Evidence-Based Pharmacotherapy

TRIUMPH OVER TRAGEDY

2016 Ohio AAP Annual Meeting
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#OhioAAPAM #Triumph4Kids

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®
Ohio Chapter

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CME Disclosure

• I have no personal financial relationships in any commercial interest related to this CME.

• I do not plan to reference off label/unapproved uses of drugs or devices.
Objectives

• Review best practices in medication management of ADHD, depression, anxiety, and disruptive behavior

• Discuss common adverse effects and contraindications/precautions

• Discuss approved indications for and monitoring of atypical antipsychotics
Guide to 8 Medications for Prescribing

Within the four drug classes, eight specific medications met each of the effectiveness, dosing and monitoring, and safety criteria. The table below gives more information about each medication and its proposed use in pediatric populations: ADHD, anxiety, or major depressive disorder (MDD). The table also notes whether the proposed use matches the FDA indication for the medication in youth. For example, the FDA has not officially approved any medication for anxiety in pediatric patients, but prescribing SSRIs for certain forms of childhood anxiety is considered community standard. Each medication listed below will be available in generic form by 2012.

<table>
<thead>
<tr>
<th>Drug (class)</th>
<th>Trade names</th>
<th>Proposed use in primary care</th>
<th>FDA indication?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate (stimulant)</td>
<td>Ritalin, Concerta and others</td>
<td>ADHD</td>
<td>Yes</td>
</tr>
<tr>
<td>Amphetamines (stimulants)</td>
<td>DexeDRine, Adderall and others</td>
<td>ADHD</td>
<td>Yes</td>
</tr>
<tr>
<td>Guanfacine (alpha-2A adrenergic agonist)</td>
<td>Tenex, Intuniv</td>
<td>ADHD</td>
<td>Yes</td>
</tr>
<tr>
<td>Clonidine (alpha-2 adrenergic agonist)</td>
<td>Catapres, Kapvay</td>
<td>ADHD</td>
<td>Yes</td>
</tr>
<tr>
<td>Atomoxetine (SNRI)</td>
<td>Strattera</td>
<td>ADHD</td>
<td>Yes</td>
</tr>
<tr>
<td>Fluoxetine (SSRI)</td>
<td>Prozac</td>
<td>Anxiety*</td>
<td>No</td>
</tr>
<tr>
<td>Sertraline (SSRI)</td>
<td>Zoloft</td>
<td>Anxiety*</td>
<td>No</td>
</tr>
<tr>
<td>Escitalopram (SSRI)</td>
<td>Lexapro</td>
<td>Anxiety</td>
<td>No</td>
</tr>
</tbody>
</table>

*Though the FDA has not officially approved fluoxetine and sertraline for treating anxiety disorders such as social phobia, separation anxiety, or generalized anxiety disorders, there is convincing evidence for using these medications for these disorders.

** Sertraline has some evidence supporting its use in MDD, but not enough evidence to support an FDA indication.
Ashley is an 8 year old girl referred for an ADHD evaluation. Her mother describes problems with inattention both at home and at school. She is in 2nd grade and is struggling in school. Her teacher notes that “she just doesn’t pay attention.” She has trouble sitting still and often disrupts the classroom. Her family is concerned that these issues are interfering with her school performance.
Ashley has also missed several days of school this year for stomach pains and headaches. Her mother has recently taken a new job, and these absences have been difficult for her family to manage. They would like to get Ashley started on ADHD medication to help her in school and reduce family stress.
Assessment Process

Presence of DSM-V Criteria

Evidence of Impairment

Behavioral rating scales

Clinician judgment

Adapted from AAP. Pediatrics. 2011.
Assessment Process

Importance of accurate diagnosis

1. Many conditions can masquerade as “attention problems”
2. There is a high degree of comorbidity in children with ADHD
## Ashley’s Vanderbilt Rating Scales

<table>
<thead>
<tr>
<th>Areas with Impairment</th>
<th>Parent</th>
<th>Teacher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total symptom score</td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td>ODD Screen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduct Disorder Screen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety/Depression Screen</td>
<td></td>
<td></td>
</tr>
<tr>
<td># Areas with Impairment</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Average Performance Score</td>
<td>3.5</td>
<td>3</td>
</tr>
</tbody>
</table>
ADHD First or Depression First?

