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Pharmacological Target Symptoms in Autism Spectrum Disorder (ASD)
- Inattention, Impulsivity & Hyperactivity (ADHD)
- Disruptive behaviors and irritability
- Repetitive behaviors and rigidity
- Depression and anxiety
- Mood disorders and psychosis
- Sleep disturbance

ADHD: ASSESSMENT
- Diagnosed based on clinical criteria
- Relies on integration of clinical information derived from variety of sources
- Comorbidity is typical and warrants consideration
- ADHD not diagnosed with neuropsychological testing, computerized assessments, labs, EEG or brain imaging

1: REVIEW RATING SCALES AND RECORDS

ADHD Rating Scales
- ADHD Rating Scale-IV: Purchase book and copy: Guilford Press
- Brown ADD Scales: Purchase: pearsonassessments.com
- SNAP-IV: Free download: www.adhd.net
- Vanderbilt Teacher/Parent Rating Scales: Free download: www.nihcq.org/toolkit

OTHER ASSESSMENT MEASURES
- BROAD-BASED RATING SCALES
  - Child Behavior Checklist (CBCL)
  - Symptom Checklist-90, Revised (SCL-90R)
- Review School Records, IEP, Previous Testing Results.
2: CONDUCT COMPREHENSIVE CLINICAL INTERVIEW

- DSM-5 ADHD Criteria
- Areas of Functional Impairment
- Comorbid Emotional and Behavioral Disorders
- Psychosocial Context

Clinical Interview

- Approach differs based on age of patient
- Developmental Considerations
  - Preschool-aged children
  - School-aged children
  - Adolescents
  - Neurodevelopmental Disorders (ASD)

DSM-5 Diagnostic Criteria

- ADHD Inattentive Symptoms
  - Fails to notice details, makes careless errors
  - Trouble maintaining attention
  - Appears not to listen even when spoken to directly
  - Trouble completing tasks or following through on instructions
  - Difficulty with organization
  - Avoids activities that require sustained attention
  - Loses or misplaces things
  - Distracted easily by extraneous stimuli
  - Forgets easily

- ADHD Hyperactive-Impulsive Symptoms
  - Frequently fidgets, taps hands/feet or squirms seated
  - Frequently gets out of seat
  - Runs and climbs when inappropriate
  - Unable to play quietly
  - Frequently “on the go” as if “driven by a motor”
  - Talks to excess
  - Blurt out answers before questions are completed
  - Trouble waiting turn or in line
  - Frequently interrupts or intrudes

DSM-5 Diagnostic Criteria

- Symptoms prior to age 12 years
- Present in 2 or more settings
- Symptoms interfere with functioning
- Not explained by another disorder
- 3 subtypes
- Specify
  - Partial remission
  - Severity (mild, moderate, severe)

3: CONFIRM OR COMPLETE MEDICAL ASSESSMENT

- Current Medical History
- Cardiac Risk Factors
- Significant Past Medical History
- Family History
Medical Assessment
- History of cardiac defects?
- Fainting or excessive SOB during exercise?
- First or second-degree family member with MI under the age of 30?
- History of Long QT syndrome or WPW?
- History of murmur or other cardiac anomalies?

4: OBTAIN EDUCATIONAL TESTING (if indicated)
- Measure Intellectual Ability
- Assess Academic Achievement

Educational Testing
- Half of those with ADHD have other measurable learning impairments
- WPPSI (preschool IQ)
- WISC (School age IQ)
- Vineland (Adaptive functioning)
- Woodcock-Johnson Tests of Achievement, WJAT, WRAT: Tests of academic achievement
- Impediments to obtaining testing
- Schools have limited resources

ADHD: TREATMENT PLANNING
- Multimodal approaches to ADHD treatment in youth have proven successful in maximizing improved global functioning
- Pharmacotherapy is the only intervention to yield large treatment effects on core symptoms
- Optimal treatment combines meds with psychosocial intervention targeting patient-specific difficulties

Psychoeducation
- Provide didactic information about ADHD, its consequences and strategies for interventions
- Useful to incorporate into the initial evaluation and follow-up visits
- Reduce stigma associated with ADHD
- Referral to useful resources
Resources for Families

**SUPPORT GROUPS**
- ADD Association: [www.add.org](http://www.add.org)
- CHADD: [www.chadd.org](http://www.chadd.org)
- Edge Foundation: [www.edgefoundation.org](http://www.edgefoundation.org)
- Learning Disabilities Assn. of America (LDA): [www.ldanatl.org](http://www.ldanatl.org)

