Psychopharmacology for the primary care provider

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Speaker Introduction
• Dr. Dawn Garzon Maaks is a PNP and PMHS with a passion for child physical and mental health. She is a seasoned speaker and author, a fellow of AANP and the American Academy of Nursing, immediate past president of NAPNAP and an associate professor at the University of Portland in Oregon.

Disclosures
I have no financial disclosures or conflicts of interest to provide
I will discuss non-FDA approved medications for use in pediatric behavioral health.

Learning Objectives
1. Integrate knowledge of the psychopharmacology of medications used for ADHD, anxiety and depression into their primary care management plans.
2. Evaluate the effectiveness of these agents in primary care patients.
3. Identify warning signs of significant medication related side effects.
4. Incorporate patient and family teaching strategies to improve psychopharmacologic treatment effectiveness.

Basic Principles of Pediatric Psychopharmacology

Are medications needed?
• Is there a clear diagnosis?
• Do the symptoms cause distress?
• Are they symptoms developmentally atypical?
• Have non-pharmacologic approaches been used?
  • Therapy, behavioral modification, parenting education?
  • Medication alone does not “fix” ADHD, anxiety or depression?
• Is the child old enough that medications should be prescribed in primary care?
Situations where primary care providers should refer for medication therapy:

- Complex disease
- Psychosis and mania
- Children with intellectual disorders, autism spectrum disorders or conditions which confound diagnosis & may require medications with greater side effects, monitoring needs, etc.
- Children who have experienced trauma or abuse
- Children with substance use disorders
- Children whose parents have significant mental health issues, substance abuse issues, or intellectual disorders

ADHD Medication Therapy

ADHD

- One of the most common behavioral issues treated in primary care
  - Incidence 8-15%
  - 3 Basic issues.
    - Inattention- lack of detail orientation, difficulty staying on track, looses things, difficulty organizing, forgetful.
    - Hyperactivity- cannot sit still, talks excessively, moves often.
    - Impulsivity- cannot wait turns, interrupts/intrudes, blurts out answers.

([Danielson et al, 2018; Woloch et al., 2014])

Subtypes

- Combined- Includes hyperactive/impulsive and inattentive symptoms
  - Most common
- Hyperactive-Impulsive
  - Fewest
- Inattentive
  - About 1/3 of cases
  - Those diagnosed often change subtype over time

Guidelines

- Treatment is largely guided by AAP guidelines
  - https://pediatrics.aappublications.org/content/128/5/1007
  - New version coming out soon!
- Society for Developmental and Behavioral Pediatrics
  - https://journals.lww.com/jrdbp/Pages/clinicalpracticeguideline.aspx

Screening

Must screen for:

- Emotional and behavioral conditions (e.g. depression, anxiety, ODD, CD, OCD, SUD)
- Developmental disorders (e.g. intellectual disorders, learning disorders, autism spectrum disorders)
- Physical conditions (e.g. sleep apnea, tics)
**Treatment**

- Focuses on:
  - Behavioral modification
  - School environment modification
  - Family/parent support and education
  - Pharmacotherapy
  - Diet
  - Sleep hygiene
  - Regular exercise

**ADHD**

- Treatment: Drug therapy and behavioral therapy for best results
- Stimulants can help with comorbid symptoms (CD and anxiety)
- Cornerstone of treatment is the stimulants- best evidence and response
- NIMH Multi-Modal Treatment of ADHD study-80% response, general response in trials 70-90%
- Specifically methylphenidate (ex. Concerta, Ritalin, Daytrana) and amphetamine/dextroamphetamine (ex. Adderall)
- Do not use stimulants under 6 without a trial of behavioral interventions- MPH is only drug
- Titrate dose to maximum effect with minimum s/e

**ADHD**

- Methylphenidate promotes dopamine release and blocks dopamine reuptake
- Amphetamines block dopamine reuptake and may elevate selective release of synthesized dopamine
- Both also affect norepinephrine
- “Not sufficient evidence for pharmacogentictesting” per AAP guidelines

