

Autism Spectrum Disorders & Attention Deficit Disorder in PEDIATRIC PRIMARY CARE

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Disclosures

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Ben Handen	Abigail Schlesinger
NIA NICHD Autism Speaks Roche	DDAP CVS DHS AAP

Here's the Plan

Discuss

Differences and Similarities between ADHD and ASD

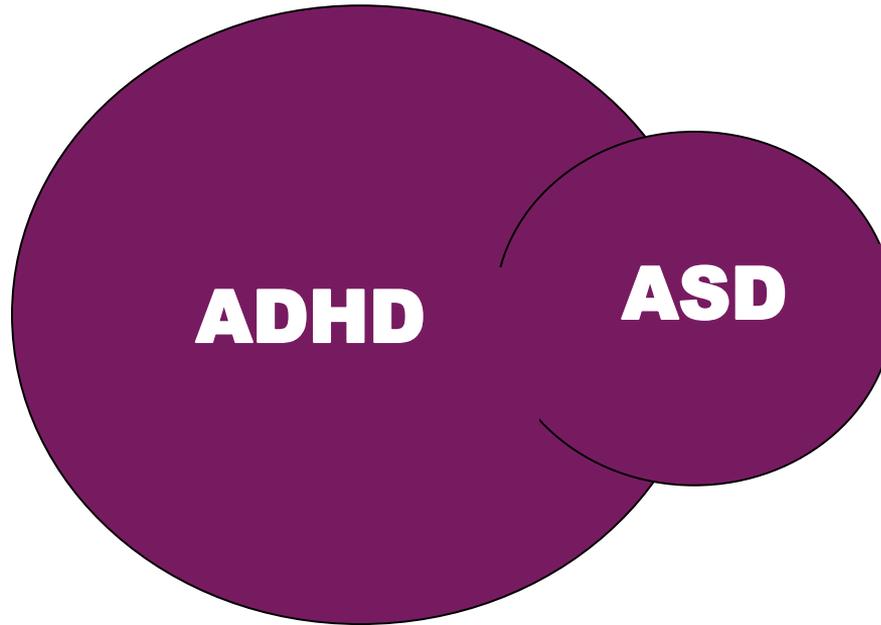
Review

Importance of clarifying symptoms and identifying treatment targets when treating ADHD & ASD

Review

Pharmacologic & Nonpharmacologic Options for ADHD and ASD

Is There an ADHD-ASD Spectrum?



Autism Spectrum Disorder (ASD) - DSM-5

- A. **Persistent** deficits in **social communication** and **social interaction**, manifested by **all three**:
- Deficits in social-emotional reciprocity
 - Deficits in nonverbal communicative behaviors used for social interaction
 - Deficits in developing, maintaining, and understanding relationships

Autism Spectrum Disorder (ASD) DSM-5

- B. **Restricted, repetitive patterns of behavior, interests, or activities**, manifested by at least two:
- **Stereotyped or repetitive** motor movements, use of objects, or speech
 - **Insistence on sameness, inflexible adherence to routines**, or **ritualized patterns**
 - **Highly restricted, fixated interests** that are abnormal in intensity or focus
 - **Hyper- or hypo-reactivity to sensory input**

Attention-Deficit/Hyperactivity Disorder

Inattentive (6 of 9)

Fidgets

Leaves seat

Runs about or climbs

Unable to play or engage in Leisure activities

“Driven by a motor”

Talks excessively

Blurts out

Difficulty waiting turn

Interrupts or intrudes

Hyperactive/Impulsivity(6 of 9)

Careless mistakes

Sustaining attention

Does not seem to listen

Does not follow through

Difficulty organizing

Avoids tasks that require sustained mental effort

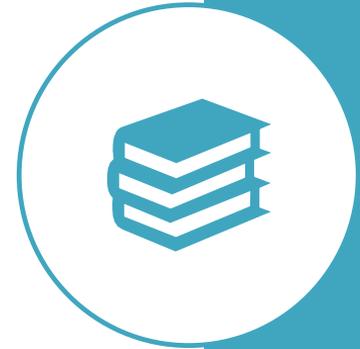
Loses things

Easily distracted

Forgetful

Interrupts or intrudes

- Sara is 5 ½ years old and comes in because her private kindergarten has threatened to “kick her out” if her behavior doesn’t improve quickly. She’s had a behavioral health therapist in the school for the last 2 months, and there is a behavioral management plan in place, but her behaviors are still a significant concern. Mom brought an email from the school for you to read