**INFORMATIVE WEBSITES**
- AACAP Facts for Families ([aacap.org](http://aacap.org))
- Healthy Children ([healthychildren.org](http://healthychildren.org))
- National Institute of Mental Health (NIMH)
- US Centers for Disease Control and Prevention

Family-Focused Interventions
- Behavioral Parent Training
- MTA Study
- Cynthia Whitham, LCSW (UCLA)
- Parent-Child Interaction Training (PCIT)
- Community Parent Education Program (COPE)
- Family Therapy
- Couples Therapy

School-Focused Interventions
- Section 504 Plans
- Individual Educational Programs (IEP)
- Behavioral Classroom Management
- Standardized Testing Accommodations

Patient-Focused Interventions
- Health Maintenance
- Pharmacotherapy
- Social and Peer-Related Activities
- Social Skills Training
- Individual Therapy

ADHD PHARMACOTHERAPY
- **History**
  - 1930s: Charles Bradley tested amphetamine on pediatric headaches
  - 1944: Ritalin synthesized
  - 1954: Ritalin identified as stimulant medication
- **Safety**
  - Lots and lots of studies!
- **Efficacy**
  - 70% initial response rate (based on >300 studies)

**MEDICATION OPTIONS**

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<thead>
<tr>
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## Methylphenidate (MPH) Preparations (FDA Approved)

<table>
<thead>
<tr>
<th>BRAND NAME</th>
<th>DOSES AVAILABLE</th>
<th>DOSING (may exceed FDA dosing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin</td>
<td>2.5, 5, 10, 20 mg</td>
<td>5-20 mg BID/TID</td>
</tr>
<tr>
<td>Methylin</td>
<td>2.5, 5, 10 chew; 10mg/5ml sol.</td>
<td>Children: 2.5-10 mg/80 mg BID/TID</td>
</tr>
<tr>
<td>Focalin</td>
<td>2.5, 5, 10 mg</td>
<td>2.5-10mg/8ID</td>
</tr>
<tr>
<td>Ritalin SR</td>
<td>20 mg</td>
<td>20-60 mg QD-BID</td>
</tr>
<tr>
<td>Metadate ER</td>
<td>20 mg</td>
<td>20-60 mg QD-BID</td>
</tr>
</tbody>
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<table>
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<th>Extended Release (MPH-ER)</th>
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<tbody>
<tr>
<td>Concerta 18, 27, 36, 54 mg</td>
<td>18-72 mg/ day</td>
</tr>
<tr>
<td>Ritalin LA 10, 20, 30, 40 mg</td>
<td>10-40 mg/day</td>
</tr>
<tr>
<td>Metadate CD 10, 20, 30, 40, 50, 60 mg</td>
<td>20-60 mg/day</td>
</tr>
<tr>
<td>Daytrana 10, 15, 20, 30 mg patch</td>
<td>10-30 mg/day</td>
</tr>
<tr>
<td>Quellvant XR 25 mg/5ml solution</td>
<td>20-60 mg/day</td>
</tr>
<tr>
<td>Focalin XR 5, 10, 15, 20, 25, 30, 35, 40 mg</td>
<td>10-40 mg/day</td>
</tr>
</tbody>
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## Amphetamine Formulations

<table>
<thead>
<tr>
<th>BRAND NAME</th>
<th>DOSES AVAILABLE</th>
<th>USUAL DOSING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexedrine</td>
<td>5, 7.5, 10, 15, 20, 30 mg</td>
<td>2.5-40 mg QD-TID</td>
</tr>
<tr>
<td>Adderall</td>
<td>5, 7.5, 10, 15, 20, 30 mg</td>
<td>5-40 mg QD-TID</td>
</tr>
<tr>
<td>Dexedrine Spansules</td>
<td>5, 10, 15 mg</td>
<td>5-40 mg QD-BID</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>5, 10, 15, 20, 25, 30 mg</td>
<td>Children: 10-30 mg/day, Adults: 10-40 mg/day</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>20, 30, 40, 50, 60, 70 mg</td>
<td>30-150mg/day</td>
</tr>
</tbody>
</table>

