Optimizing Stimulant and Non-Stimulant Therapy For ADHD in Children, Adolescents, and Adults

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Optimal Management of ADHD

- What am I treating?
- What will I treat with?
- How do I know I made the right choice?
- What if it doesn't work?
- How long should I treat?

What Am I Treating?

- Diagnosis: both categorical and dimensional
- ADHD sx
- Impairment
- Associated problems: aggression, mood lability
  academic problems, socialization
- Common comorbidities

ADHD+ Emotional Lability

- Children: 6 RCTs SMD: 0.98 (ADHD sx); 0.57 (lability sx
- Adults 0.30 MPH for ADHD sx; 0.50 (lability)

- Label “Poor Response” with poor response to lability but good to core ADHD sx

- Some response vs optimal response

Evaluation: Baseline and Follow up

- **Baseline**
  - ❑ Establish diagnosis; quantitative severity
- **Rating Scales** (parent-caregiver/teacher); at dose changes
  - ❑ Child/adolescent: Vanderbilt Rating Scale
  - ❑ Adult: Adult ADHD Self-Report Scale
  - **Follow up**
    - ❑ Adverse events
    - ❑ Adherence to treatment plan
    - ❑ Vital signs: weight, height; blood pressure, hear rate

Informed Consent and Psychoeducation

- Informed consent
  - Psychoeducation
    - Potential benefits, adverse effects
    - Treatment course
- Patient/parent preferences
- Cooperative Decision making