- “Sara never stops moving, she runs and climbs during quiet time, she’s got no friends. She doesn’t look at us when we ask her to listen. She doesn’t understand personal space. She talks nonstop. She interrupts her peers to make points. She doesn’t want to wait for lunch and runs away from the lunch room to her teachers room. Since the therapist came she is more likely to follow directions – if she realizes that we have asked her to do something. She is disruptive when it’s time to transition from free play to circle time. When she does start circle time she moves her hands excessively, can’t sit on her spot and continually interrupts her peers repeats portions of songs over and over. It is hard to judge her abilities due to her behavior.”

ADHD Hyperactive(6)

- fidgets
- leaves seat
- runs about or climbs
- unable to play or engage in leisure activities
- “driven by a motor”
- talks excessively
- blurts out
- difficulty waiting turn
- interrupts or intrudes

ADHD Inattentive(6)

- careless mistakes
- sustaining attention
- does not seem to listen
- does not follow through
- difficulty organizing
- avoids tasks that require sustained mental effort
- loses things
- easily distracted
- Forgetful
- interrupts or intrudes

Autism Spectrum Disorder(6)

ALL 3 - social communication and social interaction

- Deficits in social-emotional reciprocity
- Deficits in nonverbal communicative behaviors used for social interaction
- Deficits in developing, maintaining, and understanding relationships

AT LEAST 2 - Restricted, repetitive patterns of behavior, interests, or activities

- Stereotyped or repetitive motor movements, use of objects, or speech
- Insistence on sameness, inflexible adherence to routines, or ritualized patterns
- Highly restricted, fixated interests that are abnormal in intensity or focus
- Hyper- or hypo-reactivity to sensory input

How many
kids are we
talking
about
anyway?

- 1 in 59 children diagnosed with ASD
 - Variation by location, gender, SES & race
- 23% - 74% of kids with ADHD may have ASD
- 31% of kids with ASD have ADHD
- Comorbidity higher in clinically referred than community-based studies

Why is it hard to distinguish ADHD from ASD?

- Common symptoms/behaviors:
 - Social skills deficits
 - Inattention
 - Learning problems
 - Both occurs more frequently in males than females

ADHD & ASD Presentation Overlap

- Some common symptoms (e.g., poor peer relations, does not seem to listen when spoken to)
- Some common neuropsychological deficits (e.g., problems with planning, working memory, inhibition, mental flexibility)
- Diagnosed at early age; symptoms often chronic and persist into adulthood
- Many children diagnosed with Autism Spectrum (including the diagnosis formally known as Asperger's and High Functioning Autism) are first diagnosed (or misdiagnosed) with ADHD



Problems with Diagnosing ADHD in ASD

- Challenge in discriminating between symptoms due to ASD vs. ADHD
- ADHD symptoms must be “inconsistent with developmental level”
- How to “control for” intellectual disability
- ADHD often the first diagnosis in "high functioning kids"
- Few available diagnostic tools for assessing ADHD in ASD

Considerations Making Diagnosis

- Impact of language
 - Some symptoms not appropriate for children with limited language (e.g., “often talks excessively,” “often blurts out answers”).
- Considering Mental Age
 - Connors does not require adjustment
- Is tool normed for ID and ASD Population
 - Hyperactivity subscale of Aberrant Behavior Checklist

Same
behaviors
but different
underlying
mechanisms

Inattention –
Primary Attention
Problem
OR
Deficits in areas of
communication and
joint attention

Motor activity –
Restless & Excessive
Movement
OR
Frequent
repetitive/stereotyped
movements

Fidgetiness
Primary
OR
Anxiety in social
Situations

Social problems
Being too impulsive to
utilize skills
OR
lack of skills needed to
initiate social
interactions

Comorbidities in ASD

- Specific phobia 44% (one-third of which were fear of needles or crowds)
- Obsessive-compulsive disorder (OCD): 37%
- ADHD: 31% (two-thirds inattentive type)
- Separation anxiety disorder: 12%
- Major depressive episode: 10%
- The study was limited by a sample that was mostly male, verbal, and higher functioning as well as by the use of parental reports as the sole data source.