## FDA-Approved Non-stimulant Medications for ADHD

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Doses Available</th>
<th>Usual Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strattera (atomoxetine)</td>
<td>10, 18, 25, 40, 60, 80, 100 mg</td>
<td>0.5mg/kg to 1.2-1.4 mg/kg QD</td>
</tr>
<tr>
<td>Intuniv (guanfacine ER)</td>
<td>1, 2, 3, 4 mg</td>
<td>1-4 mg QD</td>
</tr>
<tr>
<td>Kapvay (clonidine ER)</td>
<td>0.1, 0.2 mg</td>
<td>0.1-0.4 mg QD-BID</td>
</tr>
</tbody>
</table>

## Omega-3 Fish Oil and ADHD
- Meta-analyses of studies show some benefit (Bloch et al 2011 and Konigs et al 2016)
- Anti-inflammatory properties and alters fluidity of cell membranes
- Better for milder forms of ADHD
- Dosing and tolerability
  - Higher eicosapentaenoic acid content may be better
  - 1-2 servings fatty fish per week perhaps more helpful

## Off-Label Medications
- Most have limited evidence of efficacy
- Guanfacine (Tenex)
- Clonidine (Catapres)
- Buproprion (Wellbutrin)
- Modafinil (Provigil)
- TCAs
Medication Management

- Choosing an agent
  - Start with an FDA-approved medication
  - Stimulant v. Non-Stimulant?
  - MPH v. AMPH?
  - MPH milder in meta-analysis
  - AMPH may provide better coverage for adults.
  - Can patient swallow pills?

Choosing an Algorithm

- Where to start?
  - Inattentive v. H/I v. Combined Type
- When to change agents?
- How to change agents?
- When to change from stimulant to non-stimulant?
- How soon to increase dose if ineffective?
- When to utilize combination therapy?

Medication Titration

<table>
<thead>
<tr>
<th>MEDICATION / DOSE</th>
<th># DISP / SCRIPT</th>
<th>PATIENT INSTRUCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>OROS-MPH 18 mg</td>
<td>#30</td>
<td>First 5 days: 1 tab</td>
</tr>
<tr>
<td></td>
<td>1-2 QAM AD</td>
<td>Second 5 days: 2 tabs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third 5 days: 3 tabs</td>
</tr>
<tr>
<td>D-MPH ER 5 mg</td>
<td>#30</td>
<td>First 5 days: 1 cap</td>
</tr>
<tr>
<td></td>
<td>1-2 QAM AD</td>
<td>Second 5 days: 2 caps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third 5 days: 3 caps</td>
</tr>
<tr>
<td>Patient &lt;25 kg</td>
<td>#30</td>
<td>First 5 days: 1 cap</td>
</tr>
<tr>
<td>D-MPH ER 10 mg</td>
<td>#30</td>
<td>Second 5 days: 2 caps</td>
</tr>
<tr>
<td>Patient &gt;25 kg</td>
<td></td>
<td>Third 5 days: 3 caps</td>
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<tr>
<td>MAS-ER 10 mg</td>
<td>#30</td>
<td>First 5 days: 1 cap</td>
</tr>
<tr>
<td>(5 mg in younger)</td>
<td>1-2 QAM AD</td>
<td>Second 5 days: 2 caps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third 5 days: 3 caps</td>
</tr>
<tr>
<td>LDX 20 mg</td>
<td>#30</td>
<td>First 5 days: 1 cap</td>
</tr>
<tr>
<td></td>
<td>1-2 QAM AD</td>
<td>Second 5 days: 2 caps</td>
</tr>
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<td></td>
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COMBINATION THERAPY

- Length of action insufficient?
- Addition of IR formulation
- Ascending drug plasma level to maintain efficacy
- Utilize same basic agent
- Daytrana patch
- Intolerable adverse effects at higher doses?
- Change stimulant for monotherapy
- Addition of alpha-agonist
- Strattera as mono or combination therapy

Long-Term Maintenance

- Assess H/W, pulse and BP q6 months
- Once optimal dose identified: 1 month Rx then re-evaluate
- Still optimal? Subsequent visits q3 months
- DEA allows 90-day prescription
  - 90 day supply (if covered by insurance)
  - 3 separate Rx’S, all dated day of visit
  - “DNF before (1 month); DNF before (2 months)”
Managing Adverse Events
- Appetite loss & Growth delay
- Headache, Stomachache, Nausea
- Mood lability & Irritability
- Sleep difficulties
- Psychosis
- Suicidality
- Priapism
- Tics

