Disclosures

- This discussion will contain reference to some pharmaceuticals that have not been approved by the FDA for children, adolescents and/or adults for some of the uses outlined in the lecture (“off-label”)
- Off-label use will be noted at the time of discussion of the medication
- No conflicts of interest to disclose

Learning Objectives

- Identify common psychiatric and developmental conditions that co-exist with ADHD.
- Describe medication management of ADHD and co-existing conditions in children and adolescents when indicated.
ADHD: Developmental Disorder of…

**Inattention**

With:
- Developmentally Inappropriate Levels of Symptoms
- Childhood Onset (Symptoms - Impairment)
- Cross-setting Occurrence of Symptoms
- Significant Impairment in Major Life Activities
- Exclusion of Other Disorders (psychosis)
- Onset before Age 12

**Hyperactivity/Impulsivity**

ADHD: Core Symptom Area

**Inattention**

Six or more of the following (5 in adults) - manifested often:

- Inattention to details/makes careless mistakes
- Difficulty sustaining attention
- Seems not to listen
- Fails to finish tasks
- Difficulty organizing
- Avoids tasks requiring sustained attention
- Loses things
- Easily distracted
- Forgetful

ADHD: Core Symptom Area

**Impulsivity**

Six or more of the following (5 in adults) - manifested often:

- Blurs out answer before question is finished
- Difficulty awaiting turn
- Interrupts or intrudes on others
- Fidgets
- Unable to stay seated
- Inappropriate running/climbing (restlessness)
- Difficulty in engaging in leisure activities quietly
- 'On the go'
- Talks excessively

Hyperactivity

ADHD: Core Symptom Area
ADHD: DSM-V Presentation

- ADHD Predominantly Inattentive Presentation
  - Criteria met for inattention but not for impulsivity/hyperactivity

- ADHD Predominantly Hyperactive-Impulsive Presentation
  - Criteria met for impulsivity/hyperactivity but not for inattention

- ADHD Combined Presentation
  - Criteria are met for both inattention and impulsivity/hyperactivity

ADHD: Course of the Disorder

ADHD and Co-existing (“Comorbid”) Conditions

- The rule, rather than the exception
- Comorbidity rates 50-75%
- ADHD typically presents before other disorders
- Co-existing conditions can affect the presentation, prognosis and treatment
- Presence of 1 comorbid d.o. increases risk of other comorbid disorders
- Equal rates of comorbidity found in specialty mental health clinics vs. HMO settings
ADHD Comorbidity

<table>
<thead>
<tr>
<th>Co-existing condition</th>
<th>Range (average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oppositional-defiant disorder</td>
<td>30-60% (32%)</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>8-21% (20%)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>10-40% (21%)</td>
</tr>
<tr>
<td>Depression</td>
<td>10-40% (18%)</td>
</tr>
<tr>
<td>Manic/Pediatric bipolar disorder</td>
<td>0.2-7% (8%)</td>
</tr>
<tr>
<td>Tic disorders</td>
<td>10-34% (15%)</td>
</tr>
<tr>
<td>Learning disabilities</td>
<td>10-60% (30%)</td>
</tr>
<tr>
<td>Academic Underachievement</td>
<td>40-90% (66%)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>23-60% (46%)</td>
</tr>
</tbody>
</table>

Disruptive Behavior Disorders

- 30-50% children with ADHD have another externalizing behavior disorder
- Oppositional Defiant Disorder: persistent pattern of negative and defiant behavior
- Conduct disorder: recurring pattern of severe rule breaking and violation of social norms
- Prepubertal children: rarely find ODD or CD without ADHD
- Adolescence: CD commonly occurs without ADHD

Co-existing Oppositional Defiant Disorder

- ADHD contributes to and may cause ODD.
- Occurs through the impact of ADHD on emotional self-regulation (an executive function).
- May account for findings that ADHD medications reduce ODD as much as they do ADHD.
- Some ODD is related to parenting style:
  - Inconsistent, indiscriminate, emotional, and episodically harsh and permissive
- Poor parenting can arise from parental ADHD and other high risk parental disorders.
- Early ODD predicts persistence of ADHD
Treatment Options in ADHD + ODD Patients

- ADHD sx respond well to stimulant meds in the presence of ODD, CD
  - Markedly reduces oppositional, defiant behavior
- Parent training in behavior management methods
  - 60-75% successful for children, ↓ ODD sx
  - 25-35% treatment response after 13+ yrs. of age
- May need to add problem-solving communication training after age 14 years
- With severely explosive anger: consider disruptive mood dysregulation d.o., intermittent explosive d.o. or pediatric bipolar disorder

Co-existing Conduct Disorder

- If starts early, represents a unique family subtype
  - More severe, more persistent antisocial behavior
  - Worse family psychopathology
  - Less responsive to treatment than late onset
- If starts late (>12), more related to social disadvantage, family disruption, & deviant peers
  - Major depression more likely to co-exist
  - School drop out and teen pregnancy more likely
  - Involvement of juvenile justice agencies more common

