Pharmacological Strategies in Complex ADHD

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Faculty Disclosure

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- Kempharm, Otsuka, NIH (NIDA), Ironshore, Vallon
- Licensing agreement with Ironshore (Before School Functioning Questionnaire)
- Clinical care: MGH, Bay Cove Human Services, Gavin/Phoenix, National Football League (ERM Associates), Major/Minor League Baseball
- (Co)Edited Straight Talk About Psychiatric Medications for Kids (Guilford); ADHD Across the Lifespan (Cambridge) , MGH Comprehensive Clinical Psychiatry (Elsevier), MGH Psychopharmacology and Neurotherapeutics (Elsevier)

Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), combinations, age groups, dosing, or in context to other disorders (e.g., substance use disorders)

Methylphenidate (MPH) in ADHD

Medication	Starting Dose	Maximum Dose*	Duration
Ritalin IR®	5 mg QD/BID	2 mg/kg/day	4 hr /BID
Focalin®	2.5 mg QD/BID	1 mg/kg/day	4–5 hr / BID–TID
Focalin XR	5 mg QD	1 mg/kg/day	10–12 hr QD
Daytrana®	10 mg		6–16 hr
Concerta®	18 mg QD	2 mg/kg/day	12 hr / once
Metadate CD	20 mg QD		8 hr / once
Ritalin LA	20 mg QD		8 hr /once
Quillivant®	<10 mg QD		12 hr /once
Quillichew	<10 mg QD		8 hr /once
Contempla XR (dissolve tab)	8.6 mg QD	51.8 mg	12 hr/once
Aptensio XR	10 mg QD	2 mg/kg/day	12 hr/once
Adhansia XR	25 mg QD		To 16 hr/once
Jornay (delayed release)	20 mg QD	100 mg	12 hr/once

***May exceed FDA approved dose.**

Listed above are brand names for methylphenidate in various forms
QD = 4 times a day; BID = 2 times a day; TID = 3 times a day

Wilens TE, et al. *CNS News*. 2007. Wilens TE, et al. *Postgrad Med*. 2010;122(5):97-109. Adler, Spencer, Wilens *ADHD in Children and Adults*, Cambridge Press, 2015 www.drugs.com.

Amphetamine (AMPH) in ADHD

May exceed FDA approved dose (e.g., > 20 to 30 mg/day).

Medication	Starting Dose	Maximum Dose* Usual Dosing	Duration
Adderall	2.5–5 mg QD	1.5 mg/kg/day	6 hr / BID
Adderall XR	2.5–5 mg QD		12 hr / QD
Vyvanse	30 mg QD		12–14 hr / QD
Mydayis	12.5 mg QD	50/25 mg (adults/adol)	To 16 hr/QD
Dexedrine Tablets	2.5–5 mg BID	1.5 mg/kg/day	3–5 hr / BID–QID
Evekeo	2.5–5 mg BID		3–5 hr / BID–QID
Dexedrine Spansule	5 mg QD		6 hr / QD–BID
Dyanavel XR (suspension)	2.5–5 mg QD	1.5 mg/kg/day	13 hr / QD
Adzenys XR (dissolve tab)	6.3–12.5 mg QD	12.5 mg (adolescents)	12 hr / QD

Listed above are brand names for mixed amphetamine in various forms

Wilens TE, et al. *CNS News*. 2007. Wilens TE, et al. *Postgrad Med*. 2010;122(5):97-109. Adler, Spencer, Wilens *ADHD in Children and Adults*, Cambridge Press, 2015 www.drugs.com.

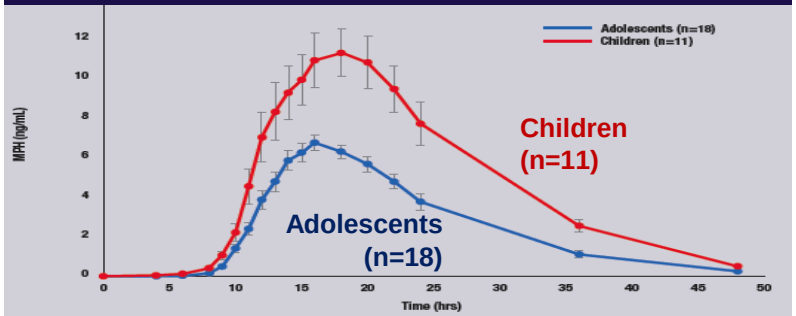
Night-Time Administered Delayed/Extended Release MPH for ADHD: Jornay

Consider for early-morning difficulties, parents who work in early AM

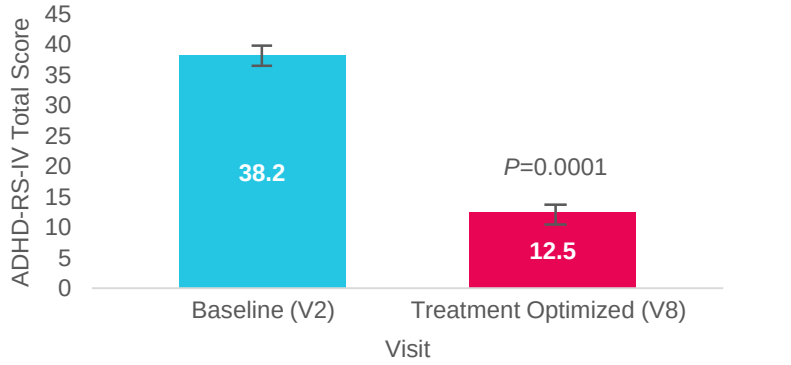
Newly approved extended-release methylphenidate

Formulation: PM administration ➔ AM release
Dosing: 20 – 100 mg QD
Capsules: 20, 40, 60, 80, 100 mg
Duration of action: 12+ hours