Interventions

• Define ADHD as a chronic condition
• Identify target outcomes
• Use stimulant medications and behavioral therapy as indicated
• Monitor treatment response systematically

Behavioral Therapy as 1st Choice

• If ADHD symptoms are mild, minimal impairment
• Uncertain of diagnosis
• Marked disagreement about diagnosis
• Parents reject medicine
• Family preference

* Combined medication plus behavioral therapy leads to LESS medication utilization
Stimulant Titration Strategies

• Start low, reassess and adjust
  – Start at ¼ - ½ child weight in kilograms
  – Younger child = smaller initial dose
  – Increase every 1-2 weeks
    • Goal - Full therapeutic effect seen with fewest side effects

• Final therapeutic dose roughly weight-based
  – Methylphenidate 1-2 mg/kg/day, SE over 1 mg/kg
  – Amphetamines up to 1 mg/kg/day, SE over 0.6 mg/kg

• Follow up monthly until stable, then quarterly
Methylphenidate Dosing

• Maximum FDA dosing per day (off-label)
  – Ritalin®, Methylin®, Methylin ER®, Metadate ER®, Ritalin SR®, Metadate CD®, Ritalin LA® 60mg (100mg for >50kg)
  – Concerta® 72mg (108mg)
  – Focalin® 20mg (50mg); Focalin XR® 30mg (50mg)
  – Daytrana® 30mg (?)

AACAP. J Am Acad Child Adolesc Psychiatr. 2007;46;89-921
Methylphenidate

• Other considerations
  – Many long acting forms can be opened and sprinkled on applesauce or pudding
    • Metadate CD®, Ritalin LA®, Focalin XR®
  – Concerta® capsule CANNOT be opened (OROS)
  – Daytrana®
    • Patch is applied at the hip; may cause skin irritation
  – Quillivant® is a new XR liquid preparation
  – Quillichew®
Amphetamine

• Start low, reassess, and adjust if needed
  – Start at 5-10mg/day
  – Increase 5-10mg/day every 1-2 weeks if limited benefits and adverse effects
  – More potent than methylphenidate, need LESS

Adapted from AACAP. J Am Acad Child Adolesc Psychiatr. 2007;46;89-921.

www.ohiomindsmatter.org
Amphetamine Dosing

• Therapeutic dose around 0.6 mg/kg/day
  – SE more likely to occur at higher doses
• Maximum FDA dosing per day (off-label)
  – Dexedrine,® Dextrostat,® Adderall,® and Dexedrine spansule® 40mg/day (60mg if >50kg)
  – Adderall XR® 30mg (60mg if >50kg)
  – Vyvanse® 70mg (?)

Adapted from AACAP. J Am Acad Child Adolesc Psychiatr. 2007;46;89-921.
Amphetamine

• Other considerations
  – Adderall XR® and Dexedrine spansule® can be opened and sprinkled
  – Vyvanse® capsule can be opened and contents dissolved in small amount of water (1-2 tsp)
  – Vyvanse® may have decreased abuse potential due to pro-drug delivery system
Neurotransmitters of Non-stimulants

- Norepinephrine reuptake inhibitor
  - Atomoxetine (Strattera®)
- Alpha2(a) agonists (enhance NE transmission)
  - Clonidine, Kapvay®
  - Guanfacine (Tenex®, Intuniv®), more selectively binds
- Dopamine reuptake inhibitor
  - Bupropion (Wellbutrin®), metabolite weak NE

