Pharmacological Management of Attention-Deficit/Hyperactivity Disorder in Pediatrics

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Abbreviations

- ADHD – Attention-deficit/hyperactivity disorders
- BP- Blood pressure
- CD- Controlled delivery
- DSM-5- *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition
- ECG- Electrocardiography
- ER- Extended release
- GI- Gastrointestinal
- HR- Heart rate
- LFTs- Liver function tests
- Mg- milligram
- mL- milliliter
- N/V- Nausea/vomiting
- ODT- Oral disintegrating tablet
- SR- Sustained release
- XR- Extended release

Objectives

- Describe the pathophysiology of ADHD
- List the DSM-5 diagnostic criteria for pediatric ADHD
- Identify first-line treatment options for pediatric ADHD
- Identify second-line and adjunctive treatment options for pediatric ADHD

Epidemiology & Etiology

- Most prevalent neurodevelopmental disorder in childhood in the United States
- ADHD diagnosis increasing
- Must occur by before age 12 to meet current diagnostic criteria

Wolraich ML, Wibbelsman CJ, Brown TE et al. Attention-deficit/hyperactivity disorder among adolescents: a review of the diagnosis, treatment, and clinical implications. Pediatrics. 2005;115(6):1734–1746. [PubMed: 15930238]

Pathophysiology

- Disorder of self-regulation or response inhibition
- Difficulty maintaining self-control, resisting distractions, and concentrating on ideas
- Dysfunction of norepinephrine and dopamine
- Genetic component

Biederman J, Faraone S. Attention-deficit hyperactivity disorder. Lancet. 2005;366:237–248. [PubMed: 16023516]

Clinical Presentation & Diagnosis

- 50-60% of patients will have one or more comorbidities
- Patients 4-18 years of age presenting with inattention, hyperactivity, impulsivity, academic and/or behavioral problems should be evaluated for ADHD
- DSM-5 Diagnostic Criteria
  - Inattentive
  - Hyperactive/Impulsivity
  - Combined

Ryan-Krause P. Attention deficit hyperactivity disorder: Part I. J Pediatr Health Care. 2010;24(3):194–198. [PubMed: 20417892]

DSM-V Criteria for ADHD

Must meet criteria for Inattention, Hyperactivity/Impulsivity, or Both

1. Inattention

17 and younger: Six or more of these symptoms must be present for at least 6 months, be inconsistent with the child's developmental level, and have a negative effect on their social and academic activities. To be endorsed, the following must occur "often":

a. Fails to pay close attention to details
b. Has trouble sustaining attention
c. Doesn't seem to listen when spoken to directly
d. Fails to follow through on instructions and fails to finish schoolwork or chores
e. Has trouble getting organized
f. Avoids or dislikes doing things that require sustained focus/thinking
g. Loses things frequently
h. Easily distracted by other things
i. Forgets things

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (DSM-5), Washington, D.C.: American Psychiatric Association)

DSM-V Criteria for ADHD

2. Hyperactivity and Impulsivity

Six or more of these symptoms must be present for at least 6 months, be inconsistent with the child's developmental level, and have a negative effect on their social and academic activities. To be endorsed, the following must occur "often":

a. Fidgets with hands/feet or squirms in chair
b. Frequently leaves chair when seating is expected
c. Runs or climbs excessively
d. Trouble playing/engaging in activities quietly
e. Acts "on the go" and as if "driven by a motor"
f. Talks excessively
g. Blurts out answers before questions are completed
h. Trouble waiting or taking turns
i. Interrupts or intrudes on what others are doing

ADHD Predominantly Inattentive Presentation (ADHD-PI)
ADHD Predominantly Hyperactive-Impulsive Presentation (ADHD-PHI)
ADHD Combined Presentation (Inattentive & Hyperactive-Impulsive) (ADHD-C)

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (DSM-5), Washington, D.C.: American Psychiatric Association)

DSM-V Criteria for ADHD

Specify if:

Mild: Six or only slightly more symptoms are endorsed and impairment in social or school functioning is minor

Moderate: Symptoms or impairment is between mild and severe

Severe: (Many symptoms are above required 6 are endorsed and/or symptoms are severe; impairment in social or school functioning is severe)

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (DSM-5), Washington, D.C.: American Psychiatric Association)

