

# “Pharmacologic Management of Autism Spectrum Disorder, ADHD & Related Disorders”

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# Faculty Disclaimers of Support

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# Learning Objectives

- \* Gain an understanding of evidence-based and novel pharmacologic methods in the treatment of autism and associated disorders
- \* Feel more confident treating children, adolescents and adults with ASD and associated disorders

# Before We Prescribe...

- \* Individualized approach
- \* Medications used to treat target symptoms/behaviors, not Autism itself: ADHD, Anxiety, Mood Disorders, Behavioral Disorders, Insomnia
- \* Medications should always be used in conjunction with behavioral therapy approaches.
- \* Many medications used off-label; side effects common
- \* Paradoxical reactions to medications more common
- \* Use of rating scales to monitor treatment efficacy



# Pretreatment Evaluation

- \* Input from patient, parents, caregivers and school, if possible
- \* How long present/how severe is problem?
- \* Multiple settings?
- \* What brings it on or makes it better/worse?
- \* Medical factors contributing?
- \* What is the course? Getting better or worse?
- \* Does it interfere with function?
- \* Other supports available?

# Standardized Rating Systems

- \* IQ & Educational Testing
- \* Speech and Language Evaluation
- \* Adaptive Functioning Assessment: i.e. Vineland ABS
- \* Aberrant Behavior Checklist (ABC)
- \* Target symptom assessments:
  - \* ADHD: Conner's, Vanderbilt, SNAP-IV (ADHD.net), Barkley, SWAM, SKAMP
  - \* Anxiety: MASC, SCARED, Beck Anxiety Inventory
  - \* Mood: CDI, BDI-Y, Kiddie-SADS, YMRS
  - \* OCD: CY-BOCS



# Who Should Prescribe?

- \* Child & Adolescent Psychiatrists
- \* Developmental Pediatricians
- \* Child Neurologists
- \* Adult Psychiatrists
- \* General Practitioners/PAs/NPs, in consultation with specialists

# Target Symptoms

- \* Inattention, Impulsivity and Hyperactivity
- \* Disruptive Behavior and Irritability
- \* Repetitive Behaviors and Rigidity
- \* Depression and Anxiety
- \* Sleep Disturbance



# Inattention, Hyperactivity & Impulsivity

- \* DSM-5 changes in diagnostic criteria
- \* Stimulants: Methylphenidates v. Amphetamines
  - \* MPH: 3 studies show improvement in ADHD in ASD(1); response lower than ADHD alone
  - \* AMPH: less clinical evidence, though still used
  - \* Large number of discontinuation in trials compared with non-ASD ADHD
  - \* AE's include insomnia, anorexia, irritability, tics, mood disturbance and social withdrawal

(1) RUPP Autism Network. RCT of MPH in PDD with hyperactivity. Arch Gen Psychiatry 2005; 62:1266.

# Inattention, Hyperactivity & Impulsivity

## \* Methylphenidate Stimulants

- \* MPH (Ritalin), dex-methylphenidate (Focalin)
- \* Ritalin LA/SR, Metadate CD/ER
- \* Concerta, Focalin XR, Quillivant (liquid), Daytrana (patch)

## \* Amphetamine-based Stimulants

- \* MAS (Adderall), dextroamphetamine (Dexedrine)
- \* Adderall XR, lisdexamfetamine (Vyvanse)



# Inattention, Hyperactivity & Impulsivity

- \* Alpha agonists: monitor BP/HR, side effects and combination trials.
  - \* Clonidine (Kapvay, patch)
    - \* Two small, cross-over studies suggest decreased irritability, stereotypy, hyperactivity, inappropriate speech and oppositional behavior (2,3)
    - \* AE's include hypotension and sedation
  - \* Guanfacine (Intuniv)
    - \* Limited studies suggest improvement (4,5)
    - \* Adverse effects include sedation, constipation, irritability and aggression

(2): Frankhauser MP et al. A DB PC study of the efficacy of transdermal clonidine in autism. J Clin Psychiatry 1992; 53:77.

(3): Jaselskis CA et al. Clonidine treatment of hyperactive and impulsive children with autistic disorder. J Clin Psychopharmacol 1992; 12:322.

(4): Posey DJ et al. Guanfacine treatment of hyperactivity and inattention in PDD: a retrospective analysis of 80 cases. J Child Adolesc Psychopharmacol 2004; 14:233.