**Black box warnings and concerns about psychosis**

- Moran et al. NEJM 380 (12), 2019- Large cohort study from two large healthcare system databases
  - 337,000 matched 13-25 year olds with new ADHD diagnosis and started stimulant
  - Matched almost 110,923 on MPH with 110,923 on AMPH
  - New diagnosis of psychosis requiring antipsychotic prescriptions resulted in 343 episodes of psychosis in matched group, 106 in MPH (0.01%) and 237 in AMPH (0.21%)
  - So new onset psychosis occurred in 1/660 patients.
- Hollis et al. Lancet Psych 6(8), 2019- Large cohort from Swedish national registers
  - 23,898 12-30 put on MPH for ADHD from 12 weeks before, and at 12 week intervals until 1 year after diagnosis for any diagnosis of psychosis
  - No evidence of MPH causing risk of psychosis in adolescents

**Tics and ADHD**

- Commonly comorbid
- Fears of stimulants precipitating tics
- Cochrane Review entitled “Pharmacologic treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders (2018)
  - Treatment with MPH, clonidine, MPH + clonidine, guanfacine and desipramine improve tic symptoms
  - Of stimulants, only high dose dextroamphetamine appeared to worsen tics (1 study)
  - Alpha agonists do not worsen tics
  - General clinical practice is that stimulants are preferred

**Treatment**

- Also options are alpha-2 adrenergic agonists like guanfacine and clonidine to help with aggression, tics, and sleep problems caused by stimulants
- Clonidine for insomnia
- A word about clonidine use
- Can see antidepressant use (SSRIs)
- Atypical antipsychotics for extreme aggression, conduct disorder comorbidity
- Also need environmental and behavioral changes- Drugs alone don’t work!!!!!!!!!!
Treatment

- Assess
- Duration of ADHD impairment/need for control
- Responses to prior medications
- Family history of ADHD treatment
- Comorbidities:
  - Anxiety
  - Enuresis- atomoxetine can help
  - Tics- controversial (about 1/3 get better)
- Ability to swallow pills

Stimulants

- Some debate over what dose should be started
  - Evidence suggests low dose (0.3 mg/kg/dose) best to enhance cognitive function (inattention) while higher doses (0.6 mg/kg/dose) are more effective for behavioral control (hyperactivity/impulsivity)
- Doses should not exceed 2 mg/kg/d for MPH and 1 mg/kg/day for AMP
- 3rd doses (if used) should be half or less of 1st and 2nd doses to minimize rebound effects and insomnia

Stimulant Side Effects

- Expected include mild anorexia, mild insomnia (<1 hr/night)
- Common include H/A and GI upset
- Decreased growth (1-2 cm from predicted height- mostly first 3 years- catch-up growth happens)
- Dose adjustment or discontinuation needed for agitation, significant H/A or GI distress, psychosis, hallucinations, increased irritability, marked somnolence, worsening anxiety/depression

Medications

- http://adhdmedicationguide.com/

Stimulants

- Are controlled substances
- Contraindications
  - Glaucoma
  - Symptomatic CV dz
  - Hyperthyroidism
  - HTN

Patient Assessment for Stimulants

- Baseline BP, pulse, height and weight to rule out contraindications and for growth monitoring
- Annual VS assessment
- Assess weight and objective measurement of loss of appetite at each visit.
- Screen for insomnia, headaches, social withdrawal, and tics
Concern with Mixed Amphetamine Salts

• Some concern about causing cardiovascular instability- Adderall XR controversy with SUD
• Led to black box warning
• New guidelines “Although concerns have been raised about sudden cardiac death among children and adolescents using stimulant medications, it is an extremely rare occurrence” and did not result in actual deaths. (Wolraich, et al, 2019, p.14)

Cardiac Pre-Evaluation

• Screen all children for:
  • Cardiac symptoms
  • Family history of sudden death, CV sx, Wolff-Parkinson-White, hypertrophic cardiomyopathy, and long QT syndrome.
  • Symptoms or concerning history merits referral before using medications.