Treatment

- Primary goals: improve behavior and increase attention or response inhibition
- Secondary goals:
  - Improve relationships with family, teachers, and peers
  - Decrease disruptive behavior in academic and social settings
  - Improve academic performance
  - Increase independence in activities
  - Minimize undesirable adverse effects in therapy

Cleveland KW, Erramouspe J. Cleveland K.W., Erramouspe J Cleveland, Kevin W., and John Erramouspe.Attention-Deficit/Hyperactivity Disorder. In: Chisholm-Burns MA, Schwinghammer TL, Wells BG, Malone PM, Kolesar JM, DiPiro JT. Chisholm-Burns M.A., Schwinghammer T.L., Wells B.G., Malone P.M., Kolesar J.M., DiPiro J.T. Eds. Marie A. Chisholm-Burns, et al.eds. *Pharmacotherapy Principles & Practice, 4e* New York, NY: McGraw-Hill; . http://ppp.mhmedical.com.cowles-proxy.drake.edu/content.aspx?bookid=1793&sectionid=120653043. Accessed August 21, 2017.

Treatment

- Non-pharmacologic (Behavioral) Therapy
  - Not recommended as first-line monotherapy
  - Behavioral therapy + stimulant therapy is better at improving oppositional and aggressive behaviors

A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. Arch Gen Psychiatry. 1999;56(12):1073-86.

Treatment

- Pharmacological Therapy:
  - Modulate neurotransmitter function in order to improve academic and social functioning
  - Stimulants
  - Non-stimulants
  - Other adjunctive therapies

Patient Case

- A pediatrician comes to you asking your opinion on a treatment option for one of his patients. The patient is a 7-year-old child who was recently diagnosed with ADHD. The patient does not have any pertinent medical history or allergies. What would be the most appropriate initial therapy?

Treatment

Stimulants

Treatment-Stimulants

- Stimulants
  - Most effective agents in treating ADHD
  - First-line therapy in patients 6 years and older
  - Have a 70%-90% response rate
  - Treatment failure: switch to different stimulant formulation
  - Decrease fidgeting and finger tapping, increase on-task classroom behavior, and positive interactions at home and in social environment, and help with conduct and anxiety disorder
  - Controlled substance

Wolraich M, Brown L, Brown RT, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2011;128(5):1007-22.

Treatment-Stimulants

- Mechanism of Action:
  - Amphetamines
    - Promote the release of catecholamines and also have the ability to block the reuptake of these catecholamines by competitive inhibition
  - Methylphenidate
    - Blocks the reuptake of dopamine and norepinephrine into presynaptic neurons

Treatment-Short acting Stimulant

Drug	Initial Dose	Titration Schedule Increments	Typical Dosing Range (Maximum Dose)
Dextroamphetamine (Dexedrine)*	2.5-5 mg every morning	2.5-5 mg/day in weekly intervals	5-20 mg twice daily (40 mg/day)
Methylphenidate (Methylin, Ritalin)**	5 mg twice daily	5-10 mg/day in weekly intervals	5-20 mg 2-3 times daily (60 mg/day)
Dexmethylphenidate (Focalin)**	2.5 mg twice daily	2.5-5 mg/day in weekly intervals	5-10 mg twice daily (20 mg/day)

*Approved by FDA for treatment of ADHD in ages 3-5

**Approved by FDA for treatment of ADHD in age ≥6 years

Table adapted from: Cleveland KW, Erramouspe J. Cleveland K.W., Erramouspe J Cleveland, Kevin W., and John Erramouspe.Attention-Deficit/Hyperactivity Disorder. In: Chisholm-Burns MA, Schwinghammer TL, Wells BG, Malone PM, Kolesar JM, DiPiro JT. Chisholm-Burns M.A., Schwinghammer T.L., Wells B.G., Malone P.M., Kolesar J.M., DiPiro J.T. Eds. Marie A. Chisholm-Burns, et al.eds. *Pharmacotherapy Principles & Practice, 4e* New York, NY: McGraw-Hill; . http://ppp.mhmedical.com.cowles-proxy.drake.edu/content.aspx?bookid=1793&sectionid=120653043. Accessed August 21, 2017.