Conduct Disorder

- Parent and family interventions required
  - Problem-solving, communication training
  - Multi-systemic therapy where available
  - Family relocation to better neighborhoods
- Meds for ADHD reduce aggressive behavior and antisocial acts; stimulants may work more rapidly to gain case control
  - Highly aggressive, explosive; may need alpha-agonists, atypical antipsychotics or mood stabilizers.
- Avoid group treatment formats due to deviancy training by aggressive peers
Disruptive Mood Dysregulation Disorder

- Meant to address concerns about potential overdiagnosis and overtreatment of bipolar disorder in children
- Dx in youth ≤ 18 yrs. who exhibit persistent irritability and frequent episodes of extreme behavioral dyscontrol
- DMDD vs. ODD: DMDD has severe and frequently recurrent outbursts and a persistent disruption in mood between outbursts.
- DMDD requires severe impairment in at least one setting (i.e., home, school, or among peers) and mild to moderate impairment in a second setting

Co-existing Pediatric Bipolar Disorder

- Rarely documented in follow-up studies to date
- Some cases are misdiagnosed (ADHD/ODD)
- Requires substitution of severe irritability for mania and chronic for episodic course
- Significant family history of bipolar disorder
- Probably a one-way comorbidity (like Tourette Syndrome)

Pediatric Bipolar Disorder

- Requires multiple medications for management long-term (mood stabilizers, atypical antipsychotics)
- May require periodic hospitalization for safety (suicidality or violence) and stabilization
- Medical management of bipolarity should be done first before managing ADHD symptoms with ADHD drugs
- Consider all-reward or non-confrontational parent training programs (Ross Greene’s Explosive Child)
Co-existing Aggression

- Stimulant monotherapy can improve aggressive behavior in ADHD, disruptive behavior disorders, chronically irritable or angry mood
- Mean time to stimulant optimization 70 days
  - 51% remission of aggressive behavior
  - 13.5% below criteria for adjunctive medication
- Sx c/w DMDD do not contraindicate stimulants as initial tx
- Aggression may not improve sufficiently in 1/3 of children—may require augmentation pharmacotherapy and extended behavioral interventions.


Co-existing Substance Use Disorder

- Youth with ADHD and co-existing CD are at highest risk for SUD
- Untreated ADHD is a significant risk factor for SUD
- Most recent outcome studies showed ↓ risk of SUD for treated ADHD
- ADHD symptom control is an important factor in ↓ risk of SUD among adolescents and adults
- With SUD or higher risk for misuse or diversion, consider medications with low abuse potential (i.e. lisdexamfetamine, atomoxetine, modafinil, bupropion)

Co-existing Anxiety Disorders

- Related in part to poor emotion regulation
- Some legitimate anxiety disorders are likely
- Most common are simple phobias or separation anxiety; GAD becomes more common with age
- Often show lower levels of impulsiveness (better course & outcomes?)
- Anxiety disorders more likely in parents and family
Anxiety Disorders

- More responsive to cognitive-behavioral therapies.
- May respond better to social skills training.
- Stimulants can exacerbate anxiety in some cases:
  - Studies are conflicting – 7 say yes but MTA study and Abikoff (2005) study did not find this effect.
  - Atomoxetine can reduce anxiety (Effect Size = 0.3-0.5).
- Family counseling may be required to limit family setting induction of anxiety.

Co-existing Major Depression

- Likely genetic linkage to ADHD
- MDD onset may not be until adolescence or later
- 27% have associated MDD by age 20
- Higher rate of MDD with CD in child & family
- Often manifest low self-esteem in childhood
- Associated with increased suicidal ideation (4x) and attempts (2x)
- Psychotherapy/Cognitive-behavioral therapy recommended
- May require mixed ADHD/SSRI therapy

Major Depressive Disorder

**Use ADHD medication first if:**
- ADHD is chief complaint
- ADHD symptoms are more disabling
- MDD is mild: No current functional impairment from depression
- Neurovegetative signs are mild
- ADHD symptoms clearly preceded MDD symptoms

**Start with Antidepressant first if:**
- Clear history of non-response to ADHD drugs
- Prominent neurovegetative signs or health is compromised
- MDD symptoms are chief present complaint
- ADHD symptoms are mild, late onset, or coincident with MDD onset.
- Suicidal ideation
Co-existing Tic Disorders

- Simple motor or vocal tics most common
- Tourette syndrome more rare
- Tourette syndrome shows one-way comorbidity
  - <2% of ADHD, but ADHD occurs in 50-80% of TS
  - ADHD is often more impairing disorder than TS

Development and Exacerbation of Tics

- Concern: use of stimulants may increase motor or vocal tics
- Approximately 15% to 30% of children with ADHD develop tics
- 50% to 60% of youths with Tourette's disorder have ADHD requiring treatment
- Current research
  - Most tics are transient and chronic tics are rare
  - Pre-existing tics: 1/3 get worse, 1/3 stay the same, 1/3 may improve