*Bolded are FDA Approved in children
Atomoxetine

• Mechanism of action
  – Selective norepinephrine reuptake inhibitor
    • NE increases signal strength in PFC
    • Antidepressant class = Black Box warning
    • Mild effect on anxiety
  – May take up to 8-12 weeks for full effect
  – Pharmacogenomic testing may assist with dosing

Atomoxetine Dosing

• Dosing recommendations
  – For <70kg: start with 0.5mg/kg/day, then increase to 1.2 – 1.4 mg/kg/day after 4-7 days
    • Max dose 1.4mg/kg/day or 100mg (lesser of 1.8mg/kd/day or 100mg)
  – For >70kg: 40mg/day, then increase to 80mg/day after 7 days
    • Max dose 100mg (increase after 2-4 weeks if needed)

AACAP. J Am Acad Child Adoles Psychiatr. 2007;46;89-921.
Atomoxetine

• Other considerations
  – Capsules CANNOT be opened or split
  – Can divide dose BID to minimize side effects
  – Must give daily
  – Dose adjustment in patients with impaired liver function
Alpha Agonists Dosing

- **Guanfacine**
  - Long acting (Intuniv®): start at 1mg daily;
    - Increase 1 mg weekly to 6 mg maximum dose [6mg or 2mg/4mg]
  - Short acting (Tenex®): start at 1mg HS or 0.5mg BID
    - Increase 1 mg weekly, max 4 mg daily [1mg/1mg/2mg]

- **Clonidine**
  - Long acting (Kapvay®): start at 0.1mg HS; 0.4 mg/day max
    - Increase 0.1 mg weekly divided BID
  - Short acting (Clonidine): start at 0.05mg HS; 0.2-4mg/day max
    - May give ¼ tab (0.025mg) AM
Alpha Agonist Dosing

• Alpha agonists – blood pressure medication
  – Slow upward and downward titration
  – No more than 1 tablet per week
  – May start with ½ tablet in the evenings to watch for sedation. If tolerates after 4-7 days, then add ½ morning dose.
  – Taper off short acting before trial of long acting
Adverse Effects

• Stimulants
  – Aggression
  – Irritability
  – Social withdrawal
  – Hypertension, tachycardia
  – Appetite suppression
  – Sleep disturbance
Serious Adverse Effects

• Contraindication
  – Mania
  – Psychosis
  – Withdrawal dyskinesia

• Precautions
  – Anxiety
  – Parental substance abuse

• Considerations
  – Tics
Adverse Effects

• Atomoxetine
  – Suicidal ideation
  – Hypertension, tachycardia
  – GI upset, appetite suppression
  – Behavioral activation

• Alpha agonists
  – Hypotension, bradycardia
  – Sedation, dizziness
Update on Ashley

• Ashley is prescribed Concerta® 18mg each morning. At one week, no side effects are noted, but no benefits are seen. Concerta® is increased to 27mg.

• At one month, Ashley is seen for a follow up visit. She is now taking 36mg each morning after another dose increase.

• Vanderbilt questionnaires are available for your review.
# Vanderbilt Rating Scales

<table>
<thead>
<tr>
<th>Areas with Impairment</th>
<th>Parent</th>
<th>Teacher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattention</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity/Impulsivity</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Total symptom score</td>
<td>46→38</td>
<td>36→20</td>
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<td>ODD Screen</td>
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</tr>
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<td>Average Performance Score</td>
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</tbody>
</table>

Consider afternoon short acting dose
What if...

• She doesn’t tolerate Concerta?
  – Consider switch to amphetamine product

• Symptoms improve but persist at the top of the dosing interval?
  – Consider switch to amphetamine product
  – If previous medications unsuccessful, consider adjunctive therapy with non-stimulant

http://ppn.mh.ohio.gov
What if...

• She is doing well, but getting headaches?
  – Self care – hydration, rest
  – Lower dose, consider different stimulant

• She is doing well, but losing weight?
  – Add calories, change time of pill
  – Consider Cyproheptadine/appetite inducer
  – Decrease dose, change stimulant

http://ppn.mh.ohio.gov
ADHD First or Depression First?