(5): Scahill L et al. A prospective open trial of guanfacine in children with PDD. J Child Adolesc Psychopharmacol 2006; 16:589.

# Inattention, Hyperactivity & Impulsivity

## \* Atomoxetine (Strattera)

- \* Limited studies suggest moderate improvement (6, 7): Hyperactive>Inattention
- \* Again, not as robust an improvement as in those without ASD

## \* Other medications

- \* Risperidone (8, 9): open label and RCTs
- \* Antiepileptics: evidence limited to small, open-label or observational studies (10, 11, 12)

## \* General Treatment Issues

- \* Rule out other factors; side effect profiles; trial and error approach

(6): Harfterkamp M et al. A randomized double-blind study of atomoxetine v. placebo for ADHD symptoms in children with ASD. *J Am Acad Child Adolesc Psychiatry* 2012; 51:733.

(7): Arnold LE et al. Atomoxetine for hyperactivity in ASD. *J Am Acad Child Adolesc Psychiatry* 2006; 45:1196.

(8): McCracken JT et al. Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 2002; 347:314.

(9): Barnard L et al. A systematic review of the use of atypical antipsychotics in autism. *J Psychopharmacol* 2002; 16:93.

(10): Hollander et al. An open trial of divalproex sodium in ASD. *J Clin Psychiatry* 2001; 62:530.

(11): Hardan AY et al. A retrospective assessment of topiramate in children and adolescents with PDD. *J Child Adolesc Psychopharmacol* 2004; 14:426.

(12): Belsito KM et al. Lamotrigine therapy for autistic disorder: a randomized, DB, placebo-controlled trial. *J Autism Dev Disord* 2001; 31:175.



# Disruptive Behavior Disorders & Irritability

- \* Symptoms include aggression, tantrums and self-injury
- \* Multiple or isolated settings?
- \* Root cause: Anxiety? Inability to communicate? ICD? Mood?
- \* Postulate cause, then initiate therapy
- \* First try non-pharmacologic therapies, if possible

# Disruptive Behavior Disorders & Irritability

- \* Only two medications FDA-approved for Irritability in ASD:
  - \* Risperidone (>5): most commonly used, effective in clinical trials (8,9)
  - \* Aripiprazole (>6): Multi-center RCTs show improvement in ABC (13,14)
- \* Anecdotal evidence: ziprasidone, lurasidone. Less metabolic effects?
- \* Adverse effects common: fatigue, vomiting, sedation, weight gain, metabolic effects, tremor, EPS = high drop-out rate in trials.
- \* Baseline EKG, AIMS, weight, BP, lab studies (CBC, CMP, Lipids, TSH, prolactin)

(13): Ching H et al. Aripiprazole for ASD. Cochrane Database Syst Rev 2012; 5:CD009043

(14): Marcus RN et al. A placebo-controlled, fixed dose study of aripiprazole in children & adolescents with irritability associated with autistic disorder. J Am Acad Child Adolesc Psychiatry 2009; 48:1110



# Disruptive Behavior Disorders & Irritability

## \* Olanzapine

- \* Several small, prospective studies showed clinical improvement
- \* Side-effect profile worse than other agents

## \* Other atypical neuroleptics

## \* Typical neuroleptics: Haloperidol, Chlorpromazine, Molindone

## \* Other agents

- \* Alpha-agonists, antiepileptics, lithium, SSRIs and beta-blockers

# Repetitive Behaviors & Rigidity

- \* Benefits v. Risks
- \* Marginal evidence of benefit, overall
- \* SSRIs, Clomipramine, Atypical Neuroleptics and VPA
- \* Ineffective in trials: Naltrexone, secretin and stimulants (15)

(15): Huffman LC et al. Management of symptoms in children with ASD: a comprehensive review of pharmacologic and complementary-alternative medicine treatments. J Dev Behav Pediatr 2011; 32:56



# Selective Serotonin Reuptake Inhibitors (SSRIs)

- \* Fewer side effects than other psychotropic medications
- \* Can help with concurrent anxiety and depression
- \* Two recent studies suggest that fluoxetine can be helpful (16, 17), while citalopram is not (18); otherwise rigorous studies lacking
- \* Fluvoxamine, sertraline, paroxetine, escitalopram: open-label or unpublished studies suggest mild improvement
- \* Black box warning for increased suicidal ideation

(16): Hollander E et al. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. *Neuropsychopharmacology* 2005; 30:582