Assessment model

- Ideally want information from three sources
 - Parents (history and standardized questionnaires)
 - Teachers (history and standardized questionnaires)
 - Observation (either from school, wrap agency or in clinic)
- As with typically developing children with ADHD, may not necessarily see symptoms in clinic
- But ideally would like to document clinically significant concerns in at least two different settings

Impact of ADHD symptoms on functioning

Vineland Adaptive Behavior Scales Standard Scores (Pearson et al, 2006)

	<u>Autistic/ADHD</u> (N=57)	<u>Autistic</u> (N=114)
Communication	68.5	87.0
Daily Living	56.6	78.7
Socialization	58.0	85.9

ADHD Symptoms in ASD

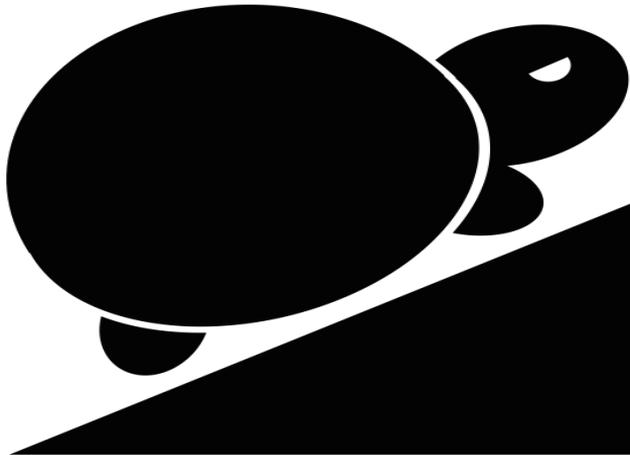
More severe impairment

Potentially altered
response to treatment

Longterm outcome is
worse

Take Home point

- Must treat ADHD symptoms in ASD Aggressively



- Start Low...
- Go Slow...
- Don't Stop Thinking!

Created by Bonegolem
from Noun Project

Treatment options



How many children with autism are prescribed psychotropic medication to Treat ADHD?



ASD Psychotropic Rates in Ohio (Witwer & Lecavalier, 2005)

Medications Within The Last 12 Months Among
Nonreferred Children With ASD, Ages 3-21 (n=353)

<u>Treatments</u>	<u>Number</u>	<u>(%)</u>
stimulants	86	(24.0)
antidepressants	76	(21.2)
antipsychotics	69	(19.5)
alpha agonists	39	(10.9)
mood stabilizers	15	(4.2)
anxiolytic/hypnotics	10	(2.8)
noradrenergic agonists	6	(1.7)
opiate blockers	5	(1.4)
antihistamines	3	(0.9)
beta blocker	1	(0.3)