Discontinuing Medication
- Persistence of symptoms?
- Scheduled breaks and monitoring of symptoms (Winter/Summer breaks, etc.)
- Individualized approach
- Medication can always be restarted
  - More easily with stimulants

Other Target Symptoms in ASD
- Disruptive behaviors and irritability
- Repetitive behaviors and rigidity
- Depression and anxiety
- Mood disorders and psychosis
- Sleep disturbance

Disruptive Behavior Disorders and Irritability: Atypical Neuroleptics
- Two medications FDA approved for irritability in ASD
  - Risperidone (>5): most commonly used, effective in clinical trials (2002)
  - Aripiprazole (>6): effective in trials (2009)
- Other agents
  - Olanzapine, quetiapine: metabolic issues
  - Ziprasidone, lurasidone: less evidence but maybe better metabolic profile

Disruptive Behavior Disorders and Irritability: Typical (1st generation) Neuroleptics
- Haloperidol, chlorpromazine and others
- Often used as either standing medication or as-needed (PRN) medication
- Adverse effects
  - Some similar to atypicals but often attenuated
  - Extrapyramidal symptoms, tardive dyskinesia and neuromalignant syndrome
Disruptive Behavior Disorders and Irritability: Other agents
- Alpha agonists, mood stabilizers, SSRIs, beta-blockers
- Continuously reevaluate cause of symptoms
- Medical issues: constipation, infection, dental caries
- Depression, anxiety (SSRIs)
- Communication issues

Repetitive Behaviors and Rigidity: Other Agents
- Assessment of benefits v. risks of treatment
- Marginal evidence of pharmacological benefit
- Agents
  - SSRIs
  - Clomipramine
  - Atypical neuroleptics and Depakote
  - Ineffective in trial: naltrexone, stimulants (Huffman 2011)

Repetitive Behaviors and Rigidity: SSRIs
- Relatively few side effects
- Can help with concurrent depressive and anxious symptoms
- Fluoxetine: 2 recent studies suggest efficacy (Hollander 2005 and 2012)
- Citalopram: 2009 study ineffective (King et al)
- Fluvoxamine, sertraline, paroxetine, escitalopram: studies suggest improvement
- Black box warning re: suicidal ideation

Repetitive Behaviors and Rigidity: Other Agents
- Clomipramine: serotonin-selective TCA, inconsistent findings (Hurwitz 2012)
- Risperidone: one study showed support (McDougle 2005)
- Valproic acid (Depakote): one small, blinded RCT showed improvement (Hollander 2006)

Depression & Anxiety
- Both common in ASD: how to assess?
- Role of therapy and psychosocial interventions
- Can contribute to SIB or aggression
- Some agents as used in non-ASD patients (few studies in ASD)
  - SSRIs, SNRIs: lower doses
  - Buspirone: one open-label study in ASD (Buitelaar 1998)

Mood Disorders & Psychotic Disorders
- Important to continually assess into adulthood
- Mania: lithium, atypical neuroleptics, benzodiazepines
- Psychosis: Typical or atypical neuroleptics
- Case examples:
  - 17 y/o female with ASD and mania
  - 23 y/o MTF TG with ASD and psychosis
Sleep Disturbance in ASD
- Extremely common
- Abnormalities in melatonin, serotonin and GABA
- Etiology?
  - Sleep hygiene
  - Obstructive sleep apnea
  - Depression

Sleep Disturbance in ASD: Treatment
- Melatonin
  - Most evidence for efficacy (Wright 2011 and Guenole 2011)
  - Short-term efficacy of initiation and maintenance
  - 3-5 mg dose to start, given 60-90 minutes prior to bedtime
  - AEs: daytime sleepiness and enuresis
  - OTC, not monitored by FDA: ask pharmacist

Sleep Disturbance in ASD: Treatment
- Trazodone
- Clonidine and guanfacine
- Quetiapine
- Diphenhydramine
- Zolpidem, Ramelteon, benzodiazepines, mirtazapine

Neuropsychological & Mind-Body Therapies
- Cognitive training
- EEG Neurofeedback & Biofeedback
- Acupuncture
- Chiropractic Adjustment
- Exercise
- Interactive Metronome Training
- Meditation/Mindfulness/Yoga/Massage
- Repetitive TMS
- Sensory Integration Training
- Vision Therapy

References