Stimulants

• Think about dose frequency
• Stigma, compliance
• High risk of abuse
• Concerta (MPH) is in indigestible vehicle so can’t crush (Write OROS only if generic)
• Quillivant XR (MPH), Adzenys ER (AMPH), Dynavel XR (AMPH) are in liquid form so good for those who can’t swallow pills
• Are chewable versions MPH (short acting and Quillichew ER MPH)
• ODT MPH (Contempla XR), ODT AMPH (Adzeys XR-ODT, Eveko ODT) versions as well
• Daytrana MPH patches

Non-stimulant Medicines

• Atomoxetine (Strattera)
  • Taken orally once or twice daily,
  • Selective norepinephrine reuptake inhibitor
  • Indicated age 6 yo and older
  • Common side effects- decreased appetite, tiredness, N/V, dizziness, mood swings and upset stomach
  • Rare instances of hepatotoxicity

Atomoxetine (Strattera)

• Contraindications.
  • Drug allergy to components.
  • Narrow-angle glaucoma.
  • Uses MAOI.
  • Use with caution for people with hypertension or cardiovascular disease.
  • Takes 2-8 weeks for full response- so doesn’t work right away
  • Titrate up dose to minimize SE
  • Common S/E- somnolence and GI distress
  • Black box warning with suicidal ideation
  • Rare- hepatitis

Alpha-2 Adrenergic Agonists

• Guanfacine and clonidine
  • May take 1 to 2 weeks to see effect
  • Also effective at helping with concentration, first line if tics
Alpha-Adrenergic Agonists

- Indicated for aggression, anger, significant insomnia
- Need baseline ECG*
- Common SE- drowsiness, headache, constipation, dizziness, dry mouth, abdominal pain, irritability, bradycardia and hypotension
- Contraindications- cardiovascular disease, hepatic or renal impairment

Guanfacine (Intuniv)

- Alpha 2-adrenergic receptor stimulant, known antihypertensive
- Is a sustained release- no crushing
- Max 4 mg/day- start at 1 mg and slowly wean up
- Can take up to 2 weeks to work
- Avoid taking with fatty meal

Clonidine (Kapvay)

- Best started at night
- Sustained release
- Comes in patch and oral version
- Usually requires BID dosing
- Can take up to 2 weeks for effect

Alpha Adrenergics

- Indicated 6yo and older
- Drug Interactions- beta blockers, MAOIs, sedating antihistamines, alpha 2 blockers
- Don’t D/C abruptly can cause rebound HTN

ADHD Follow-Up

- Phone f/u after 1 week. May be needed until dose stable and no longer titrating.
- See 1 month after starting therapy and monthly until dose stable and no weight loss.
- Stable visits every 3-4 months
- Annual ht and weight.
- BP at least every 6 months
  - But before and after dose changes

Other Drug Issues

- Weekend and summer “holidays”
- Abuse potential and resale value
- Which came first- the chicken or the egg with regards to comorbidities
Anxiety and Depression Medication Therapy

Depression - DSM V Criteria

- 5 or more symptoms (most of the day, nearly every day) for at least 2 weeks period, affect neurocognitive and affect, impair function, & represent a change from previous function:
  - Must have 1 of these
  - Depressed mood - either subjective report or observations made by others.
  - Marked diminished interest or pleasure in all, or almost all, activities.
  - Change in appetite or weight

Diagnosis - DSM V Criteria

4. Insomnia or hypersomnia.
5. Impaired concentration; indecision
6. Low energy or fatigue.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional & not merely self-reproach or guilt about being sick).
8. Recurrent thoughts of death or suicidal ideation
  - Symptoms are not caused by bereavement.
  - Remember children grieve too and often present with different symptoms than adults.

Diagnosis - DSM V Criteria

- Symptoms impair social, academic, occupational or other important areas of functioning.
- Dysthymic disorder is a depressed or irritable mood for the majority of days in the past 2 years that is less intense but more chronic than MDD.