Treatment-Pricing Considerations-30 Day-Supply

Short-Acting Rapid-Onset Stimulants		
Dextroamphetamine		
Generic	5-mg tablet twice daily	$
Methylphenidate		
Generic	5-, 10-, or 20-mg tablet twice daily	$
Dexmethylphenidate		
Generic	2.5-mg tablet twice daily	$
Generic	5- or 10- mg tablet twice daily	$$

$, less than $40; $$, $40–$79; $$$, $80–$120; $$$$, greater than $120

Table adapted from: Cleveland KW, Erramouspe J. Cleveland K.W., Erramouspe J Cleveland, Kevin W., and John Erramouspe.Attention-Deficit/Hyperactivity Disorder. In: Chisholm-Burns MA, Schwinghammer TL, Wells BG, Malone PM, Kolesar JM, DiPiro JT. Chisholm-Burns M.A., Schwinghammer T.L., Wells B.G., Malone P.M., Kolesar J.M., DiPiro J.T. Eds. Marie A. Chisholm-Burns, et al.eds. *Pharmacotherapy Principles & Practice, 4e* New York, NY: McGraw-Hill; . http://ppp.mhmedical.com.cowles-proxy.drake.edu/content.aspx?bookid=1793&sectionid=120653043. Accessed August 21, 2017.

Treatment-Intermediate Acting Stimulant

Drug	Initial Dose	Titration Schedule Increments	Typical Dosing Range (Maximum Dose)
Dextroamphetamine -amphetamine (Adderall)*	2.5-5mg once to twice daily	2.5-5 mg/day in weekly intervals	10-30 mg every morning or 5-20 mg twice daily (40 mg/day)
Methylphenidate (Ritalin SR, Metadate ER, Methylin ER)**	10 mg once daily	10 mg/day in weekly intervals	20-40 mg daily in the am (60 mg/day)
Dextroamphetamine (Dexedrine Spansule)**	5 mg every am	5 mg/day in weekly intervals	5-30 mg daily or 5-15 mg twice daily (40 mg/day)

*Approved by FDA for treatment of ADHD in ages 3-5

**Approved by FDA for treatment of ADHD in age ≥6 years

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Treatment-Pricing Considerations-30 Day-Supply

Intermediate-Acting Slower-Onset Stimulants		
Dextroamphetamine/ amphetamine		
Generic	5-, 7.5-, 10-, 12.5-, 20-, or 30-mg daily	$
Methylphenidate		
Generic	10- or 20-mg ER tablet daily	$
Dextroamphetamine		
Generic	10- or 15-mg capsule daily	$$$$

$, less than $40; $$, $40–$79; $$$, $80–$120; $$$$, greater than $120

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Treatment-Extended Acting Stimulant

Drug	Initial Dose	Titration Schedule Increments	Typical Dosing Range (Maximum Dose)
Methylphenidate**			
(Concerta)	18 mg every am	9-18 mg/day in weekly intervals	18-54 mg every am (54 mg/day in children)
(Metadate CD)	20 mg every am	10-20 mg/day in weekly intervals	20-40 mg daily in the am (60 mg/day)
(Ritalin LA)	20 mg every am	10 mg/day in weekly intervals	20-40 mg daily in the am (60 mg/day)
(Quillvant XR)	20 mg every am	10-20 mg/day in weekly intervals	20-40 mg daily in the am (60 mg/day)
Dextroamphetamine/ amphetamine (Adderall XR)**	5-10 mg every am	5-10 mg/day in weekly intervals	10-30 mg every am or 5-15 mg twice daily (30 mg/day)
Dexmethylphenidate (Focalin XR)**	5 mg every am	5 mg/day in weekly intervals	10-20 mg daily in the am (20 mg/day)
Lisdexamfetamine (Vyvanse)**	30 mg every am	10-20 mg/day in weekly intervals	30-70 mg daily in the am (70 mg/day)

**Approved by FDA for treatment of ADHD in age ≥6 years

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Treatment-Pricing Considerations-30 Day-Supply

Extended-Acting Rapid-Onset Stimulants		
Methylphenidate		
Concerta (brand & generics)	18-, 27-, 36-, or 54-mg tablet daily	$$$$
Metadate CD (brand & generics)	10-, 20-, 30-mg capsule daily	$$$$
Ritalin LA (brand & generics)	10- 20- mg capsule daily	$$$$
Quilivant XR	10, 20, 25, or 30 mg of suspension daily	$$$$
Dextroamphetamine/ Amphetamine		
Adderall XR (brand & generics)	5-, 10-, 15-, 20-, 25-, or 30-mg capsule daily	$$$$
Dexmethylphenidate		
Focalin XR (brand & generics)	5-, 10-, 15-, 20-, 25-, 30-, 35-, 40- mg capsule daily	$$$$