Kamimura-Nishimura, Brinkman, Froehlich TE 2019

Effect Sizes of ADHD Medications

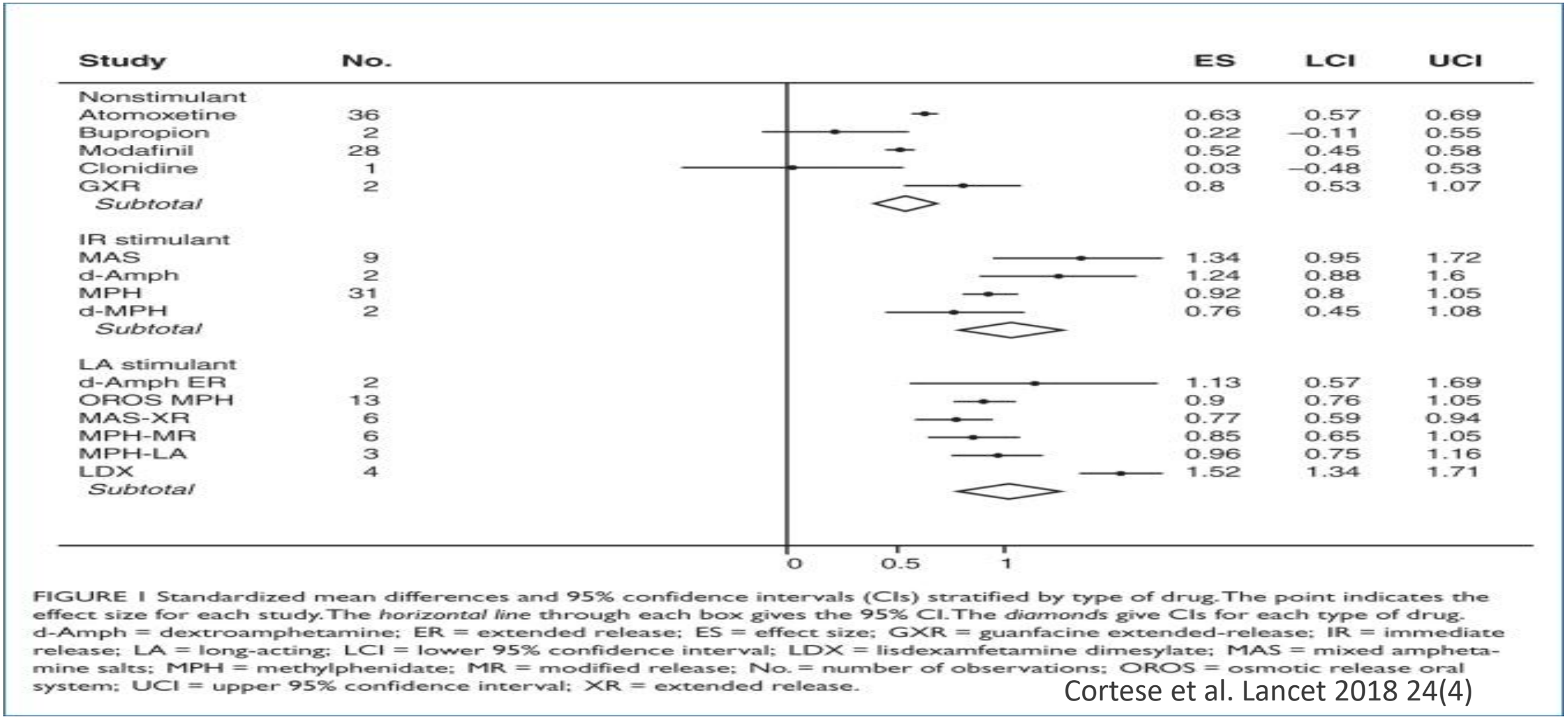


FIGURE 1 Standardized mean differences and 95% confidence intervals (CIs) stratified by type of drug. The point indicates the effect size for each study. The *horizontal line* through each box gives the 95% CI. The *diamonds* give CIs for each type of drug. d-Amph = dextroamphetamine; ER = extended release; ES = effect size; GXR = guanfacine extended-release; IR = immediate release; LA = long-acting; LCI = lower 95% confidence interval; LDX = lisdexamfetamine dimesylate; MAS = mixed amphetamine salts; MPH = methylphenidate; MR = modified release; No. = number of observations; OROS = osmotic release oral system; UCI = upper 95% confidence interval; XR = extended release.

Cortese et al. Lancet 2018 24(4)

Selection of an Agent: Effect Sizes

Standardized way to compare the strength of relationship between two variables

- Stimulants >0.8; 0.64 (adults)
  - Amphetamines 0.85-119 (children); 0.64 (adults)
  - Methylphenidate 0.78-0.92 (children) 0.9 (adults)
- Alpha agonists
  - Clonidine 0.58
  - Guanfacine 0.5
- Norepinephrine re-uptake inhibitors
  - Atomoxetine 0.30-0.60
  - Viloxazine 0.547-0.623

Cortese et al. Lancet 2018 24(4)

Network Meta-Analysis of ADHD Drug Clinical Trials (Cortese et al 2018)

Agents	**Efficacy**	Tolerability
Amphetamines	Greater reduction of ADHD scores No difference in efficacy between higher or lower doses	More side effects (compared with MPH)
Methylphenidate Bupropion atomoxetine	Superior to placebo	methylphenidate, and atomoxetine less tolerated than placebo
Modafinil Guanfacine Clonidine		Modafinil less tolerated than placebo

Selection of Medication and Formulation

- Stimulants
  - Methylphenidate
  - Amphetamine
  - Duration
    - Immediate Release (2-4 hours)
    - Intermediate release (6-8 hours)
    - Extended release (8-13 hours)

FDA-Approved Stimulants for ADHD

Trade Name	Generic Name	Approved Age (years)
Adderall®	Mixed amphetamine salts	3 and older
Adderall XR®	Mixed amphetamine salts (extended release)	6 and older
Concerta®	OROS methylphenidate (sustained release)	6 and older
Dexedrine® spanules	Dextroamphetamine (sustained release)	6 and older
Dexedrine®	Dextroamphetamine	3 and older
Dextrostat®	Dextroamphetamine	3 and older
Focalin™	Dexmethylphenidate	6 and older
Focalin XR™	Dexmethylphenidate (extended release)	6 and older
Metadate® ER	Methylphenidate (sustained release)	6 and older
Metadate® CD	Methylphenidate (extended release)	6 and older
Ritalin®	Methylphenidate	6 and older
Ritalin® SR	Methylphenidate (sustained release)	6 and older
Ritalin® LA	Methylphenidate (extended release)	6 and older

