Pharmacological Management of Autism Spectrum Disorder and ADHD: Help Group Summit 2016

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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
- Broad-Band Rating Scales
- School Records

ADHD RATING SCALES

RATING SCALE	HOW OBTAINED
ADHD Rating Scale-IV	Purchase book and copy: Guilford Press
Brown ADD Scales	Purchase: pearsonassessments.com
Conners, 3rd-Edition Teacher and Parent Rating Scales	Purchase: mhs.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

DSM-5 Diagnostic Criteria

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
Blurts 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)

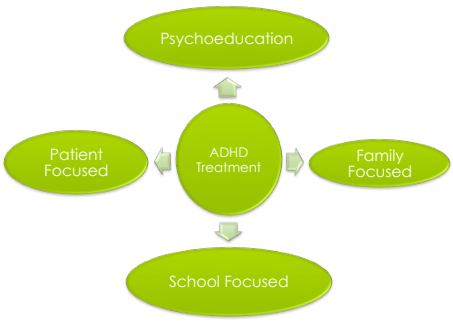
- Measure Intellectual Ability
- Assess Academic Achievement

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, WIAT, 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
Children & Adults with ADD (CHADD): www.chadd.org
Edge Foundation: www.edgefoundation.org
Learning Disabilities Assn. of America (LDA): www.Ldanatl.org

INFORMATIVE WEBSITES
AACAP Facts for Families (aacap.org)
Healthy Children (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

STIMULANTS	NONSTIMULANTS	OFF-LABEL MEDS
		IR alpha-2 agonists
Methylphenidates	Atomoxetine	Buproprion
D-MPH	ER Alpha-2 agonists	Modafinil
D-Amphetamines		TCAs
Mixed Amphetamine Salts		Antipsychotics
Lisdexamfetamine		MAO Inhibitors

Methylphenidate (MPH) Preparations (FDA Approved)

BRAND NAME	DOSES AVAILABLE	DOSING (may exceed FDA dosing)
Ritalin	2.5, 5, 10, 20 mg	5-20 BID/TID
Methylin	2.5, 5, 10 chew; 10mg/ 5ml sol.	Children: 2.5-10 mg/ BID-TID
Focalin	2.5, 5, 10 mg	2.5-10mg/ BID
Ritalin SR	20 mg	20-60 mg QD-BID
Metadate ER	20 mg	20-60 mg QD-BID

MPH Preparations

Extended Release	(MPH-ER)	
Concerta	18, 27, 36, 54 mg	18-72 mg/ day
Ritalin LA	10, 20, 30, 40 mg	10-40 mg /day
Metadate CD	10, 20, 30, 40, 50, 60 mg	20-60 mg /day
Daytrana	10, 15, 20, 30 mg patch	10-30 mg/ day
Quillivant XR	25 mg/ 5mL solution	20-60 mg/ day
Focalin XR	5, 10, 15, 20, 25, 30, 35, 40 mg	10-40 mg/ day

Amphetamine Formulations

BRAND NAME	DOSES AVAILABLE	USUAL DOSING
IMMEDIATE RELEASE		
Dexedrine	5, 7.5, 10, 15, 20, 30 mg	2.5-40 mg QD-TID
Adderall	5, 7.5, 10, 12.5, 15, 20, 30 mg	5-40 mg QD-TID
SUSTAINED RELEASE		
Dexedrine Spansules	5, 10, 15 mg	5-40 mg/ QD-BID
EXTENDED RELEASE		
Adderall XR	5, 10, 15, 20, 25, 30 mg	Children: 10-30 mg/day Adults: 10-60 mg /day
Vyvanse	20, 30, 40, 50, 60, 70 mg	30-70 mg/ day

FDA-Approved Non-stimulant Medications for ADHD

Brand Name	Doses Available	Usual Dosing
NORADRENERGIC REUPTAKE INHIBITORS		
Strattera (atomoxetine)	10, 18, 25, 40, 60, 80, 100 mg	0.5 mg/ kg to 1.2-1.4 mg/ kg QD
ALPHA-2 AGONISTS		
Intuniv (guanfacine ER)	1, 2, 3, 4 mg	1-4 mg QD
Kapvay (clonidine ER)	0.1, 0.2 mg	0.1-.04 mg/ QD-BID

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)
  - Bupropion (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

MEDICATION / DOSE	# DISP / SCRIPT	PATIENT INSTRUCTIONS
OROS-MPH 18 mg	#30	First 5 days: 1 tab
	1-2 QAM AD	Second 5 days: 2 tabs
		Third 5 days: 3 tabs
D-MPH ER 5 mg	#30	First 5 days: 1 cap
Patient <25 kg	1-2 QAM AD	Second 5 days: 2 caps
		Third 5 days: 3 caps
D-MPH ER 10mg	#30	First 5 days: 1 cap
Patient >25 kg		Second 5 days: 2 caps
		Third 5 days: 3 caps

Medication Titration

MEDICATION / DOSE	# DISP / SCRIPT	PATIENT INSTRUCTIONS
MAS-ER 10 mg	#30	First 5 days: 1 cap
(5 mg in younger)	1-2 QAM AD	Second 5 days: 2 caps
		Third 5 days: 3 caps
LDX 20 mg	#30	First 5 days: 1 cap
	1-2 QAM AD	Second 5 days: 2 caps
		Third 5 days: 3 caps

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
- Rebound hyperactivity
- 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: Atypical Neuroleptics

- Adverse effects of atypical neuroleptics
  - Sedation, weight gain, hypercholesterolemia, diabetes, tremor, EPS and akithesia, hyperprolactinemia
- Baseline evaluation
  - Lab work, weight, AIMS, EKG, vital signs
  - Lab: CBC, CMP, prolactin, Lipids, HgbA1C
- Routine monitoring of above

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

- 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
- Same 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 hygeine
  - 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

- McGough, James J. "ADHD." Oxford American Psychiatry Library, 2014.
- Schneider, B and Enenbach, M. "Managing the Risks of ADHD Treatment." Curr Psychiatry Rep. 2014 Oct; 16(10): 479.