Lecture 23

PSYCHOSTIMULANTS:

- One of the most common & extensively studied childhood disorders
- Stimulants are one of the most extensively studied class of medications
- A controversial diagnostic/therapeutic area since ADHD is a diagnosis of exclusion
- Core AD/HD symptoms: inattention, hyperactivity and impulsivity

GOALS OF THERAPY:

- Reduce impairment in academic performance, self-esteem, social and interpersonal relationships
- Reduce rates of personal injury, substance use, motor vehicle accidents, teen pregnancy, incarceration, school/work difficulties
- Prevent/minimize drug adverse effects
- Educate families about AD/HD and its treatment
- Focus on restoring normal functioning

EPIDEMIOLOGY OF AD/HD:

- Estimated prevalence of AD/HD in children: 5.8-8.7%
- 3:1 male:female ratio observed in clinical trials
- Mean onset: age 3 (several sx must onset prior to age 12 per DSM-5 criteria)
  - Symptoms persist into adulthood in 60-70%

AD/HD COURSE SPECIFIERS:

- Primarily hyperactive-impulsive
- Primarily inattentive
- Combined
- Common comorbidities: anxiety, OCD, depression, ODD, Tourette’s autism

PATHOGENESIS:

- Abnormalities in frontal lobe, basal ganglia, caudate nucleus, cerebellum, nucleus accumbens & other areas play a role in AD/HD
- A disorder of executive functioning, which affects:
  - Response inhibition
  - Planning
  - Verbal & emotional regulation
  - Motor control
  - Changing mental set

WHAT DOES NOT CAUSE AD/HD:

- Allergies to food additives/preservatives
- Poor parenting
- Television/video games
- Hormonal abnormalities
- Vestibular system abnormalities
- Diet (sugar, wheat, dairy)

DSM-5 AD/HD CRITERIA:

- A clinical diagnosis has to be made; presently no reliable imaging study available to diagnose ADHD
- 6+ symptoms from inattentive and/or hyperactive/impulsive criteria (9 criteria each)
- 5+ symptoms required for patients age 17 and up
- Frequent behavior pattern, more severe than others at comparable development levels
- Several symptoms onset prior to age 12
- Symptoms persist for greater than 6 months
- Symptoms appear in 2 or more settings
- Symptoms cause functional impairment in 1 or more settings

CADDRA AD/HD GUIDELINES:

1st line: long-acting stimulants
2nd line: short-acting stimulants, guanfacine XR
3rd line: clonidine, bupropion, TCAs

MULTIMODAL TREATMENT STUDY: CT (combined therapy) = Rx (TID methylphenidate) > BT (behavior treatment) = UC (usual care)

BEHAVIOR MANAGEMENT:

- An essential part of AD/HD treatment
- Time outs, daily review of good & bad behaviors
- Token Reward System (ex// Star Chart – exchange stars for privileges or small gift of child’s choice
- Consistency between parents, teachers & other caregivers important

PSYCHOSTIMULANTS:

MOA:

- Attention, motor activity mediated by DA, NE
- Both amphetamine & methylphenidate inhibit reuptake of DA & NR
- Amphetamine also promotes release of endogenous DA & NE from synaptic vesicles
- Effects: rapid onset/offset

DEXTRAMPHETAMINE (DEXEDRINE):

- Plain tablets: IR
  - Onset: 1-2 hours
  - Duration: 4-6 hours
- Dexedrine Spansules: contains IR & DR granules
  - Onset: 2-3 hours
  - Duration: 7-8 hours
  - May open/sprinkle
- Full benefit under BC PharmaCare coverage

LISDEXAMPHETAMINE (VINNASE):

- Prodrug stimulant formulation: lysine moiety cleaved off by hydrolytic enzymes found on RBCs → releases active d-amphetamine
- Designed to reduce abuse liability: same kinetics for a dose if taken orally, inhaled or injected
- Onset: 1-2 hours; duration: up to 14 hours
- Can open capsule and dissolve contents in plain water, yogurt or orange juice

MIXED AMPHETAMINE SALTS (ADDERALL XR):