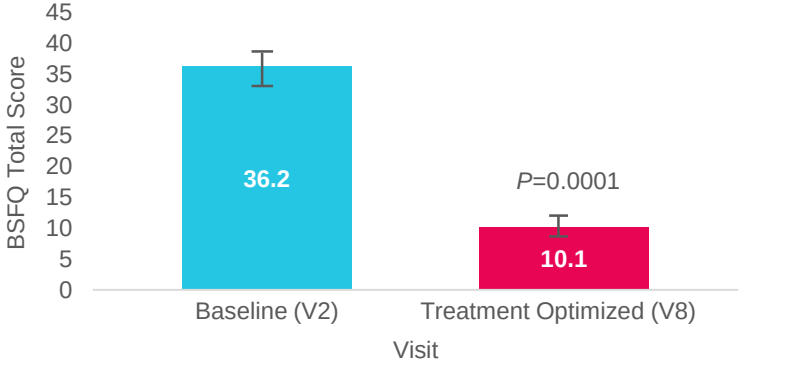
Mean Observed MPH Plasma Concentration (± S.E.M.) Following a Single Evening Administration of HLD200 (54 mg)



ADHD-RS-IV Total Score at Visit 2 and Visit 8



BSFQ Total Score at Visit 2 and Visit 8



Ironshore Pharmaceutical 6-week open study (presented) followed by controlled trial (not shown) n=43 children aged 6-12 years
Findings: Improvement in ADHD RS, Before School Functioning Scale, DPRMB
Adverse effects: Stimulant like—no major effects on sleep

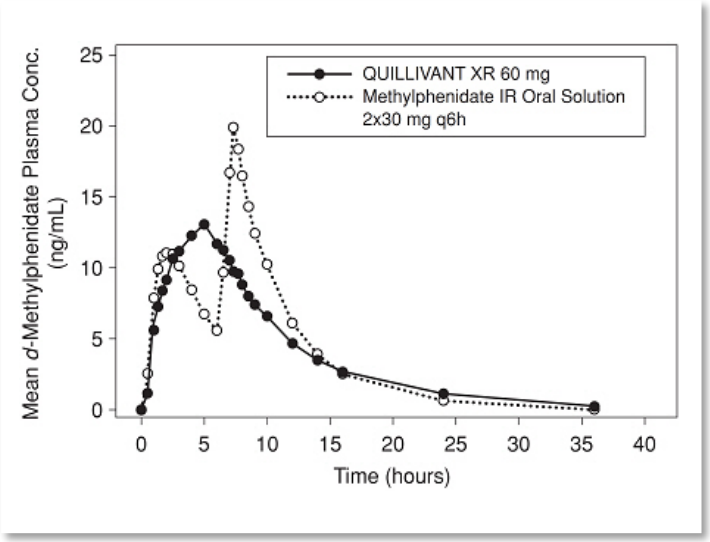
Drugs.com; Plizka et al, *J Child Adolesc Psychopharm* 2017; Wilens et al., APSARD 2018; Wigal et al. AACAP 2018

Extended Release MPH Solution and Chewable Preparations

Consider for difficulty swallowing pills

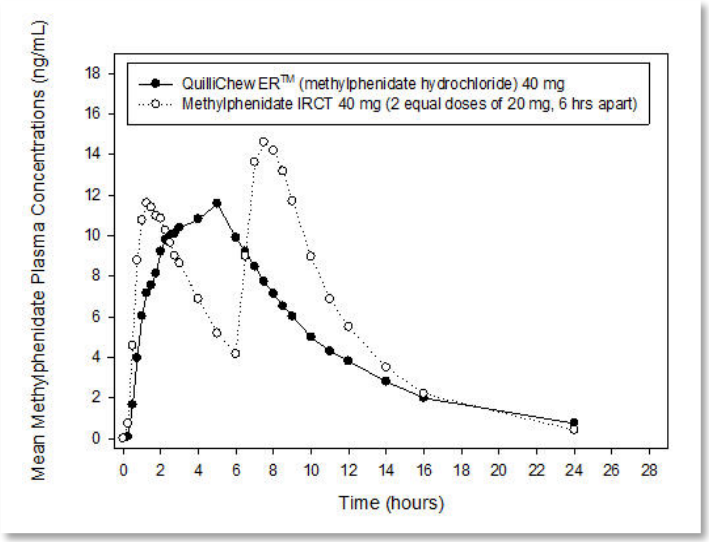
Quillivant XR

- Suspension
- 12 hour duration
- 25 mg/5 cc (tsp)
- Dosing to 60 mg daily
- Approved in pediatrics



QuilliChew ER

- Chewable tablet
- 8 hour duration
- 20 s, 30 s, 40 mg tablets
- Dosing to 60 mg daily
- Approved in pediatrics



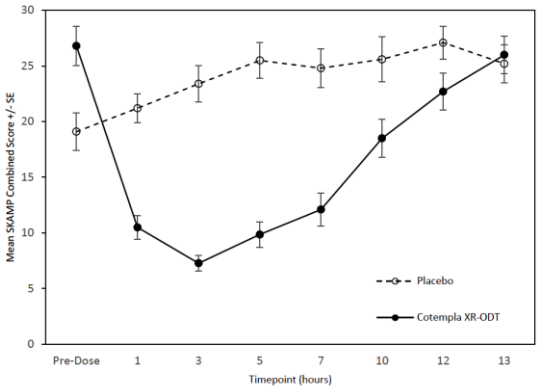
Rx list.com; PI

Extended-Release Compounds

Consider for difficulty swallowing pills

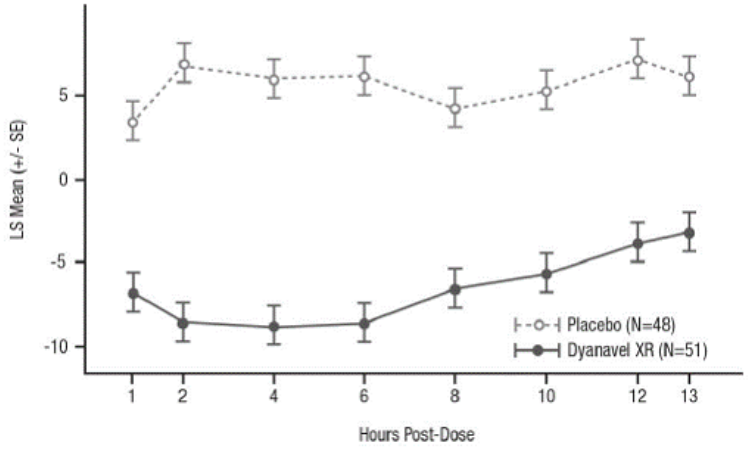
Extended-release methylphenidate (Contempla XR)