(17): Hollander E et al. A double-blind placebo-controlled trial of fluoxetine for repetitive behaviors and global severity in adult autism spectrum disorders. *Am J. Psychiatry* 2012; 169(5):540

(18): King BH et al. Lack of efficacy of citalopram in children with ASD and high levels of repetitive behavior: citalopram ineffective in children with autism. *Arch Gen Psychiatry* 2009; 66:583

# Other Medications for Repetitive Behaviors in Autism

- \* Clomipramine: serotonin-selective TCA, inconsistent findings (19-21)
- \* Risperidone: One study showed some support (22)
- \* Valproic Acid: One small, blinded RCT showed improvement (23)

(19): Gordon CT et al. A DB comparison of clomipramine, desipramine and placebo in the treatment of AD. *Arch Gen Psychiatry* 1993; 50:441

(20): Remington G et al. Clomipramine v. haloperidol in the treatment of autistic disorder: a DB, PC, crossover study. *J Clin Psychopharmacol* 2001; 21:440

(21): Hurwitz R. Tricyclic antidepressants for ASD in children and adolescents. *Cochrane Database Syst Rev* 2012; 3:CD008372

(22): McDougle CJ et al. Risperidone for the core symptom domains of autism; results from the study by the autism network of RUPP. *Am J Psychiatry* 2005; 162:1142

(23): Hollander et al. Divalproex sodium v. placebo in the treatment of repetitive behaviors in ASD. *Int J Neuropsychopharmacol* 2006; 9:209



# Anxiety

- \* Common in ASD
- \* Can contribute to aggressive or self-injurious behaviors
- \* Use same therapies as in non-ASD individuals (24, 25)
- \* Individualized multimodal approach
- \* Buspirone: one open-label study suggests improvement (26)

(24): White SW et al. Anxiety in children and adolescents with ASD. Clin Psychol Rev 2009; 29:216

(25): Ipser JC et al. Pharmacotherapy for anxiety disorders in children & adolescents. Cochrane Database Syst Rev 2009; CD005170

(26) Buitelaar JK et al. Buspirone in the management of anxiety and irritability in children with PDD: results of an open-label study. J Clin Psychiatry 1998; 59:56

# Mood Lability in ASD

- \* Number of agents used, none specifically studied in ASD
- \* Lithium, SSRIs
- \* Atypical neuroleptics



# Depression in ASD

- \* How to assess?
- \* Counseling and psychosocial interventions first
- \* Treat with same medications as non-ASD patients (SSRI, SNRI)
- \* “Start low, go slow”

# Sleep Disturbance in ASD

- \* Common problem in this population
- \* Associated with abnormalities in melatonin, serotonin, GABA
- \* Evaluate thoroughly for other causes (hygiene, OSA)
- \* Little evidence for pharmacologic intervention, none FDA-approved



# Sleep Disturbance Treatment

- \* **Melatonin:** Suggested improvement in observational, open-label studies and small RCTs (27,28)
  - \* Results suggest short-term efficacy of initiation and maintenance
  - \* 0.5/1mg to 10mg typical dose, given 30-90 minutes before bed
  - \* AEs: daytime sleepiness and enuresis
  - \* OTC, not monitored by FDA: melatonin as only active ingredient better

(27): Wright et al. Melatonin v placebo in children with ASD and severe sleep problems not amenable to behaviour management strategies: a randomised controlled crossover trial. *J Autism Dev Disord* 2011; 41:175

(28): Guenole F et al. Melatonin for disordered sleep in individuals with ASD: systematic review and discussion. *Sleep Med Rev* 2011; 15:379

# Sleep Disturbance Treatment

- \* Other available agents (without much evidence):
  - \* Trazodone
  - \* Clonidine & Guanfacine
  - \* Quetiapine
  - \* Diphenhydramine
  - \* Zolpidem, Mirtazapine, Atypicals, Benzodiazepines, Ramelteon (melatonin-receptor agonist)



# In Conclusion

- \* Treat individual symptoms associated with ASD
- \* Utilize non-pharmacologic methods when possible
- \* Follow evidence-based guidelines, but understand that there are very few such guidelines in this population
- \* Start low, go slow!
- \* Be hyperaware of adverse effects and how this population can manifest them; also paradoxical reactions

**A**lways

**U**nique

**T**otally

**I**nteresting

**S**OMETIMES

**M**YSTERIOUS



Thank You!