- Mix of 4 different amphetamine salts (75% D-AMP, 25% L-AMP)
- XR capsules contain 50% IR beads, 50% DR beads (may open/sprinkle)
  - Onset: 1-2 hours
  - Duration: up to 12 hours
  - Adderall IR tabs in US, but not in Canada
- Generic versions covered by PharmaCare

METHYLPHENIDATE (RITALIN (SR)):

- Plain (IR) tablets:
  - Onset: 1-2 hours
  - Duration: 3-5 hours
- SR tablets: kinetics variable
  - Onset: 2-3 hours
  - Duration: 4-6 hours
- Can start with IR form, ensure tolerance, then switch to long-acting forms
- Full benefit under B PharmaCare coverage

METHYLPHENIDATE MLR (BIPHENTIN):

- 40% IR beads, 60% CR beads (multi-layer)
- Initial peak at 2 hours, 2nd peak at 6-7 hrs
- Can open/sprinkle

METHYLPHENIDATE OROS (CONCERTA):

- Onset: 1-2 hr, duration: up to 12 hr
- Generic CONCERTA = long-acting MPH tabs BUT NOT OROS formulation
  - Bioequivalent per Health Canada (but not 1st line per CADDRA)
  - Switching from brand → generic may note change in duration
    - Cmax TEVA = 18% higher
    - AUC TEVA = 5% higher
    - Tmax TEVA = 4.6 hours
    - CONCERTA = 7.6 HOURS

NERVINE MENTHOLatum

“Rising Release Profile”
PSYCHOSTIMULANTS (CONTINUED):

STIMULANT ADVERSE EFFECTS: * = higher in amphetamines

- CNS: Insomnia, anxiety*, activation, irritability* (rebound), worsening tics, psychosis/mania
- HEENT: Xerostomia, mydriasis
- CVS: Increased HR & BP, palpitations
- RESP: URI, sinusitis, cough
- GI: Anorexia*, nausea, abdominal pain, wt loss
- GU: Urinary retention, rare priapism
- OTHER: Growth delay* (ht & wt), rash, leukopenia, anemia

STIMULANT EFFECTS ON GROWTH:
- Children on MPH txt x 3 yrs grew ~ 2 cm less in ht & weighed ~ 3 kg less
  - All pts had drug holiday = may not generalize to continuous txt
- AMPH vs. MPH: no difference in effect on growth; stimulants had impact on weight (pts thinner over time)
  - Effect on wt greater with AMPH compared to MPH
- Freely available growth charts – plot ht & wt over time
  - ADHD pts often smaller/lighter at baseline
  - Pts should grow along their growth curve over time
  - If pt “falling off” their curve, consider a drug holiday, or drug with less effect on growth
  - Catch up growth expected in late adolescence

NON-STIMULANTS:

ATOMOXETINE:
- Non-stimulant NRI with low abuse potential
- Delayed onset of action: 3-6 weeks
  - Titrate dosage up gradually (taken once daily)
  - Continuous symptom coverage once working (24 hrs)
- Half-life: 5 hours, but half-life prolonged, Cmax & AUC higher in CYP2D6 poor metabolizers or with concurrent strong CYP2D6 inhibitors

CLINICAL USE:
- 2nd line treatment due to lower response rate/effect size compared to stimulants, but an important alternative
  - Concerta > Atomoxetine > placebo at week 6
  - Lisdexamfetamine > atomoxetine at week 9
- Atomoxetine effective for both inattentive and hyperactive/impulsive symptoms
  - Clinically may be useful for inattentive symptoms or with comorbid anxiety disorder
- Can combine with stimulants after inadequate response to each agent alone

ADVERSE EFFECTS:
- No known discontinuation syndrome; tapering off atomoxetine is NOT required but some prescribers opt to do so
- Increased aggression possible in pts with psychiatric comorbidities
- Rare: liver injury, suicidal ideation/attempt
- 2011 warning: ↑ heart rate/blood pressure

ADJUNCTIVE ANTIPSYCHOTIC USE:
- SGAs for treatment of disruptive behaviors in children should not be used as 1st line treatment
- Adjunctive treatment (low-dose) to manage aggression, impulsivity
  - Risperidone, quetiapine, aripiprazole
- Metabolic abnormalities in lipids, glucose may occur even in “skinny little AD/HD kids”