- Formulation: oral disintegrating tablets
- Dosing: 8.6 – 25.9 mg QD
- Tablets: 8.6, 17.3, 25.9 mg
- Duration of action: 12 hours



Amphetamine extended release (Dynavel)

- Composition: Suspension of 3.2 to1 ratio of d- to l-amphetamine
- Dosing: 2.5 to 5 mg QD
- Duration of action: 13 hours



Drugs.com

Extended-Extended Release AMPH [Mydayis®] or MPH [Adhansia XR] for Adult / Adolescent ADHD

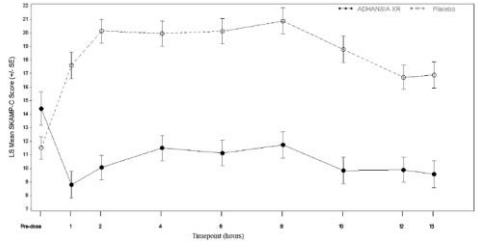
Consider for Very Extended Coverage

- **Mydais**: "Very" extended mixed AMPH (eg, XR2)
- Composition: Mixed AMPH salts
- Dosing: 12.5 to 25 mg QD (> 13 years old) or 50 mg (adults)
- Capsules: 12.5, 25, 37.5, 50 mg
- Duration of action: 16 hours (onset at 2 to 4 hours)

- **Adhansia XR**: MPH product
- Capsules: 25, 35, 45, 55, 70, or 85 mg

(up to 100 mg tested in adults)

- Duration of action: 16 hours (onset within 1 hr)



LS = Least squares.
SE = Standard Error.
The raw mean and SE bars are presented at the pre-dose timepoint, rather than the LS mean and SE bars.

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

For Early AM ADHD Management Guanfacine XR Has Similar Efficacy with AM or PM Administration

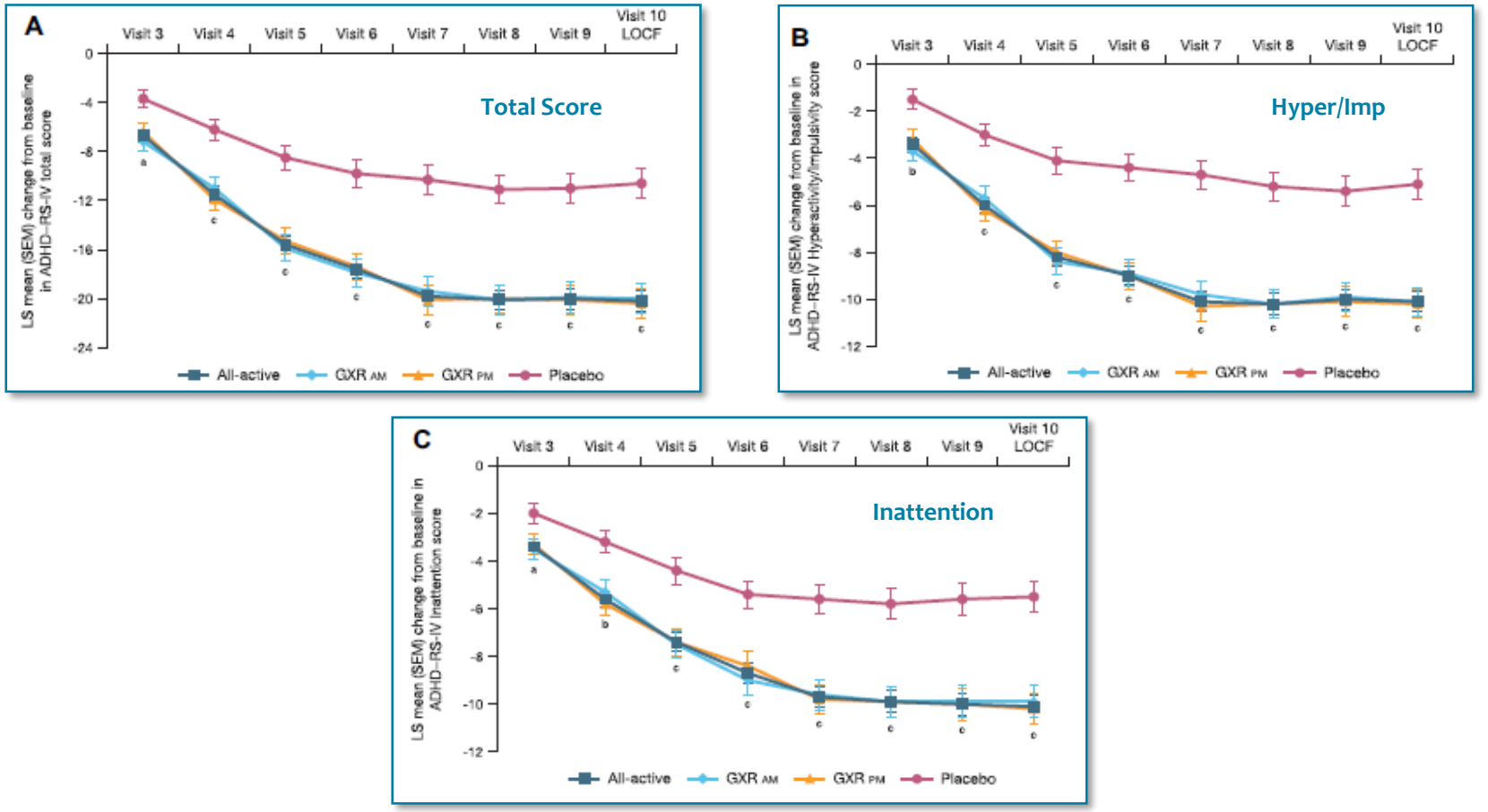


FIGURE 2 Mean change from baseline in attention-deficit/hyperactivity disorder (ADHD) Rating Scale–IV (ADHD-RS-IV) scores by visit. Note: (A) Total score. (B) Hyperactivity/Impulsivity subscale. (C) Inattention subscale. All *p* values are based on type III sum of squares from an analysis of covariance (ANCOVA) model. GXR = guanfacine extended release; LOCF = last observation carried forward; LS = least squares; SEM = standard error of the mean. [c]$p < .05$ versus placebo based on change from baseline (visit 2). [b]$p < .01$ versus placebo based on change from baseline (visit 2). [a]$p < .001$ versus placebo based on change from baseline (visit 2).

