapy (CBT, family) and psychosocial interventions
- Off-label use of stimulants (high comorbidity with ADHD), as well as mood stabilizers (Divalproex and Lithium)
- Atypical Antipsychotics used as well (Risperidone has some evidence)
- Bottom line is treat with psychotherapy and use medications for any comorbid psychiatric disorders.

Autism Spectrum Pharmacotherapy

- NO medications approved for core symptoms
- Medications often used to treat related symptoms, such as depression, anxiety, and aggression
- Aggression: Risperidone is FDA approved
  - Methylphenidate, Clonidine and naltrexone have preliminary data
- Insistence on Sameness: Lexapro has preliminary data, done at UIC
- Anxiety: often use SSRIs, at low doses
- Patients with autism are often very sensitive to adverse effects, even at low doses

Thanks!

- Any Questions? Comments? Complaints?
- Contact Information:
  - Email: avermani@psych.uic.edu
  - Phone: 312.413.2985

Citations

- 1.http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143565.htm
- **2. Treatment of Resistant Depression in Adolescents (TORDIA): week 24 outcomes. Am J Psychiatry. 2010 Jul;167(7):782-91.**
- **3. Cognitive Behavioral Therapy, Sertraline, or a Combination in Childhood Anxiety N Engl J Med 2008; 359:2753-2766**
- 4. Puig M: Body composition and growth. In Nutrition in Pediatrics, ed. 2, edited by WA Walker and JB Watkins. Hamilton, Ontario, BC Decker, 1996.
- 5. Polanczyk, G Epidemiology of ADHD across the lifespan. Curr Opinion Psych 20(386-92); 2007
- 6. Martin, A. Lewis's Child and Adolescent psychiatry, a comprehensive textbook, Fourth Ed. 2007, 432 – 439.
- **7. The MTA cooperative Group, A 14 month randomized clinical trial of treatment strategies for attention deficit hyperactivity disorder. Arch of Gen Psychiatry, 1999; 56;1073-1086.**
- 8. Faraone, Comparing the efficacy of stimulants for ADHD in children and adolescents using a meta-analysis. Eur Child and Adolescent Psychiatry (2010)19; 353-364

Citations

- 9. Mental Health: A Report of the Surgeon General 1999; Chapter 3.
- 10. Gibbons, R. The Relationship between Antidepressant Rates and Rates of Early Adolescent Suicide. American J. Psychiatry 163:11, November 2006.
- **11. Bridge, J. Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment. JAMA (2007) 297:15: 1683-96.**
- 12. Miller M, Azrael D, Hepburn L, Hemenway D, Lippmann SJ. The association between changes in household firearm ownership and rates of suicide in the United States, 1981-2002. Injury Prevention 2006;12:178-182
- **13. Vitiello B, et al. (2007). Effectiveness of methylphenidate in the 10-month continuation phase of the preschoolers with ADHD treatment study (PATS). Journal of Child and Adolescent Psychopharmacology, 17(5): 593-603.**
- 14. CHMP meeting on Paroxetine and other SSRIs. European Medicines Agency. 2004-12-09.

Citations

- 15. John Walkup, Child and Adolescent Psychopharmacology: Integrating Current Data into Clinical Practice. January 21, 2012.
- 16. March J. Expert Consensus guidelines: treatment of obsessive compulsive disorder. J. Clinical Psychiatry. 1997; 58(1-72).