Drug Therapy

- On 10/15/04, FDA issued a public health advisory related to an increased risk of suicidality associated with use of antidepressants in childhood.
  - No actual suicides in trials.
  - Two fold increase in base rate of suicide in 1st mo (esp. 1st 9 days): no control group.
  - In 2007, FDA voted to extend warning to 25 year-olds.

Suicide Rates in United States - 2001-2018, 1 to 24 year-olds

WISQARS data (CDC): https://wisqars.vid cân.oz/
Course of Response

- First Week
  - Decreased Anxiety
  - Improvement in Sleep
  - Improvement in Appetite
  - Increased Activity, Sex Drive, Self-care, and Memory
  - Thinking and Movements Normalize
  - Sleeping and Eating Patterns Normalize

- 1-3 Weeks
  - Relief of Depressed Mood
  - Less Hopeless/Helpless
  - Thoughts of Suicide Subside

- 2-4 Weeks
  - Increased Activity, Sex Drive, Self-care, and Memory
  - Thinking and Movements Normalize
  - Sleeping and Eating Patterns Normalize

- Relief of Depressed Mood
  - Less Hopeless/Helpless
  - Thoughts of Suicide Subside

GLAD-PC


- Studies show treatment improves outcomes over no treatment
- RCTs reviewed show overall improvement in suicidality with treatment & worsening and suicidality after treatment is uncommon
- Do not use older antidepressants (TCAs and MAOIs)
- Must always take care to establish safety and/or suicidality!
- Best is medication plus CBT
- Moderate to severe cases require MH consult
  - Mild medication or therapy
  - Moderate to severe medication plus therapy

SSRIs

- Examples: Sertraline (Zoloft), Paroxetine (Paxil), Fluoxetine (Prozac), Citalopram (Celexa), Escitalopram (Lexapro), and Fluvoxamine (Luvox).
- Paroxetine should not be used under 18
- Fluoxetine has most evidence for effectiveness but is associated with arrhythmias including TdP and QT prolongation
- SE: Nausea, diarrhea, H/A, HTN, dry mouth, nervousness, insomnia, sexual dysfunction, sleepiness, behavioral activation.
- Large safety margin

SNRIs

- Examples: venlafaxine (Effexor) and duloxetine
- None are FDA approved for depression
- Both show efficacy with depression and anxiety in RCTs but venlafaxine is associated with increased treatment-emergent suicidality in the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) study (Brent et al: Am J Psychiatry 2009; 166: pp. 418-426)
- Hypothesized that may be caused by the fact that the serotonin system matures earlier than the noradrenergic system (Strawn, et al., 2018)

SSRIs

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<th>FDA Approved</th>
<th>Name</th>
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<tbody>
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<td>Clomipramine*</td>
<td></td>
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<td></td>
<td>Fluoxetine</td>
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<td></td>
<td></td>
<td>Sertraline</td>
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<tr>
<td>Name</td>
<td>Age</td>
<td>Indication</td>
<td>Dose</td>
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<tr>
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<td>10+</td>
<td>MDD</td>
<td>10 mg daily; Start 5 mg to 10 after a week</td>
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<td>Escitalopram</td>
<td>7+</td>
<td>MDD</td>
<td>10-15 mg daily; Start 10 mg to 15-30 mg/day</td>
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<td>Fluoxetine</td>
<td>8+</td>
<td>MDD</td>
<td>50-150 mg/day; Start 25-50 mg/day</td>
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<tr>
<td>Sertraline</td>
<td>6+</td>
<td>MDD</td>
<td>6-120 mg/24 h (60-240 mg daily)</td>
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*Clomipramine is a tricyclic antidepressant (TCA). TCAs are associated with increased side-effect profiles. If in risk, and narrow safety window, also not GLAD-PC approved
Dosing Guidelines

- Start at the lowest possible dose.
- Re-evaluate need for dosing if stable 6-12 months with slow wean off medications.
- Titrating up doses helps with
- Side effects include: GI upset, diaphoresis, H/A, appetite change, sleep change (nightmares, impaired sleep), behavioral activation, libido, emergence, suicidality, evolving psychopathology

Which works best?