Tic disorders

- If mild or episodic, require no treatment.
- Stimulants may exacerbate, ameliorate, or not affect tics.
- Atomoxetine, alpha agonists do not adversely affect tics.
- If tics or TS are socially disabling, consider behavior therapies.
- If TS is as or more disabling than ADHD, medically manage the tics first.
  - alpha agonists, atypical antipsychotics
- RCT of ADHD + tic disorders-best results for both conditions with MPH + clonidine.
Co-existing Obsessive-Compulsive Disorder

- Rare, but more common in those with TS or + FH TS
- One way comorbidity (OCD-50% have ADHD)
- Triad: OCD, TS, ADHD
- Risk increases slightly with age
- OC behavior more likely (11%) in children with ADHD
- Associated with lower family history of ADHD
- Better attention at school
- Perfectionism, possibly greater inhibition & ODD at home


OCD or OC Behavior

- Being less symptomatic argues for trying behavioral interventions before medication.
- Screen for co-existing Tourette syndrome.
- Stimulants may exacerbate obsessive and compulsive or ritualistic behaviors.
- Atomoxetine, alpha agonists do not adversely affect tics and may also have less effect on OC behavior.

Autism Spectrum Disorder and ADHD

- Core sx of ADHD are frequent in children with ASD.
- Autism sx not common in children with ADHD though + social difficulties.
- Because of high frequency of ADHD sx in ASD, children with ASD may be initially dx with ADHD.
- DSM V now ‘allows’ comorbidity.
ASD & ADHD: Targeting inattention, hyperactivity, impulse control

Stimulants
- less effective than in typical ADHD, but still effective.
- ‘ADHD’ not exactly the same. Internal distractibility, psychomotor agitation.
- Study-preschoolers: 50% improvement, 50% with side effects.
- RUPP MPH study: 50% response rate, SE - irritability, decreased appetite, difficulty falling asleep, emotional outbursts

Alpha2 Agonists
- 2 positive small placebo controlled trials
- clonidine → ↓ hyperarousal
- guanfacine → ↓ hyperactivity

Atomoxetine
- Noradrenergic reuptake inhibitor
- 2 positive RCT
- ↓ hyperactivity
- No change in stereotypic behavior, irritability

Co-existing Learning Disabilities
- Co-existing Reading, Spelling and Math Disorders do not improve with medication treatment
- Additional educational interventions will be needed for these co-existing disorders
- Co-existing handwriting and comprehension deficits are likely to improve from stimulants if secondary to ADHD itself
- ADHD pts. with co-existing math disorder may be less likely to respond to stimulants (37%) than those with reading disorder (67%) or no LD (75%)


Co-existing Seizure Disorders
- Etiology of inattention multifactorial.
- Stems from underlying cerebral differences, effects of seizures, side effects of AEDs, sleep disruption.
- M:F ratio closer to 1:1.
- Higher rates of ADHD-inattentive type vs general population.
- Stimulant medication still first line medication does not increase seizure frequency.
Co-existing Sleep Problems

- Mainly delayed onset and greater night waking leading to shorter sleep time.
- More activity during sleep.
- May exacerbate attention problems in school.
- Causes: behaviorally based insomnia, circadian rhythm sleep disorder, restless legs syndrome, poor sleep practices, psychiatric comorbidities, medications, associated medical conditions, ADHD per se.

ADHD and Sleep Problems

- Treating sleep disorder may improve attention at school but sleep disorder is not the cause of clinical ADHD.
- Stimulants may cause or exacerbate insomnia (30-54% of cases); clinicians report 20%+ have improved sleep.
- Advise parents to transition from highly stimulating activities to lesser ones before bedtime.
- Institute good sleep hygiene with consistent sleep schedule. Keep lights off or low lighting in room with background noise (music).

ADHD and Sleep Problems

- Limited data to support diphenhydramine, clonidine, mirtazapine, trazodone, selective benzodiazepine receptor agonists (e.g. zolpidem)
- Melatonin, alpha agonists may be useful for short periods to induce sleep and re-establish new sleep-wake cycle
  - Clonidine may wake up after sedation effects wane (~4 hrs)
- Melatonin
  - 2 RCT, 1 open label support use to reduce sleep-onset delay*
    - 0.5-9 mg/dose, 60 minutes prior to bedtime
  - Unknown long term side effects
  - Rare side effects of enuresis, daytime sleepiness

*Cortese et al. JAMCAP 2013
ADHD - Monitoring and Follow-up

- Ongoing collaboration between physicians, parents, school, child
- Objective monitoring of medication effects
  - Child Attention Problems Scale (CAP)*
  - Vanderbilt Parent and Teacher F/U Scale*
- After achieving stable treatment plan, develop systematic monitoring plan
  - Periodic visits and other contacts
  - Assess
    - Adherence
    - Target outcomes
    - Side effects

*Available at dbpeds.org

Helpful Websites for Parents

- www.help4adhd.org
- http://www.adhdmedicationguide.com/

Selected References