6 to 12 years, dosing 1 to 4 mg/day. GXR AM (n=107), GXR PM (n=114), or placebo (n=112).

Newcorn JH, et al. *J Am Acad Child Adolesc Psychiatry*. 2013;52(9):921-930.

Refractory ADHD

Prominent Executive Function Deficits

- Organizational training/coaching (focus on specific dysfunction)
- Use of norepinephrine agent - ATMX, alpha agonist, TCA, bupropion (alone or combined with stimulant, modafinil)*
- Memantine* (alone, in combination with stimulants)
- Vortioxetine* (anecdotal only)
- Investigational:
  - Nicotinic/cholinergic agents*
    - Indirect: donepezil, galantamine
      - Systematic data negative
      - Case reports positive
    - Direct: nicotinic agents/gum/patch*
  - Triamine reuptake inhibitors*

***Not FDA approved for ADHD**

Adler, Spencer, Wilens (eds) *ADHD Across Lifespan*:Cambridge Press 2015

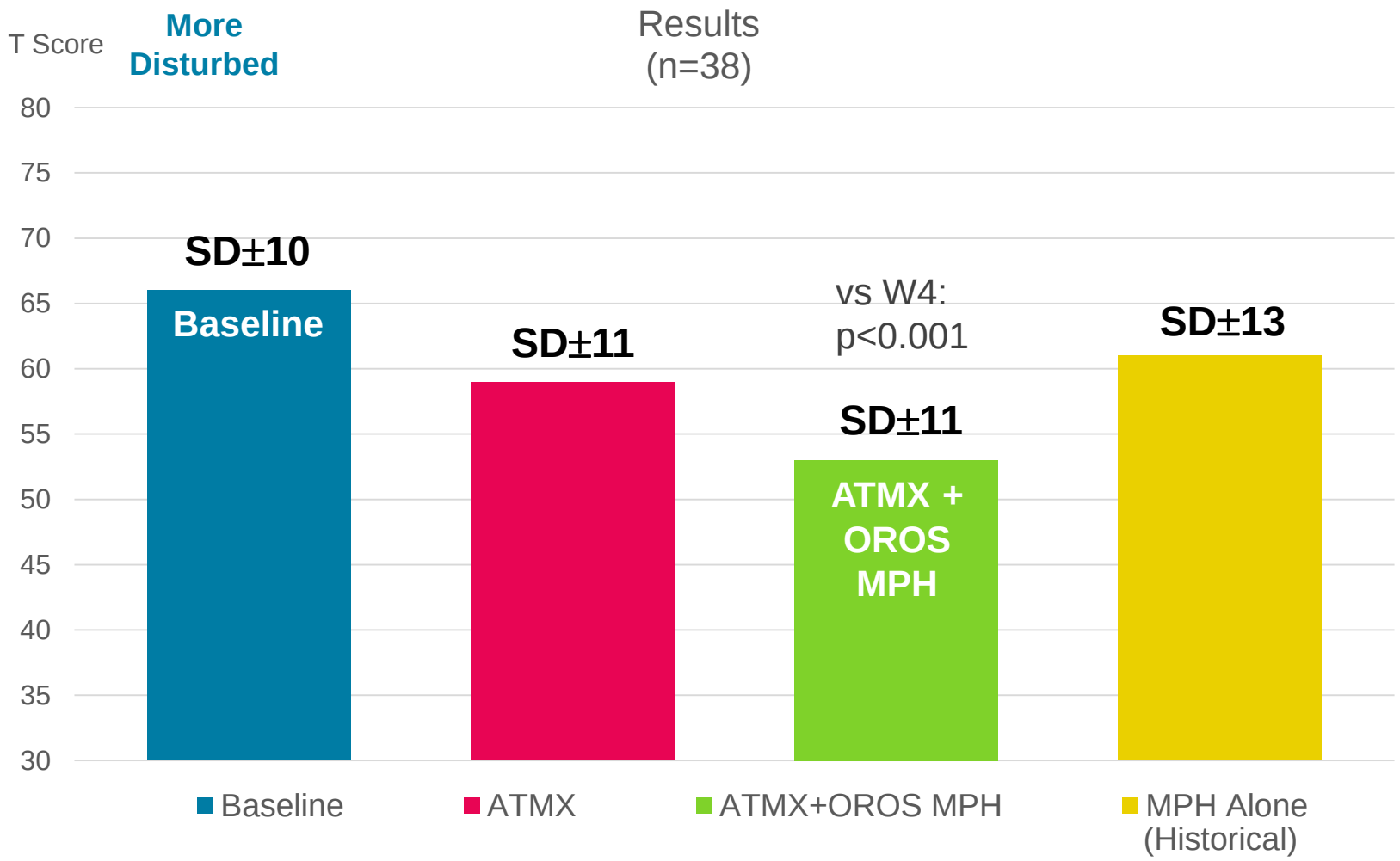
Combination of Atomoxetine (ATMX) plus Stimulants in the Treatment Of ADHD

- Qualitative analysis of existing studies
  - N = 3 prospective (1RCT)+ 7 retrospective reports
- Predominately children/adolescent with inadequate response to stimulants
- Most often used stimulant = methylphenidate
- Conclusions
  - Small sample sizes
  - *"Existing evidence suggests, but does not confirm, that this drug combination may benefit some, but not all, patients who have tried several ADHD medications without success"*