- Cipriani et al. (2016: Lancet 388(1004): P881-890) did a meta-analysis for RCTs to establish comparative effectiveness of medications for treatment of pediatric MDD.
  - Only fluoxetine was statistically significant compared to placebo
  - Fluoxetine was tolerated better than duloxetine
    - "Fluoxetine is probably the best option to consider when a pharmacological treatment is indicated."2
  - Imipramine, venlafaxine and duloxetine caused more drug discontinuations due to side effects than placebo
  - If maximum dose is reached with only partial remission,

Serotonin Syndrome

- Can be fatal
- HTN, diaphoresis, agitation, dizziness & weakness
- Can happen if SSRI and St Johns Wort
- Stops when D/C drugs

Discontinuation Syndrome

- Caused by SSRI and SNRI
  - Duloxetine and longer half-life SSRI (fluoxetine)
- Happens when medications stopped without tapering
  - Often described as "the flu"
  - We have serotonin receptors in the GI tract
- Symptoms - dizziness, N/V, fatigue, irritability, H/A, insomnia, diarrhea, chills, paresthesias, vivid dreams, and rarely psychosis, suicidality and a feeling of being removed from oneself

Adjunctive Therapy

- Remove obvious weapons from the home and make inaccessible those unwilling to remove. Parents should keep/monitor medication
  - Most common mechanisms for suicide in teens is guns, medication and suffocation.
- Provide call number so to access help 24/7 if emergency.
- Work on healthy diet, good sleep hygiene and regular exercise

Generalized anxiety

- Characterized by marked worry and anxiety that the individual finds hard to control- causes distress and is not developmentally typical
  - Irritability
  - Fatigue
  - Sleep problems
  - Difficulty sleeping
  - Impaired concentration
  - Somatization
  - Need for reassurance
  - Self-consciousness
- More common in children with behavioral inhibition, those with negative experiences that condition for phobias, CA/N, ASD, SAD, parental psychiatric disorders, & environmental stress
• A meta-analysis of 9 RCTs (sertraline, fluoxetine, fluvoxamine, venlafaxine, paroxetine, duloxetine, atomoxetine) found both SSRI and SNRI improved symptoms at 2 weeks, but at week 2 there were class differences that showed that SSRIs work better and were significantly different for the next 10 weeks.
• ½ of treatment response for both groups happens by week 4
• SSRI treatment response is no differ over time for high vs. low SSRI doses but higher doses resulted in improved symptoms at 2 weeks


Other medications
• Buspirone- not FDA approved and poor data in children and teens
• Bupropione- not FDA approved and poor data in children and teens
• Venlafaxine ER- not FDA approved, RCTs show effectiveness in GAD, social anxiety
• Clomipramine- not FDA approved, RCT data shows effectiveness in OCD
• Atomoxetine- not FDA approved for anxiety but RCTs show effectiveness in treating co-occurring ADHD and anxiety.


References

<table>
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<tr>
<th>Name</th>
<th>Age</th>
<th>Indication</th>
<th>Dose</th>
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<td>Duloxetine</td>
<td>7+</td>
<td>GAD</td>
<td>30-40 mg daily Start 30 mg↑ to 60 after week 2</td>
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<td>Escitalopram</td>
<td>12+</td>
<td>ODD</td>
<td>10 mg daily Start 5↑ to 10 after a week</td>
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<tr>
<td>Fluoxetine</td>
<td>8+</td>
<td>ODD</td>
<td>20-40 mg daily Start 10↑ by 10↑ by 10 by 15 mg</td>
</tr>
<tr>
<td>Sertraline</td>
<td>6+</td>
<td>ODD</td>
<td>6-12 yo: 25-100 mg daily 13-17 yo: 50-200 mg daily Start lowest dose and ↑ by 25-50 mg/week</td>
</tr>
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