![Flowchart diagram](image)

Fig. 2 Algorithm for the psychopharmacological treatment of ADHD and comorbid depressive disorder. (*See Hughes et al., unpublished, 2005.)

If mild depression

- Active support and monitoring 6–8 weeks (every 1–2 wk)\(^a\)

If persistent

- Consider consultation by mental health to determine management plan

If improved

- Manage in PC
  1. Initiate medication and/or therapy in PC\(^a\) with evidence-based antidepressant and/or psychotherapy
  2. Monitor for symptoms and adverse events\(^c\)
  3. Consider ongoing mental health consultation

If partially improved

- If partially improved after 6–8 wk
  1. Consider
     - Adding medication if have not already; increasing to maximum dosage as tolerated if already on medication
     - Adding therapy if have not already
     - Consulting with mental health
  2. Provide further education, review safety plan\(^a\) and continue ongoing monitoring

If not improved

- If not improved after 6–8 wk
  1. Reassess diagnosis
  2. Consider
     - Adding medication if have not already; increasing to maximum dosage as tolerated if already on medication; changing medication if already on maximum dose of current medication
     - Adding therapy if have not already
     - Consulting with mental health
  3. Provide further education, review safety plan\(^a\) and continue ongoing monitoring

If improved after 6–8 wk

- If improved
  1. Continue medication for 1 yr after full resolution of symptoms (based on adult literature). AACAP recommendation recommends monthly monitor for 6 mo after full remission.
  2. Continue to monitor for 6–24 mo with regular follow-up whether or not referred to mental health
  3. Maintain contact with mental health if such treatment continues.

SSRI Indications

• Anxiety Disorders
  – **Sertraline (Zoloft®):** FDA indicated age 6 and up for OCD
  – **Fluoxetine (Prozac®):** FDA indicated OCD age 7 and up

• Depression
  – **Fluoxetine (Prozac®):** FDA indicated age 8 and up
  – **Escitalopram (Lexapro®):** FDA indicated age 12 and up

When moderate to severe impairment is present
# Selective Serotonin Reuptake Inhibitors (SSRI’s)

<table>
<thead>
<tr>
<th>SSRI</th>
<th>Starting Dose, mg</th>
<th>Increments, mg</th>
<th>Effective Dose, mg</th>
<th>Maximum Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (Prozac®)</td>
<td>2.5, 5</td>
<td>10-20</td>
<td>20-40</td>
<td>60</td>
</tr>
<tr>
<td>Sertraline (Zoloft®)</td>
<td>12.5, 25</td>
<td>25</td>
<td>50</td>
<td>200</td>
</tr>
<tr>
<td>Escitalopram (Lexapro®)</td>
<td>2.5, 5</td>
<td>5</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>

SSRI’s

- Start low, reassess, and adjust as needed
  - Increase dose after 1-2 weeks, then monitor
  - Maximal effectiveness after 4-6 weeks
  - Continue for 9-12 months after symptoms resolve
  - Taper when discontinuing to avoid withdrawal effects

Medication for depression and anxiety disorders can be approached similarly
BLACK BOX WARNING

– Issued in 2004 after concerns about an increase in suicidal thinking in children prescribed SSRI’s, revised 2016
  • 24 clinical trials reviewed; over 4000 children
  • No completed suicides
  • Prevalence of suicidal thoughts/actions 2X higher in those taking SSRIs (2% vs. 4%, not significant only trend)
  • Greatest risk in first 1-2 months, depression is also a risk

– Close monitoring for suicidal thinking is recommended
  • Phone contact 1-2 weeks (nurse, therapist)
  • Face to face with physician 4-6 weeks after initiation