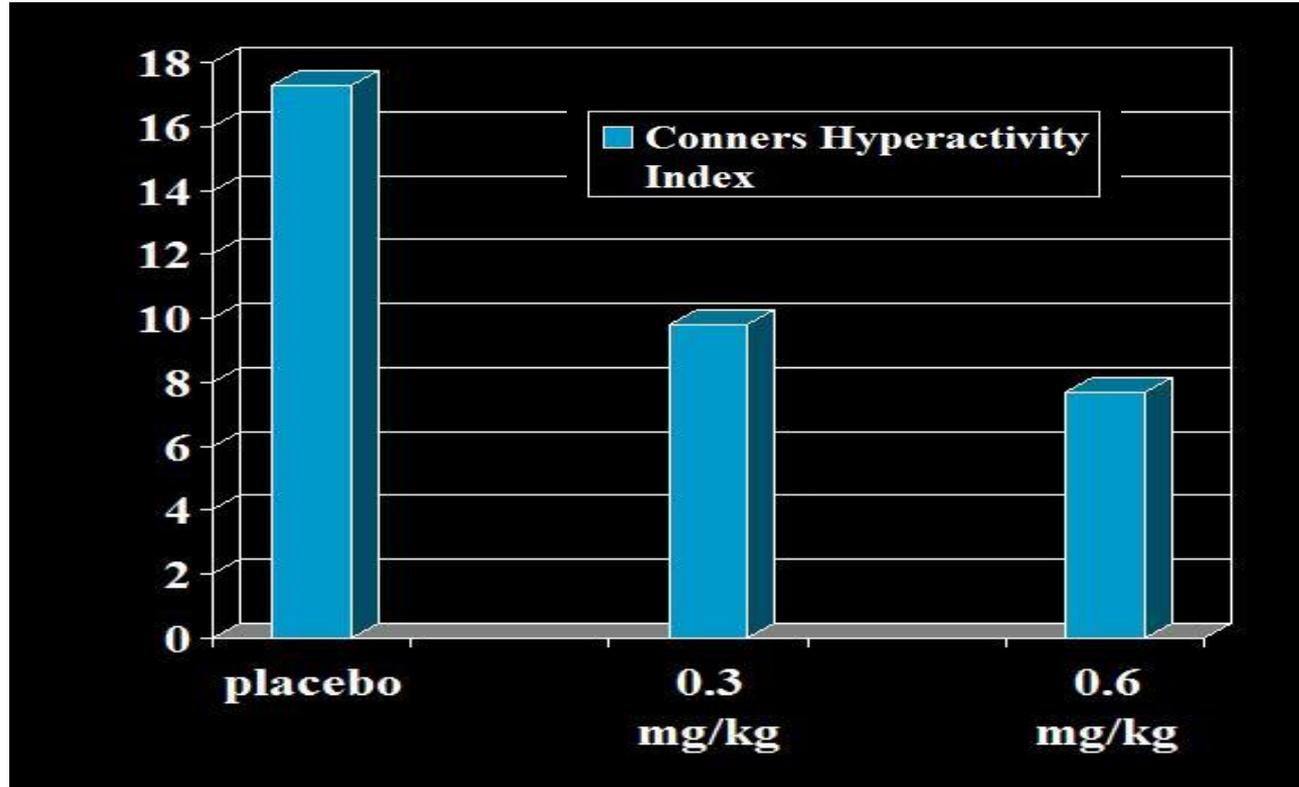
Do Stimulants Work in Autism?

- Prior to 1995, many thought stimulants didn't work in Autism
- Most studies were not well controlled
- Until 2005, largest controlled study had only 13 children
- In 2005, a double-blind study of 72 children was published(RUPP)

Handen, Johnson & Lubetsky, 2000
Ritalin and Autism

- 8 of 13 children had a $\geq 50\%$ on Conners scale
- No change in primary symptoms of ASD (based upon the CARS)
- Side Effects: increased sadness, drowsiness

Handen, Johnson & Lubetsky, 2000 Ritalin and Autism (n=13)



RUPP MPH Study, 2005

- Cross-over design: placebo, low, medium and high MPH doses (1 week per condition)
- N=72; 74% Autistic Disorder 26% PDD NOS or Asperger's Disorder
- Doses given b.i.d. (0.125, 0.25, 0.50 mg/kg per dose) with smaller third dose in late afternoon
- Dependent Measures: Aberrant Behavior Checklist, CGI

RUPP MPH Study Results

- 13 (18%) subjects discontinued - side effects
- 35 (49%) classified as responders (decrease of $\geq 25\%$ on the ABC Hyperactivity subscale and CGI-I of 1 or 2)
- Effects sizes, d , of 0.29, 0.54, and 0.40
- Age, IQ and ASD subtype not found to influence outcome

Preschoolers with PDD and ADHD (Ghuman et al., 2009)

- 14 preschoolers, 3-5 years
- 12 with PDD; 2 with ID
- Mean IQ: 75 (SD 18)
- 1-week placebo lead-in; single-blind MPH titration; 4 week D-B crossover (2 weeks placebo, 2 weeks MPH)
- Dependent Measures: Conners, Nisonger, CGI

Recommendation

- There is Strong Support for the use of Ritalin in ASD
- There are no studies involving other stimulants, such as Adderall, although likely have a similar response rate.
- Stimulants are FDA approved for treatment of ADHD in children and adults

Stimulant Alternatives/Adjuncts

Alpha-2 Agonists	Short Acting	Long Acting
	Clonidine (Catapres)	Clonidine ER (Kapvay)
	Guanfacine (Tenex)	Guanfacine ER (Intuniv)
Atomoxetine (Strattera)		

Alpha-2 Agonists

Clonidine (Catapres/Kapvay) & Guanfacine (Tenex/Intuniv)

- Action in Prefrontal Cortex helps ADHD
- Action in Brain Stem can decrease sympathetic activity, decrease blood pressure
 - Side effects are largely from decreased sympathetic activity (i.e., dry mouth, sedation)
 - Hypotension
- Takes weeks to see full effect