ANTIDEPRESSANT IN AD/HD:
- 3rd line treatments in children
  - Limited evidence supports efficacy of TCAs (nortriptyline, desipramine) and bupropion (DNRI) in children
  - Choose agents that increase NE, DA transmission
    - Venlafaxine (SNRI) effective in adult AD/HD
    - SSRIs not effective in AD/HD

GUANFACINE XR:
- Alpha2 agonist: reduces central NE firing rates, increases connectivity in prefrontal cortex circuit
- Approved in Canada for ages 6-17
  - Helps both inattentive & hyperactive/impulsive sx
  - May help sleep & aggression/oppositional sx
- Long-acting form of an old antihypertensive drug taken once daily
  - AM or PM dosing = no difference
  - taper off to avoid rebound hypertension
- IR form in USA, but not in Canada
  - Do not split/crush/chew (increased AEs)

CLONIDINE:
- Non-selective alpha2 agonist
- 3rd line treatment
  - Useful for aggression, hostility, impulsive behavior, hyperarousal, insomnia
- Children usually need 3 to 4 divided doses per day
  - Titrate dose upward gradually
  - Bulk of dose at bedtime (sedative effects may be helpful)
  - taper off gradually to avoid rebound hypertension
- Clonidine XR available in US but not in Canada

AD/HD PEARLS:
- Use behavioral treatments concurrently
- Can often observe stimulant wearing off (rebound) = adjust timing, formulation, or use adjunctive doses
- Switching from short to long-acting stimulants = total mg daily dose requirement may be a bit higher
- Ask about drug coverage before starting txt – many can’t afford long-acting stimulants/ATX/GXR (and BC PharmaCare coverage is limited)
**ADHD IN SPECIAL POPULATIONS:**

<table>
<thead>
<tr>
<th>ADULTS</th>
<th>OLDER ADULTS</th>
<th>PREGNANCY &amp; LACTATION</th>
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<tbody>
<tr>
<td>• ADHD increasingly diagnosed in adults following DSM5 diagnostic criteria update</td>
<td>• Lack of studies in pts age &gt; 50</td>
<td>• Limited studies; more info on MPH than amphetamines</td>
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<td>• Reduced hyperactivity, inattention remains</td>
<td>• Quality of symptoms may change</td>
<td>o Unclear consequences</td>
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<td>• Mood and anxiety disorder comorbidities</td>
<td>o Hyperactivity ➔ restlessness, fidgeting</td>
<td>• Small studies of MPH associated with fetal loss</td>
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<td>• Similar 1st/2nd line treatments</td>
<td>o Inattention ➔ poor planning/time management</td>
<td>o Malformation risk appears low</td>
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<td>o CBT useful</td>
<td>• Symptomatic patients may benefit from treatment</td>
<td>• Stimulants may transfer to breast milk</td>
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<tr>
<td>• More likely to consider bupropion, SNRIs or even nortriptyline than children</td>
<td>o Smaller effect sizes</td>
<td>o Specific guidance lacking</td>
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<td>• Some agents are off-label in adults</td>
<td>o Adverse effect burden problematic</td>
<td>• Benefit may outweigh fetal risks</td>
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<td>• Abuse/diversion considerations</td>
<td>• Prior medical assessment essential</td>
<td>o Untreated mental illness also negatively impacts development</td>
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<td></td>
<td>• Low/slow dose titration</td>
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</tbody>
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- Older adults: Lack of studies in pts age > 50
- Older adults: Quality of symptoms may change
  - Hyperactivity ➔ restlessness, fidgeting
  - Inattention ➔ poor planning/time management
- Older adults: Symptomatic patients may benefit from treatment
  - Smaller effect sizes
  - Adverse effect burden problematic
- Older adults: Prior medical assessment essential
- Older adults: Low/slow dose titration

- Pregnancy & lactation: Limited studies; more info on MPH than amphetamines
  - Unclear consequences
  - Small studies of MPH associated with fetal loss
  - Malformation risk appears low
  - Stimulants may transfer to breast milk
  - Specific guidance lacking
  - Benefit may outweigh fetal risks
  - Untreated mental illness also negatively impacts development