Truer et. al. *J Child Adolesc Psychopharmacol*. 2013 Apr; 23(3): 179–193

Osmotic-Release Oral System (OROS) MPH plus ATMX*

Improvement Characterized by the BRIEF: Initiation



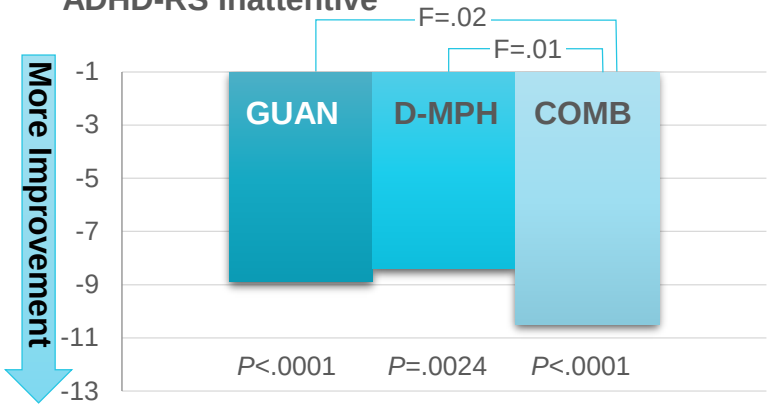
*Not FDA approved for ADHD

Wilens et al. J Child Adolesc Psychopharm: 2009

Combined (COMB) Stimulant and Guanfacine for ADHD: Comparative Study

8-week RCT, 3-arm trial in 207 participants

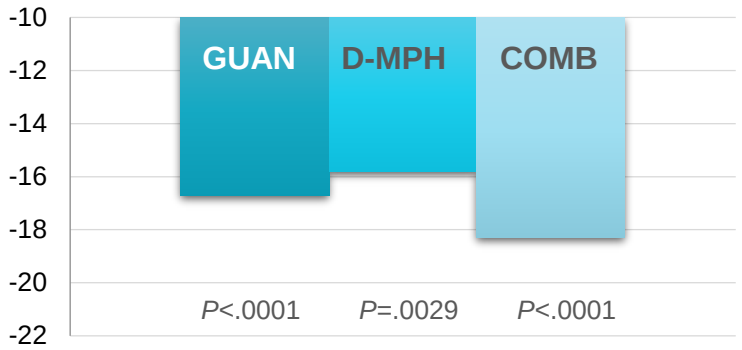
ADHD-RS Inattentive*



Med Group $p<0.0001$; Visit $p=0.0002$

Baseline:	21.1	21.3	20.4

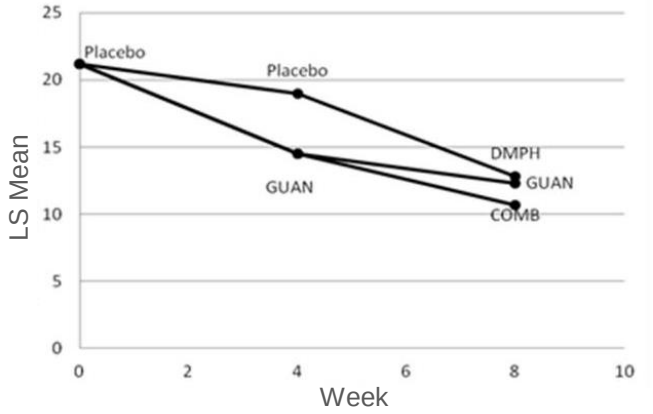
ADHD-RS Total*



Med Group $p<0.0001$; Visit $p=0.0002$

Baseline:	36.8	35.6	35.6

ADHD-RS-IV Inattention Subscale
LS Means for Current Treatment By Time



Age: 7 – 14 years

Sample Size: GUAN (n=68), D-MPH (n=69), COMB (n=70)

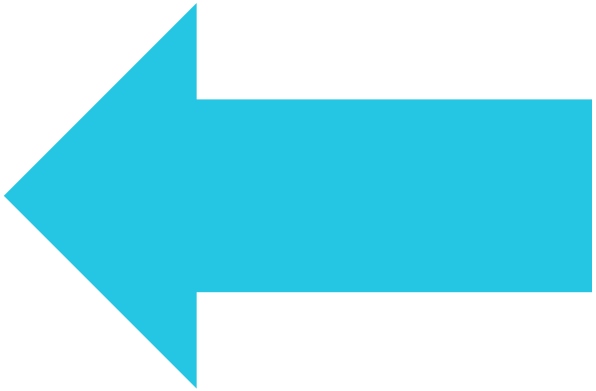
Dosing: GUAN (1-3 mg/day), D-MPH (5-20 mg/day)