Alpha-2 Agonists

Clonidine (Catapres/Kapvay) & Guanfacine (Tenex/Intuniv)

- Pros:
 - Moderately effective (hyperactivity & impulsivity, insomnia, treatment emergent tics, & aggression)
- Cons:
 - Side Effects: Rebound HTN/tachycardia, hypotension, sedation, dizziness, constipation, H/A, fatigue, sudden death in combination with stimulants
 - Contraindications: CAD, impaired liver/renal function

Alpha-2 Agonists

Routine PE/VS prior to initiation of Rx

Contraindications: CAD, impaired liver/renal function

Side Effects: Rebound HTN/tachycardia, hypotention, sedation, dizziness, constipation, H/A, fatigue

Dosage: Start with HS and titrate toward morning(or afternoon)

Monitor BP, but ECG not routinely necessary

Guanfacine (Tenex)

<45 kg start 0.5mg at
bedtime >45 kg start 1mg
at bedtime

Can increase to 0.5 bid-tid
for total of 2mg (<40kg); 3
mg (<45kg); 4mg (>45kg)

Guanfacine ER(Intuniv)

1 mg to 7mg (0.05-0.12 mg/kg)
once daily

- 6-12 not much data over 4mg
- 13 and above not much data over 7mg

Begin at a dose of 1 mg once daily at night and adjust 1 mg/week.

Can change to AM once child/adolescent adjusts to dose

Guanfacine ER (Intuniv)

Do not

- Crush, chew or break tablets before swallowing.
- Administer with high-fat meals,
- Substitute with short acting guanfacine 1-1 (different pharmacokinetic profiles)
- Cross titrate with short acting (stop short acting then start long-acting)

Do: discontinue with a taper (1 mg every 3 to 7 days to avoid rebound hypertension.)

Clonidine (Catapres)

- Start - <45kg 0.05mg at bedtime
>45kg 0.1mg at bedtime
- Titrate – <40kg 0.2mg; <45
0.3mg; >45 0.4mg
- Sedation decreases with time
- Often only given at bedtime, but
can be given more than once a
day
- Additional evidence in Tourette's

Kapvay (Clonidine ER)

- Dosing 0.1-0.2 bid at am and bedtime – increase by 0.1 every week
- More common side effects may include: drowsiness, tiredness, irritability, nightmares, sleeplessness, constipation, dry mouth, decreased appetite, dizziness.
- Less common side effects may include: low blood pressure, low heart rate
- Tablets should not be crushed, chewed or broken before swallowing.
- Do not substitute for other clonidine products on a mg-per-mg basis, because of differing pharmacokinetic profiles.
- When discontinuing, taper the dose in decrements of no more than 0.1 mg every 3 to 7 days.

Atomoxetine (Strattera): Efficacy in Children & Adolescents

- 24-hour duration of action with once-daily dosing
- Incidence of insomnia comparable with placebo (for children/adolescents)
- Not contraindicated in patients with tics and anxiety
- Nonstimulant/noncontrolled substance
- May improve some measures of functional outcome (not just core ADHD symptoms)
- DOSING:
 - 0.5 mg/kg qam (e.g. 10mg x4d, then double)
 - 1.4mg/kg or 100mg

Atomoxetine (Strattera): Side Effects

- Children and Adolescents:
 - Decreased appetite (15%)
 - Av. wt loss of 2 – 4 LB in first 3 months, then resume normal growth
 - Dizziness (5%)
 - Dyspepsia (5%)
 - Sedation
 - BP/HR
- Liver Toxicity – rare side effect
- Has black box warning for suicidality.