Newer Methylphenidate Formulations

- **QuilliChew ER** 20, 30, 40 mg.
- **Quillivant XR** suspension, extended release (25 mg per 5 mL or 5 mg per mL).
- **Methylin** 5 mg, 10 mg, and 20 mg
- **Methylin ER** 10 mg and 20 mg
- **Methylin Oral Solution**, 5 mg/5 mL, 10 mg/5 mL
- **Delexis** MPH DR/ER (taken in pm for am coverage) not yet marketed

Newer Amphetamine Formulations

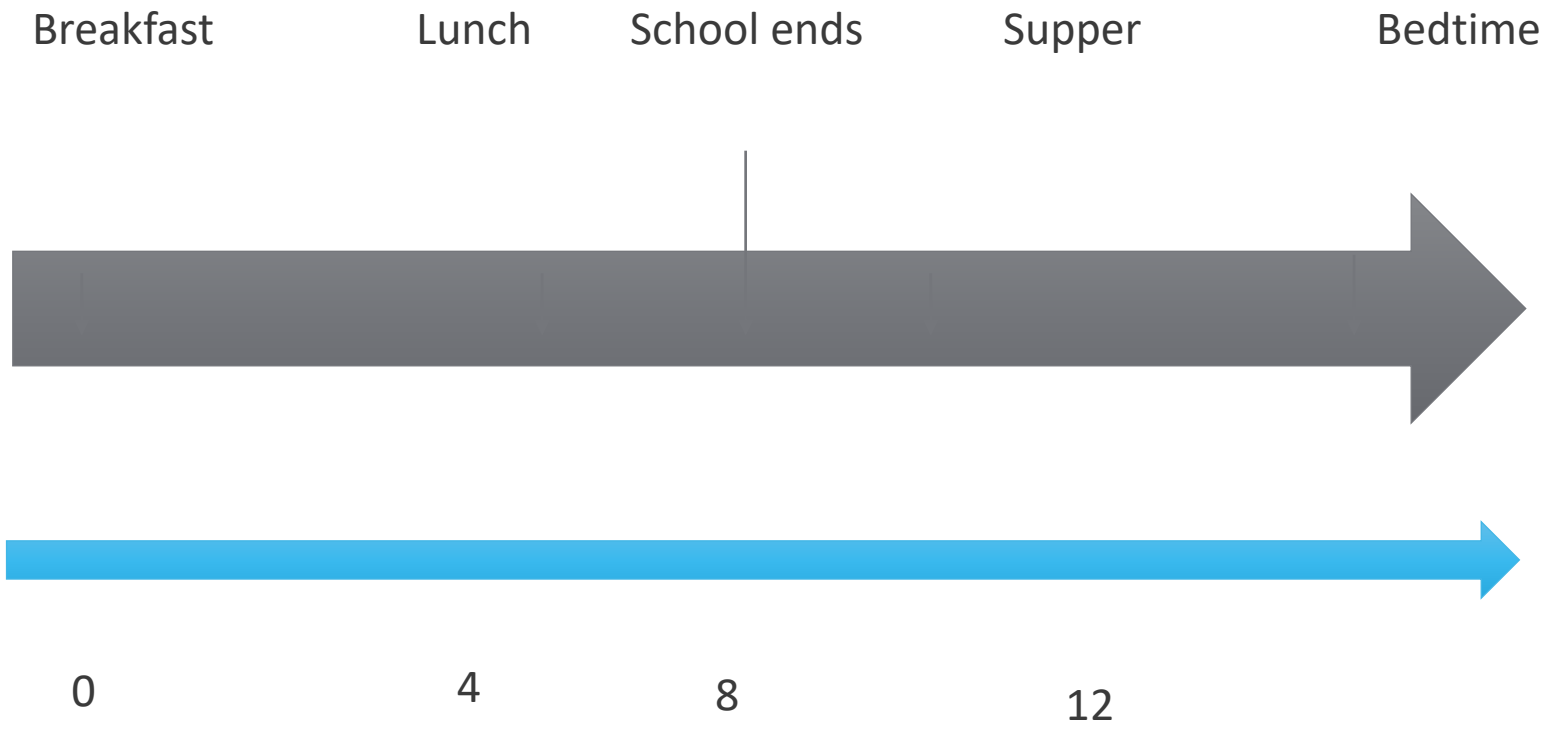
- **ProCentra** (dextroamphetamine sulfate) Oral solution 5 mg/5 ml
- **Zenzedi** (dextroamphetamine sulfate) 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg or 30 mg
- **Mydayis** Mixed amphetamine salts **SER** 12.5 mg, 25 mg, 37.5 mg, 50 mg
- **Adzenys** XR-ODT(amphetamine) 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg,18.8 mg.
- **Evekeo** (mixed amphetamine salts) 5, 10 mg