***Denotes least squares mean end point changes in ADHD Rating Scale Score versus baseline**

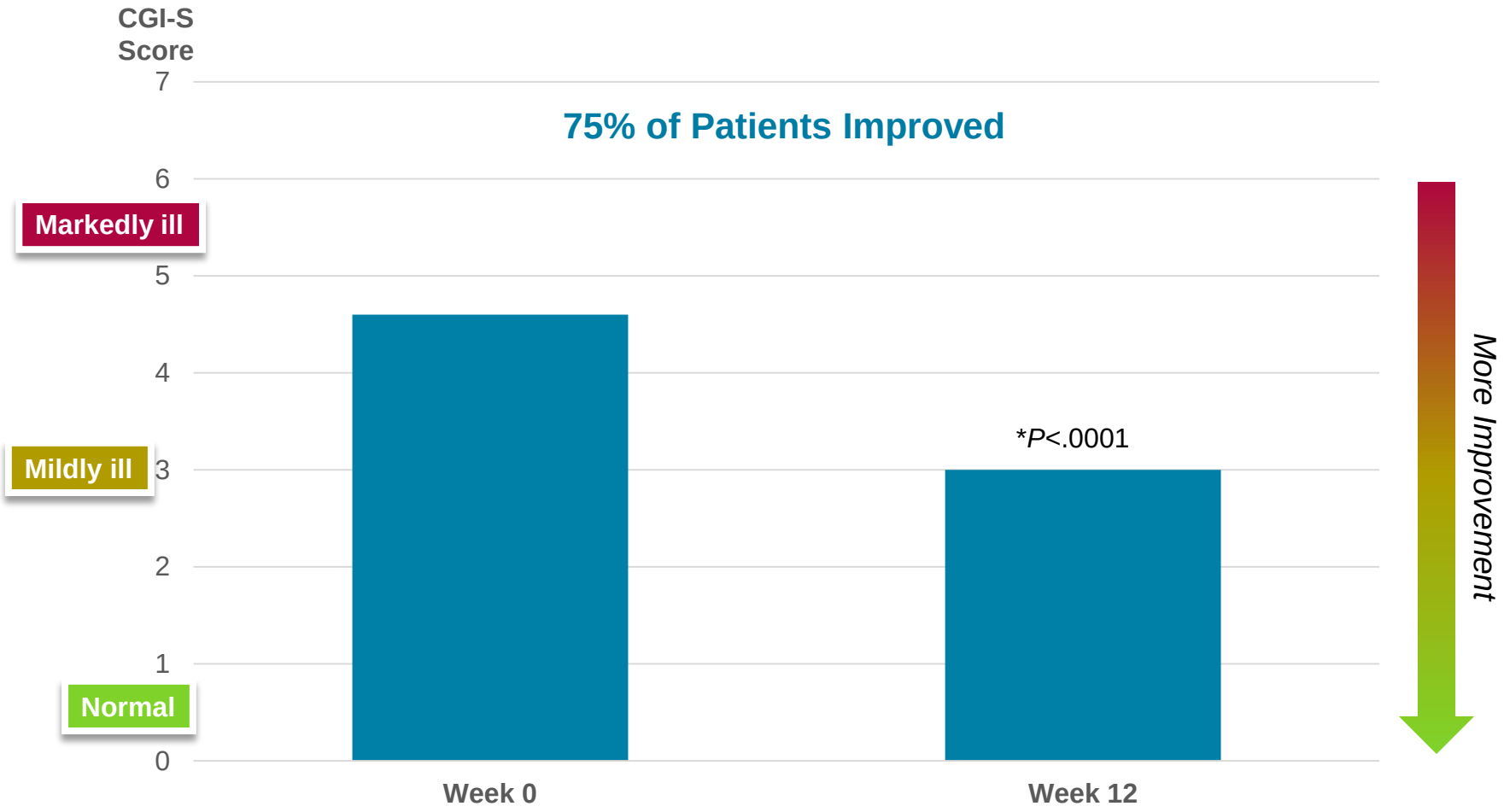
McCracken JT et al. Combined Stimulant and Guanfacine Administration in ADHD: A Controlled, Comparative Study. *J Am Acad Child Adolesc Psychiatry*. 2016 Aug;55(8):657-666

Pharmacotherapy of ADHD Comorbidity

- Evidence of improved ADHD outcome with *treated comorbidity*
  - Anxiety
  - Substance Use Disorders
  - Mood
    - Dysregulation
    - Depression
    - Bipolar disorder



MGH Open Study:
Fish Oils Reduce Emotional Dysregulation in Medication-Treated Children with ADHD



N=10. CGI-S = CGI–Severity.

Wilens TE, et al. *J Child Adolesc Psychopharmacol*. 2017;27(8):755-756.

Bupropion in Adolescents with Comorbid ADHD and Depression

*(**Note: ADHD improved in those with improved depression**)*

Objective: To determine whether bupropion sustained release (SR) is effective and well-tolerated in adolescents with comorbid attention-deficit/hyperactivity disorder (ADHD) and depression.

Method: Subjects were 24 adolescents (aged 11-16 years old) with ADHD and either major depressive disorder or dysthymic disorder. After a 2-week, single-blind placebo lead-in, subjects were treated for 8+ weeks with bupropion SR at doses flexibly titrated up to 3 mg/kg b.i.d. (mean final doses: 2.2 mg/kg q A.M. and 1.7 mg/kg q P.M.). Outcomes were global improvement in ADHD and depression (clinician-rated), along with changes in depressive symptomatology (parent- and child-rated), ADHD symptomatology (parent- and teacher-rated), and functional impairment (parent-rated).

Results: Clinicians rated 14 subjects (58%) responders in both depression and ADHD, 7 (29%) responders in depression only, and 1 (4%) a responder in ADHD only. Compared with post-placebo ratings, final parents' ($p < .0005$) and children's ($p = .016$) ratings of depressive symptomatology improved significantly, as did parents' ($p < .0005$) but not teachers' ($p = .080$) ratings of ADHD symptomatology. Final ratings of functional impairment improved significantly from enrollment ($p < .0005$). No subject discontinued medication because of side effects.

Conclusions: Bupropion SR may be effective and well-tolerated in adolescents with comorbid ADHD and depressive disorders. However, randomized, placebo-controlled studies are needed.

Paroxetine & AMPH for ADHD in adults

- Multisite 5 month RCT in 98 adults with ADHD
- 50% with lifetime comorbid MDD or ANX
- Paroxetine, d-AMPH, Combination, Placebo
- Findings:
  - Paroxetine had no effect on ADHD
  - D-AMPH + paroxetine/placebo effective for ADHD
  - Trend to improvement in mood and anxiety in paroxetine groups (low HAM scores to start; CGI showing improvement)
  - Additive side effects with paroxetine and d-AMPH