SSRI Adverse Effects

- Nausea, GI discomfort
- Appetite changes
- Headaches
- Dizziness
- Insomnia
- Activation
- Bipolar switching
- Sexual dysfunction
- Suicidal thinking
- Vivid dreams (teens)

http://www.glad-pc.org/
SSRI’s

• Contraindications
  – Bipolar disorder
  – Psychosis

• Interactions/precautions
  – Caution with serotonergics
    • TCAs, Lithium, Cocaine
  – Serotonin syndrome
    • Mental status changes
    • Autonomic instability
    • Tremor, myoclonus
Summary

• Consider the risks and benefits of medication
• Discuss openly with patients and families
• Develop a process for continued monitoring
• Respond promptly to concerns
Ashley’s 6 year old brother, Antwon, has also been diagnosed with ADHD. He is taking Adderall XR®, and symptoms have improved. He continues to have problems with refusing to follow directions. He tends to get angry easily. He often tries to get back at people and can be spiteful. When his mother tries to set limits, he has tantrums that last for several minutes. His mother notes that things at home have been very stressful because of his behavior.
Antwon has also been diagnosed with Oppositional Defiant Disorder. His mother doesn’t know if more medication is the right choice, but she doesn’t know what else to do. She feels that they are “at the end of their rope.”

Is medication appropriate for the treatment of Oppositional Defiant Disorder?
Oppositional Defiant Disorder

• Behavioral interventions are first line treatment
  – Office based interventions
  – Parent training programs
    • Incredible Years
    • Parent Child Interaction Training
    • Triple P Positive Parenting Program

Oppositional Defiant Disorder

- Medications can be considered as adjunctive treatment but are NOT curative
  - Maximally treat underlying ADHD symptoms first, if present
  - Use is off-label and not well studied
    - Alpha-agonists
    - Atypical antipsychotic medications
      - Impulsive aggression with autism, mental retardation
  - Consider consultation with PPN
Antipsychotics Overview

- Antipsychotic medications are used to stabilize patients in crisis
- Symptoms targeted typically involve aggression and/or mania, possible psychosis
- Most common first line medication is risperidone or aripiprazole
- Second line medication may be quetiapine
Antipsychotics and Primary Care

• Stewards of medical health that may be affected by Antipsychotic medications
  – Metabolic Syndrome: when to consider Metformin
  – Orthostatic effects
  – Antihistaminergic effects – dry mouth, constipation
• Need to understand the medical monitoring
• Act as a bridge
Antipsychotic Side Effects

• Sedation
• WEIGHT GAIN (even aripiprazole)
• Metabolic effects
  – Increased glucose, insulin resistance, dyslipidemia (especially TG)
  – Baseline: CBC, BMP, LFTs, Fasting Lipids and Glucose
  – Every 6 months: Fasting glucose and lipids, Hgb A1c
Antipsychotic Adverse Effects

- Dystonia, Oculogyric crisis, parkinsonism
- Akathisia
- Withdrawal Dyskinesia
- Tardive Dyskinesia
- Prolactin elevation
  - Highest in risperidone
  - Aripiprazole may lower it
- QTC prolongation (ziprasidone)
Atypical Antipsychotic Medications

• Dramatic increase in prescribing
  – Children in foster care
  – Children with Severe Emotional Disturbance (SED)
  – Children with ADHD

• Concerns
  – Safety
  – Questionable efficacy
  – Cost
Update on Antwon

• Antwon’s mother participated in a parent training program for children with disruptive behavior
• Antwon receives additional school supports designed to increase desirable behavior
• You work with Anton’s family to maximize treatment of ADHD symptoms
Summary

• Medications can be an effective component of a comprehensive treatment plan
• Evidence-informed resources are available to guide care
  – Pediatric Psychiatry Network
  – Ohio Minds Matter
  – E-Learning modules from Building Mental Wellness (BMW)
References

ADHD Medications

• Most recent guidance based on strength of evidence:
  Methylphenidate ~ Amphetamine
  >> Atomoxetine
  > Long acting Guanfacine
  > Long acting Clonidine