$, less than $40; $$, $40–$79; $$$, $80–$120; $$$$, greater than $120

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Treatment-Pricing Considerations-30 Day-Supply

Extended-Acting Slower-Onset Stimulants		
Lisdexafetamine		
Vyvanse	20-, 30-, 40-, 50-, 60-, or 70-mg	$$$$

$, less than $40; $$, $40–$79; $$$, $80–$120; $$$$, greater than $120

Table adapted from: Cleveland KW, Erramouspe J. Cleveland K.W., Erramouspe J Cleveland, Kevin W., and John Erramouspe.Attention-Deficit/Hyperactivity Disorder. In: Chisholm-Burns MA, Schwinghammer TL, Wells BG, Malone PM, Kolesar JM, DiPiro JT. Chisholm-Burns M.A., Schwinghammer T.L., Wells B.G., Malone P.M., Kolesar J.M., DiPiro J.T. Eds. Marie A. Chisholm-Burns, et al.eds. *Pharmacotherapy Principles & Practice, 4e* New York, NY: McGraw-Hill; . http://ppp.mhmedical.com.cowles-proxy.drake.edu/content.aspx?bookid=1793&sectionid=120653043. Accessed August 21, 2017.

Treatment-Dosage forms of Methylphenidate

Drug/Dosage Form	Strengths Available (mg)
Capsule ER (Metadate CD)	10*, 20*, 30*, 50*, 60*
Capsule ER 24 Hour	
Aptensio XR	10, 15, 20, 30, 50, 60*
Ritalin LA	10, 20*, 30, 40*
Patch, Transdermal (Daytrana)	10mg/9 hr; 15mg/9hr; 20mg/9hr; 30mg/9hr
Solution (Methylin)	5mg/5mL (500 mL)*;10mg/5mL (500mL)*
Suspension Reconstituted (Quillivant XR)	25mg/5mL (60mL, 120mL, 150mL, 180mL)
Tablet (Ritalin)	5*, 10*, 20*
Tablet Chewable (Methylin)	2.5*, 5*, 10*
Tablet Chewable ER (QuilliChew ER)	20, 30, 40
Tablet ER (Concerta, Metadate ER, Ritalin SR)	10*, 18*, 20*, 27*, 36*, 54*
Tablet ER 24 Hour	18*, 27*, 36*, 54*
Tablet ER ODT (Complera XR-ODT)	8.6, 17.3, 25.9

*denotes strength available in generic

Treatment- Dosage forms of Other Stimulants

Drug/Dosage Form	Strengths Available (mg)
Dexmethylphenidate (Focalin XR) ER 24 hour capsule	5*, 10*, 15*, 20*, 25*, 30*, 35*, 40*
Dexmethylphenidate (Focalin) tablet	2.5*, 5*, 10*
Dextroamphetamine (Dexedrine) ER 24 hour capsule	5*, 10*, 15*
Dextroamphetamine (Procentra) Oral Solution	5 mg/5mL*
Dextroamphetamine (Zenzedi) Tablet	2.5, 5*, 7.5, 10*, 15, 20, 30
Dextroamphetamine/Amphetamine (Adderall XR, Mydayis) ER Capsule	5*, 10*, 15*, 20*, 25*,30* (Adderall XR) 12.5, 25, 37.5, 50 (Mydayis)
Dextroamphetamine/Amphetamine (Adderall)	5*, 7.5*, 10*, 12.5*, 15*, 20*, 30*
Lisdexamfetamine (Vyvanse) Capsules	10, 20, 30, 40, 50, 60, 70
Lisdexamfetamine (Vyvanse) Chewable	10, 20, 30, 40, 50, 60

*denotes strength available in generic

Stimulant Conversion

- Considered to be equally efficacious when using equivalent dosing
- Conversion:
  - 2 mg methylphenidate = 1mg dextroamphetamine/amphetamine = 1 mg dexmethylphenidate
  - Lisdexamfetamine
    - 30 mg = 10 mg mixed AMP
    - 50 mg = 20 mg mixed AMP
    - 70 mg = 30 mg mixed AMP

Patient Case

- The same pediatrician also has another medication question for you. He received a phone call from one of his patient's mother, stating that her daughter was getting very agitated and irritable in the morning while at school. Her daughter takes methylphenidate IR 30mg in the morning. What adjustment would be most appropriate to help alleviate the patient's agitation and irritability?