Weiss M et al, J Clin Psych 2006: 67(4):611-9

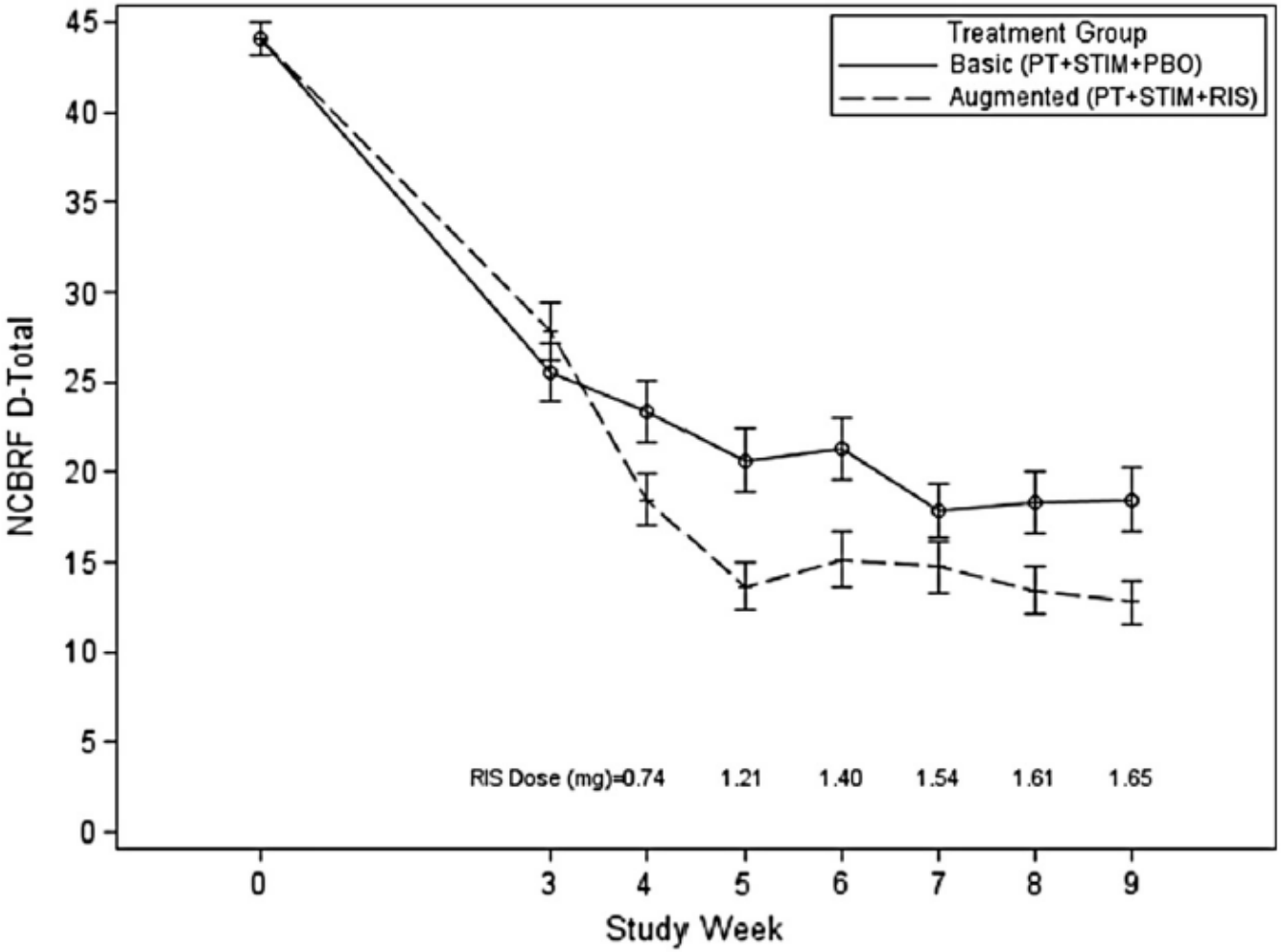
What Does Risperidone Add to Parent Training and Stimulants for Severe Aggression in Child ADHD?

- 4-site RCT
- ADHD plus severe physical aggression (ODD N=124; CD N=84)
- 9 week trial comparing PT + STIM + placebo (Basic treatment; n=84) with PT + STIM + RIS (Augmented treatment; n=84)
- Children received psychostimulant (usually OROS methylphenidate) for 3 weeks, titrated for optimal effect, while parents received PT
- If there was room for improvement at end of week 3, placebo or risperidone was added
- Assessments included parent ratings on the Nisonger Child Behavior Rating Form (Disruptive-Total subscale was the primary outcome) and Antisocial Behavior Scale; blinded clinicians rated change on the Clinical Global Impressions Scale

Aman MG, Bukstein OG, Gadow KD, et al. What does risperidone add to parent training and stimulant for severe aggression in child attention-deficit/hyperactivity disorder? J Am Acad Child Adolesc Psychiatry 2014 Jan;53(1):47-60 e41.

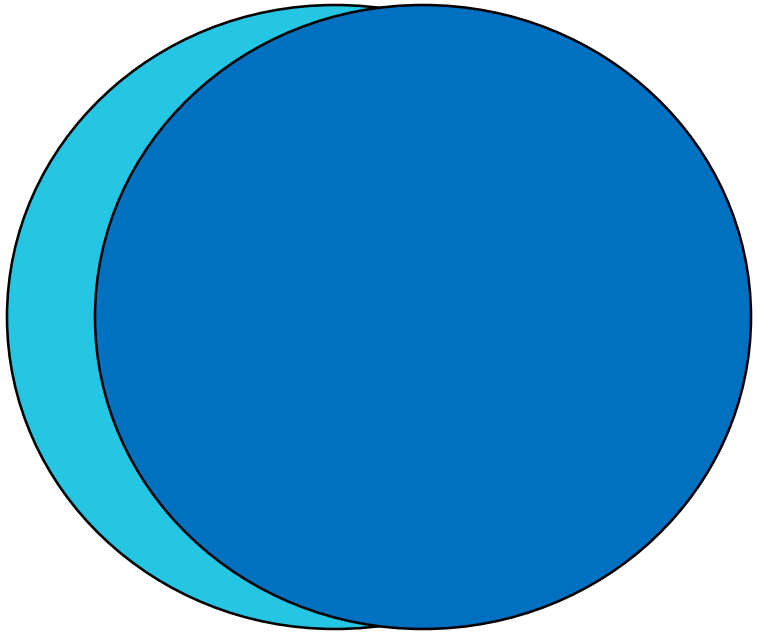
Risperidone Improved Outcome in Stimulant Treated Aggressive Children with ADHD

(treatment-by-time interaction, p=0.0049)



Aman MG, Bukstein OG, Gadow KD, et al. What does risperidone add to parent training and stimulant for severe aggression in child attention-deficit/hyperactivity disorder? J Am Acad Child Adolesc Psychiatry 2014 Jan;53(1):47-60 e41.