When to consider Atomoxetine (Strattera)

- History of adverse effect to stimulants
- Comorbid anxiety, depression, tics, enuresis or Tourette's
- Require 24 hour symptom relief
- Severe stimulant rebound
- Personal or family history of substance abuse
- Concern about insomnia or appetite suppression

Atypical Antipsychotics

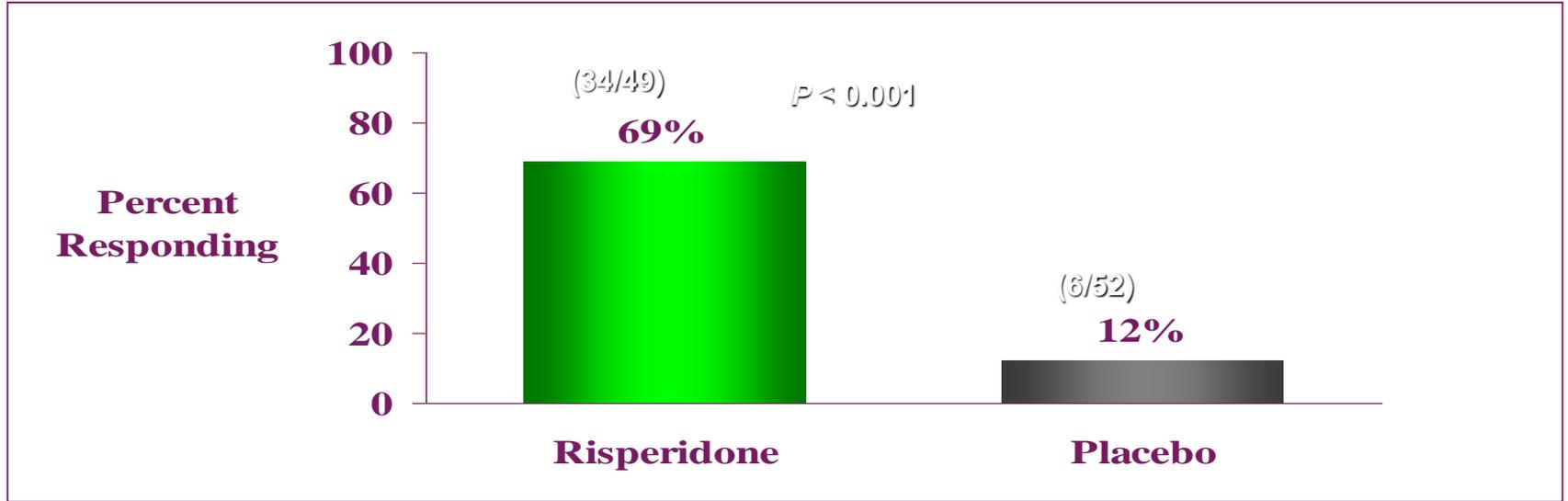
- Activate dopamine neurons in prefrontal cortex and limbic regions
- Decrease agitation/irritability, but also affects hyperactivity
- Not an option unless have additional co-morbid diagnoses (or dangerous ADHD symptoms)
- Risperidone, quetiapine, ziprasidone, aripiprazole and olanzapine



RUPP-PI Design

- 24-week, D-B trial
- N=49 for Med alone; N=75 for Med + PMT
- Age: 4-13 years, IQ>35, ABC Irritability subscale \geq 18
- Autistic, PDD-NOS, or Asperger's Disorder
- Taking no other psychotropic medications

Acute Risperidone Trial: RUPP (N=101)



Risperidone Hyperactivity Effects in ASD (RUPP)

Mean ABC Hyperactivity Subscale (p<0.001)

	<u>Baseline</u>	<u>8 Week</u>
Risperidone	31.8±9.6	17.0±9.7
Placebo	32.3±8.5	27.6±10.6

Using Risperidone – by the book(PDR)

Autism

- Irritability associated with autistic disorder in children aged 5-16 years
 - 5-16 years (<20 kg): 0.25 mg/day PO initially; may be increased after ≥ 4 days to recommended dosage of 0.5 mg/day
 - 5-16 years (≥ 20 kg): 0.5 mg/day PO initially; may be increased after ≥ 4 days to recommended dosage of 1 mg/day
- Insufficient response to recommended dosage
 - dosage may be adjusted after minimum of 14 days and at least every 2 weeks thereafter
 - <20 kg: Adjusted in increments of 0.25 mg/day; not to exceed 1 mg/day
 - ≥ 20 kg: Adjusted in increments of 0.5 mg/day; not to exceed 2.5 mg/day

Using Aripiprazole – by the Book(PDR)