Treatment-Stimulant Adverse Reactions

- Can be generalized to the whole class
- Most can be managed by changing the dosing schedule
- Serious side effects require discontinuation of medication
- To prevent potential drug-food interactions and absorption issues, stimulants should be given 30-60 minutes before eating
- Growth suppression
- Substance abuse

Wilens TE, Faraone SV, Biederman J et al. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics. 2003;111:179–185. [PubMed: 12509574]

Treatment-Stimulants & Growth Suppression

Effect of stimulants on height and weight: a review of the literature

Objective: Stimulant medications are effective treatments for attention-deficit/hyperactivity disorder, but concerns remain about their effects on growth.

Methods: We provide a quantitative analysis of longitudinal studies about deficits in expected growth among children with attention-deficit/hyperactivity disorder treated with stimulant medication. Study selection criteria were use of DSM criteria or clear operational definitions for hyperactivity or minimal brain dysfunction; outcome measures including raw, standardized, or percentile measurement of change in height and/or weight; first assessment of effects on growth occurred during childhood; and follow-up for at least 1 year. For issues not suitable for quantitative analyses, we provide a systematic, qualitative review.

Results: The quantitative analyses showed that treatment with stimulant medication led to statistically significant delays in height and weight. This review found statistically significant evidence of attenuation of these deficits over time. The qualitative review suggested that growth deficits may be dose dependent, deficits may not differ between methylphenidate and amphetamine, treatment cessation may lead to normalization of growth, and further research should assess the idea that attention-deficit/hyperactivity disorder itself may be associated with dysregulated growth.

Conclusions: Treatment with stimulants in childhood modestly reduced expected height and weight. Although these effects attenuate over time and some data suggest that ultimate adult growth parameters are not affected, more work is needed to clarify the effects of continuous treatment from childhood to adulthood. Although physicians should monitor height, deficits in height and weight do not appear to be a clinical concern for most children treated with stimulants.

Faraone SV, Biederman J, Morley CP, Spencer TJ. Effect of stimulants on height and weight: a review of the literature. J Am Acad Child Adolesc Psychiatry. 2008;47(9):994-1009.

Treatment-Stimulant Use & Substance Abuse

Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature.

Objective: Concerns exist that stimulant therapy of youths with attention-deficit/hyperactivity disorder (ADHD) may result in an increased risk for subsequent substance use disorders (SUD). We investigated all long-term studies in which pharmacologically treated and untreated youths with ADHD were examined for later SUD outcomes.

Methods: A search of all available prospective and retrospective studies of children, adolescents, and adults with ADHD that had information relating childhood exposure to stimulant therapy and later SUD outcome in adolescence or adulthood was conducted through PubMed supplemented with data from scientific presentations. Meta-analysis was used to evaluate the relationship between stimulant therapy and subsequent SUD in youths with ADHD in general while addressing specifically differential effects on alcohol use disorders or drug use disorders and the potential effects of covariates.

Results: Six studies--2 with follow-up in adolescence and 4 in young adulthood--were included and comprised 674 medicated subjects and 360 unmedicated subjects who were followed at least 4 years. The pooled estimate of the odds ratio indicated a 1.9-fold reduction in risk for SUD in youths who were treated with stimulants compared with youths who did not receive pharmacotherapy for ADHD ($z = 2.1$; 95% confidence interval for odds ratio [OR]: 1.1-3.6). We found similar reductions in risk for later drug and alcohol use disorders ($z = 1.1$). Studies that reported follow-up into adolescence showed a greater protective effect on the development of SUD (OR: 5.8) than studies that followed subjects into adulthood (OR: 1.4). Additional analyses showed that the results could not be accounted for by any single study or by publication bias.

Conclusions: Our results suggest that stimulant therapy in childhood is associated with a reduction in the risk for subsequent drug and alcohol use disorders.