ADHD & BPD in Youth



Joshi, G, Wilens TE. Comorbid Conditions in Youth with and At Risk for Bipolar Disorder. In: Strakowski S, Delbello M, and Adler C (eds). Bipolar Disorder in Youth: Presentation, Treatment and Neurobiology. Oxford University Press, 2015. 56-93

Effect of Methylphenidate on ADHD in Stabilized Youth with Bipolar Disorder

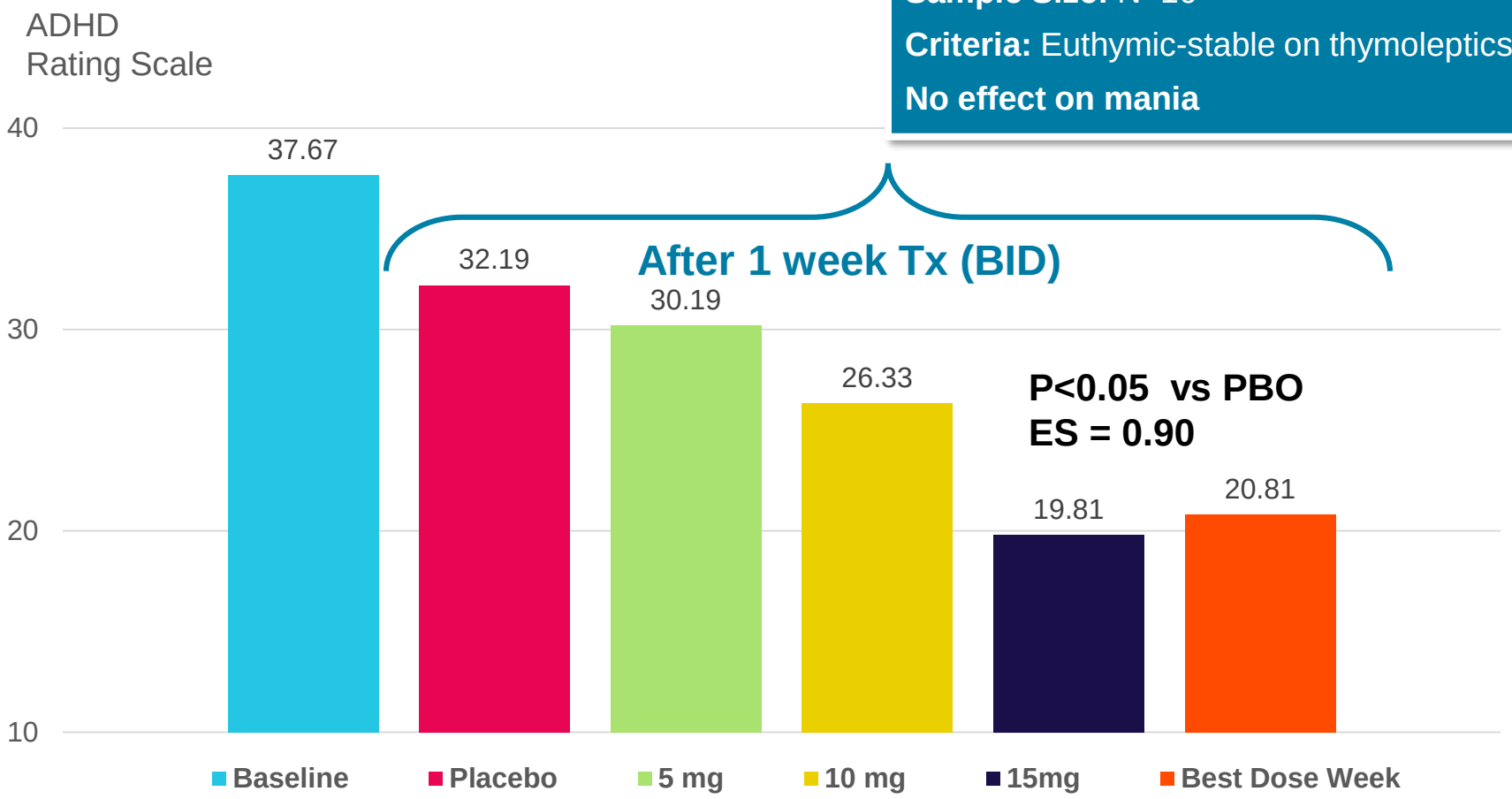
Measures at Baseline and After 1 Week of Treatment

Age: 4 – 17 (mean 11 yrs)

Sample Size: N=16

Criteria: Euthymic-stable on thymoleptics

No effect on mania



ARS-IV: Parent-completed ADHD Rating Scale-IV

Findling R. et al., *JAACAP* 2007. 46:11:1445-1453

Stimulants Do Not Activate Mania in Mood-Stabilized Adults with Bipolar and ADHD

Results from the Swedish Registry Study (N=2,307)

TABLE 2. Risk of Mania in Patients With Comorbid Bipolar Disorder and ADHD Following Methylphenidate Treatment, Based on Mania Diagnoses and New Prescriptions for Antipsychotics and Mood Stabilizers[a]

Group	Hazard Ratio	p	95% CI	Mania Events (12-Month Follow-Up) N	Mania Events (12-Month Follow-Up) Rate[b]
No mood-stabilizing medication[c] (N=718)				61	0.08
0–3 months	6.67	0.002	1.98–22.4		
3–6 months	9.67	<0.001	2.94–31.7		
Mood-stabilizing medication[d] (N=1,103)				195	0.18
0–3 months	0.56	0.010	0.36–0.87		
3–6 months	0.91	0.758	0.50–1.67		

Viktorin A, et al. *Am J Psychiatry*. 2017 Apr 1;174(4):341-348.

Summary

- Consider dose-response issues when using stimulants to enhance response rate.
- New stimulant preparations may improve outcomes.
- Use of combined pharmacotherapy/psychotherapy may be necessary for refractory ADHD and/or ADHD with comorbidity.
- Mood dysregulation benefits from treatments of mood and of ADHD

QUESTIONS?