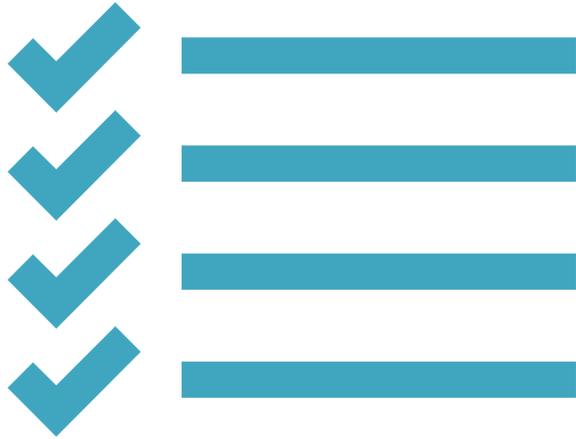
Autism

- Indicated for irritability associated with autistic disorder
- <6 years: Safety and efficacy not established
- 6-17 years: 2 mg/day PO initially; increase gradually at ≥ 1 week intervals to target dosage of 5 mg/day; may gradually be further increase PRN to 10 mg/day or higher; not to exceed 15 mg/day



Parent training

Parent Management Training

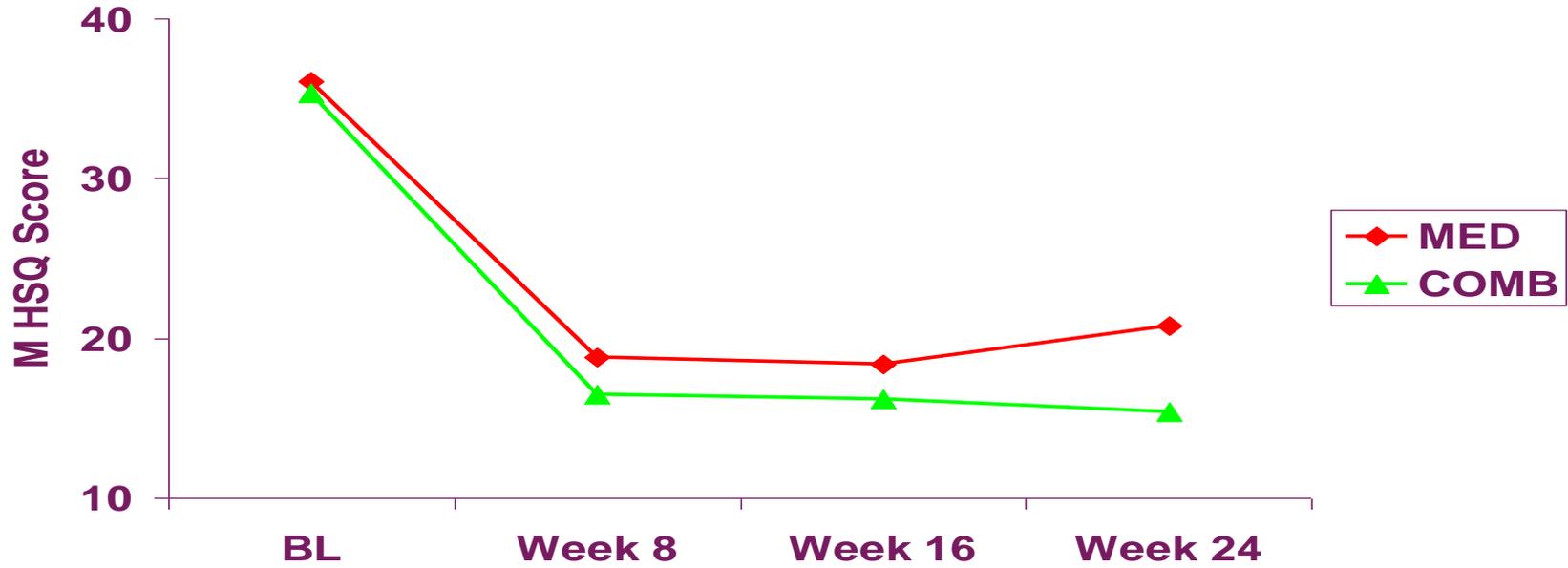


- Eleven core sessions within first 16 weeks
 - (Basics of ABA, Prevention Strategies, Reinforcement, Planned Ignoring, Compliance Training)
- Five optional sessions (e.g., time out, sleep problems)
- Twice monthly booster sessions from weeks 16-24