Wilens TE, Faraone SV, Biederman J et al. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics. 2003;111:179–185. [PubMed: 12509574]

Treatment-Stimulant Adverse Reactions & Management

Adverse Effects	Management	Monitoring
GI upset, nausea, decreased appetite, potential growth delay	Administer after breakfast and lunch Encourage high-calorie meals/beverages and snacks after dinner Divide dose Change to short-acting stimulant D/c on weekends and during holidays	Height, weight, BP, pulse ECG if warranted Eating and sleeping patterns Evaluate every 2-4 weeks until stable dose is achieved; then every 3 months
Insomnia	Move dose(s) earlier in the day and d/c later day dose if problem persists Change to shorter-acting stimulant Consider adjunct hypnotic (ex melatonin) or alternative medication (ex guanfacine, bupropion)	
Headache	Decrease dose Change to longer-acting stimulant or non stimulant (ex atomoxetine) Consider analgesic (ex acetaminophen)	
Irritability, dysphoria, agitation	Early onset (peak related): decrease dose or change to longer-acting stimulant Late onset (withdrawal related): change to longer-acting stimulant Evaluate for comorbidity and treat if present	
Tics	Decrease dose Change to a different stimulant or a non stimulant	

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Treatment

Non-stimulants

Treatment- Atomoxetine

- Selectively inhibits reuptake of adrenergic neurotransmitters
- Maximum therapeutic efficacy may take 4 weeks
- Side effects: increase in BP & HR
- Superior efficacy over placebo, and either equivalent efficacy compared with suboptimal dose of IR methylphenidate or inferior to ER methylphenidate formulations
- May be used as a second- or third-line therapy
- Concerns: price

Wang Y, Zheng Y, Du Y et al. Atomoxetine versus methylphenidate in paediatric outpatients with attention deficit hyperactivity disorder: A randomized, double-blind comparison trial. Aust N Z J Psychiatry. 2007;41(3):222–230. [PubMed: 17464703]

Treatment- Atomoxetine vs Methylphenidate

Comparative efficacy of methylphenidate and atomoxetine in the treatment of attention deficit hyperactivity disorder in children and adolescents: A systematic review and meta-analysis.

Background: The aim of this study was to directly compare efficacy of atomoxetine and methylphenidate in treatment of children and adolescents 6- 18 years.

Methods: All published, randomized, open label or double blind trials, comparing the efficacy of methylphenidate with atomoxetine in treatment of children diagnosed with ADHD, using DSM-IV criteria were included in this study; ADHD Rating Scale-IV-Parent Version: Investigator Administered and Scored scores was used. The standardized mean difference was used as a measure of effect size.

Results: Eleven studies were included with a total of 2,772 participants. The meta-analysis did not find a significant difference in the efficacy between methylphenidate and atomoxetine. Sub group analysis showed a significant standardized mean difference favoring OROS methylphenidate; immediate release methylphenidate was not superior to atomoxetine. Open label trials did not make a difference in the standardized mean difference. There was significant heterogeneity among the studies. Subgroup analysis demonstrated that heterogeneity was because of the open label trials.

Conclusions: Atomoxetine and methylphenidate showed comparable efficacy in the treatment of children and adolescents with ADHD. However, Osmotic Release Oral System (OROS) methylphenidate is more effective than atomoxetine in treatment of ADHD in children and adolescents that is suggested as a first-line treatment in ADHD. Moreover, comparing the immediate release (IR) methylphenidate to atomoxetine did not lead to the benefit of IR methylphenidate.

Rezaei G, Hosseini SA, Akbari sari A, et al. Comparative efficacy of methylphenidate and atomoxetine in the treatment of attention deficit hyperactivity disorder in children and adolescents: A systematic review and meta-analysis. Med J Islam Repub Iran. 2016;30:325.