Adequate Trial (stimulants)

- Titrate dose until at least FDA dose limits
- No room for improvement , or
- Unacceptable/intolerable adverse events

Greenhill et al., JAACAP 1996 35 (10)

Daily Timeline



Assessing Drug Response

- Evaluate target ADHD symptoms
- Parent/teacher/other informant rating scales
- Self-ratings: adolescent/adults
- Monthly (until stable) then quarterly
- Consider severity and concurrent treatment

How High Do I Go?
Total individual and Daily Dose

- Methylphenidate
  - Oros MPH: 72 mg; other MPH preparations: 60 mg
  - up to 20 mg may be given as a later pm dose
- Amphetamine
  - D-amphetamine 40 mg; Mixed salts 40 mg
  - Lisdexamfetamine: 70 mg
- Some “outliers” - advance as tolerated, evaluate response carefully
- Look for long-term “tolerance”: alternate stimulants (methylphenidate/amphetamine)

Use Of Stimulants

- Try at least 2 stimulants (one AMP and one MPH) before proceeding to alternatives
- Titrate up dose to control of ADHD target sx
- If multiple daily dosing, consider long-acting agents
- Use adjunct behavioral therapies
- Monitor compliance
- Consider comorbidity

Stimulant Response

- 25-30% with poor or no stimulant response

Review #1
- 41% of children Tx with IR respond equal to MPH and AMP
- 28% better with AMP
- 16% better with MPH
- 15% poor/no response to either MPH/AMP

Review #2
- 91 % respond to either or both MPH/AMP

Review #3
- 53% response both stim classes
- 39% only one stimulant class
- 8% no response

Cortese, Newcorn, and Coghill, 2021
Arnold, 2000
Hodgkins et al., 2012
Ramtevelt et al 2013

Medication Follow up

- Managing treatment related side effects
  - ask specific questions re: side effects
- Provide a schedule for initial titration (initial dosage adjustment) and monitoring; 1-4 weeks; weekly contacts (phone)
- Providing a schedule for monitoring the drug maintenance phase
  - Monthly (until stable) then quarterly
  - Consider severity and concurrent treatment

When Medication Does Not Work?

- Correct diagnosis? (or comorbidity)
- Correct Dose? …and duration of trial
- Correct Medication?
- Correct Intervention? – need for concurrent psychosocial intervention
- Adherence

Pharmacogenetics of ADHD Medications

- How an individual's genetic makeup affects their response to various medication: hpw they metabolize
- Slow, deliberate titration for all patients
- **Methylphenidate:** carboxylesterase 1 enzyme (CES1).
- **Mixed Amphetamine Salts**: CYP2D6
- **Atomoxetine** cytochrome p450 2D6 (CYP2D6)
  - initiating the atomoxetine dose at 0.5 mg/kg/day and only titrating up to 1.2 mg/kg/day after 4 weeks if tolerate starting dose and don't experience sufficient improvement in symptoms
  - monitoring through C_{max} concentrations to help guide dose adjustments
- **Viloxazine:** CYP2D6 enzyme; multiple metabolism pathways
- **Guanfacine:** CYP3A4/5
- **Clonidine:** CYP2D6

Wang et al Clin Drug Investig. 2024 May;44(5):303-317
Brown JT Methods in Molecular Biology, vol 2547.