RUPP-PI Study of Risperidone and Parent Training

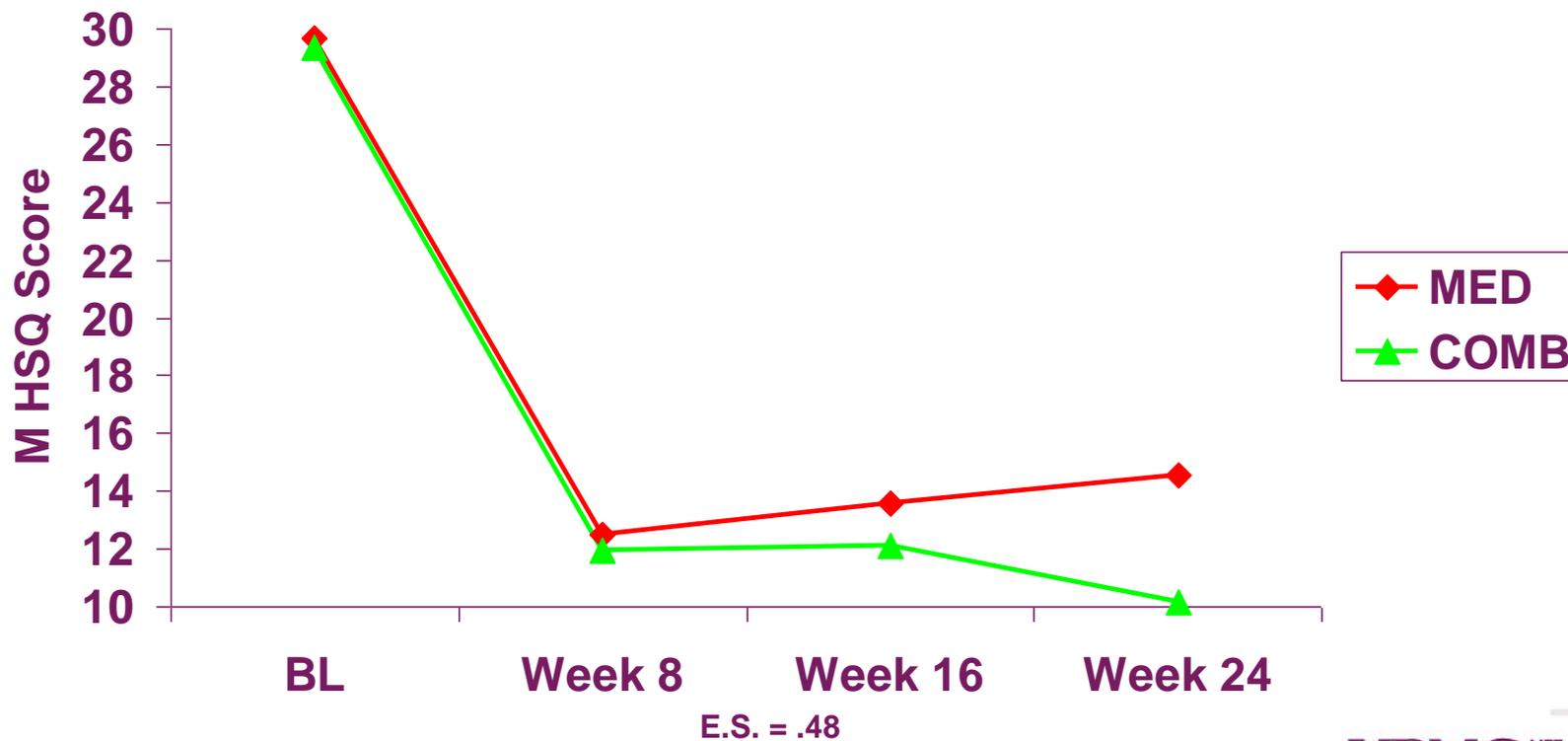


ABC Hyperactivity/Noncompliance



E.S. = .55

ABC Irritability



Risperidone dose and parent training

- Risperidone dose was 12% lower with combined treatment
- 2.26 mg/day vs 1.98 mg/day ($p=.04$)

Summary

- A large number of children with ASD display ADHD symptoms
- Strong support for stimulants and risperidone (risperidone should be limited to more severe cases)
- Moderate support for atomoxetine, clonidine and guanfacine
- Children with ASD are more prone to side effects and response rates tend to be lower in comparison to typically developing children (especially for stimulants, atomoxetine, and clonidine/guanfacine)

Thank You