Managing Treatment Related Side Effects

- Ask specific questions re: side effects
- Provide a schedule for initial titration (initial dosage adjustment) and monitoring; 2-4 weeks
- Weekly contacts (phone)
- Providing a schedule for monitoring the drug maintenance phase
  - monthly (until stable) then quarterly
  - consider severity and concurrent treatment

Monitoring Weight and Height

- Use serial plotting of height and weight on growth charts
- 1-2 times per year, and more frequently if practical.
- If change in height or weight that crosses 2 percentile lines, possible aberrant growth trajectory.
- Consider Drug Holidays
- Consider switching the patient to another ADHD medication
- Carefully balance the benefits of medication treatment with the risks of small reductions in height gain

Trouble-Shooting with Stimulants

- Variable duration of effect: Pharmacogenetic testing
- Methylphenidate XR oral suspension
- Methylphenidate delayed and extended release capsules
- Methylphenidate transdermal patch
- Methylphenidate ER chewable tablets
- Methylphenidate XR-ODT (dissolving)
- Amphetamine ER Oral suspension 2.5 mg/mL (amphetamine base)
- Dextroamphetamine transdermal patch

Flexibility: What Do I Need medication for?

- School, social, specific tasks*
- Drug “Holidays”
- Weekend dosing*
- PM doses*
  - Piggy-back long-acting formulations*
    - ❑PRN

*Stimulants

Management of Patients with ADHD Non-Responsive to Stimulants

1. Proper titration
2. Maximum dose?
3. Drug/preparation working well at any times during the day; need to change the dose/preparation to get a more balanced effect?
4. Targeting the right symptoms?
5. Behavioral explanation for the drug “wearing off”; Tolerance to medication?
6. Stressor, family issues?
7. Comorbidity?

Adapted from: Coghill, 2020;
Cortese, Newcorn, and Coghill, 2021

Psychosocial Treatments

- Children: Behavioral Interventions – parent management training (PMT)
- Adolescents: Behavioral/family interventions; CBT
- Adults: CBT

Tourjman et al., 2022

Why Non-stimulant Treatments for ADHD?

Problems with the stimulants

- Schedule II drugs (abuse liability, diversion, medico-legal concerns)
- Parent preference for nonstimulants
- 30% do not adequately respond or cannot tolerate stimulant treatment
- Short duration of action (adherence, embarrassment)
- Side effect profile adversely impacting sleep, appetite, mood, and anxiety
- Concerns about cardiovascular effects, growth suppression, and tic development

Non-Stimulants

- After Stimulant Trial….
- Children: Alpha agonists (clonidine, guanfacine), then norepinephrine reuptake inhibitor (atomoxetine, viloxazine)
- Adolescents: norepinephrine reuptake inhibitor
- Adults: norepinephrine reuptake inhibitor
- Atomoxetine: may require 6+ weeks; up to 1.2-1.4 mg/kg

Non-Stimulant Medication

Medication	Mode of action	Dosage schedule
TCAS	NE, 5HT, Hist	2-5 mg/kg/day bid to tid
bupropion (Wellbutrin)	DA	100-150/200 mg q am to bid
venlafaxine (Effexor/XR)	5HT, NE	37.5 to 150 mg mg q am to bid
clonidine (catapress) guafacine (Tenex)		0.05 mg – 0.2 mg q d to qid
Atomoxetine (Strattera)	NERI	1.2-1.6 mg/kg/day(to bid)
Viloxazine (Qelbree)_	NERI	100-600 mg/daily
Modafinal (Providgel)		300-400 mg/daily

* FDA Approved

Adjunctive Medications

- Alpha agonists (clonidine, guanfacine); IR, ER
  - All day dosing
  - PM (after-school) dosing
  - Stimulant withdrawal (“rebound”)
  - Bedtime dosing
- Atomoxetine
- Viloxazine

Carlson GA, Kelly J. Child Adolesc Psychopharmacol. 2003

Treuer et al, J Child Adolesc Psychopharm 2013(3)

Adjunctive Interventions Medications/Polypharmacy

- Avoid polypharmacy whenever possible
- Careful evaluation of each specific medication trial
- Discontinue ineffective medications
- Psychosocial treatments (not really adjunctive)
- Monitor specific adverse events (side effects) and compliance

Thank You