Treatment-Clonidine & Guanfacine

- Central α_2-adrenergic agonists that inhibit the release of norepinephrine presynaptically
- Less effective that stimulants, but used as adjuncts to stimulants
- ER formulations: guanfacine (Intuniv) and clonidine (Kapvay)
- Side effects: low blood pressure, sedation

Scrahill L. Alpha-2 adrenergic agonists in children with inattention, hyperactivity and impulsiveness. CNS Drugs. 2009;23(Suppl 1):43–49. [PubMed: 19621977]

Treatment-Guanfacine

Profile of Guanfacine Extended Release and its Potential in the Treatment of Attention-Deficit Hyperactivity Disorder

- Background: The α2-adrenergic receptor agonist guanfacine, in its extended-release formulation (GXR), is the most recent nonstimulant medication approved in several countries for the treatment of attention-deficit hyperactivity disorder (ADHD) as monotherapy and as adjunctive pharmacotherapy to stimulants in children and adolescents.
- Objective: The present paper aims to review comprehensively and critically the pharmacodynamic and pharmacokinetic characteristics and the published evidence on the efficacy and safety profile of GXR in the treatment of ADHD.
- Methods: A comprehensive search of relevant databases was conducted to identify studies published in peer-reviewed journals until January 15, 2015.
- Results: As evidenced in short-term randomized controlled trials and in long-term open-label extension studies, GXR has been shown to be effective as monotherapy in the treatment of ADHD. Furthermore, GXR has also been found to be effective as adjunctive therapy to stimulant medications in patients with suboptimal responses to stimulants. Many of the adverse reactions associated with GXR, particularly sedation-related effects, were dose-related, transient, mild to moderate in severity, and did not interfere with attention or overall efficacy. There are no reports of serious cardiovascular adverse events associated with GXR alone or in combination with psychostimulants.

Martinez-raga J, Knecht C, De alvaro R. Profile of guanfacine extended release and its potential in the treatment of attention-deficit hyperactivity disorder. Neuropsychiatr Dis Treat. 2015;11:1359-70.

Treatment-Bupropion

- Monocyclic antidepressant that inhibits reuptake of norepinephrine and dopamine
- Studies suggest it may be as effective as methylphenidate
- Side effects: insomnia, headache, nausea
- C/I: seizure disorders and eating disorders
- Good choice for comorbid depression

Maneeton N, Maneeton B, Intaprasert S, Woottiluk P. A systematic review of randomized controlled trials of bupropion versus methylphenidate in the treatment of attention-deficit/hyperactivity disorder. Neuropsychiatr Dis Treat. 2014;10:1439–1449. [PubMed: 25120365]

Treatment- Bupropion vs Methylphenidate

A systematic review of randomized controlled trials of bupropion versus methylphenidate in the treatment of attention-deficit/hyperactivity disorder

Background: Some trials have suggested that bupropion, as well as methylphenidate, is beneficial in the treatment of attention-deficit/hyperactivity disorder

Objectives: The purpose of this systematic review was to summarize the efficacy, acceptability, and tolerability of bupropion in comparison with methylphenidate for ADHD treatment. Included studies were randomized controlled trials (RCTs) that compared bupropion and methylphenidate. Clinical studies conducted between January 1991 and January 2014 were reviewed.

Results: A total of 146 subjects in four RCTs comparing bupropion with methylphenidate in the treatment of ADHD were included. The pooled mean changed scores of the Iowa-Conner's Abbreviated Parent and Teacher Questionnaires and the ADHD Rating Scale-IV for parents and teachers of children and adolescents with ADHD in the bupropion- and methylphenidate-treated groups were not significantly different. Additionally, the pooled mean changed score in adult ADHD between the two groups, measured by the ADHD Rating Scale-IV and the Adult ADHD Rating Scale, was also not significantly different. The pooled rates of response, overall discontinuation, and discontinuation due to adverse events between the two groups were not significantly different.

Conclusions: Based on limited data from this systematic review, bupropion was as effective as methylphenidate for ADHD patients. Additionally, tolerability and acceptability were also comparable. However, these findings should be considered as very preliminary results. To confirm this evidence, further studies in this area should be conducted.

Maneeton N, Maneeton B, Intaprasert S, Woottiluk P. A systematic review of randomized controlled trials of bupropion versus methylphenidate in the treatment of attention-deficit/hyperactivity disorder. Neuropsychiatr Dis Treat. 2014;10:1439–1449. [PubMed: 25120365]

Treatment-Non-stimulants

Drug	Initial Dose	Titration Schedule Increments	Typical Dosing Range (Maximum Dose)
Atomoxetine (Strattera)**	≤70 kg: 0.5 mg/kg/day divided once to twice daily	To target dose of 1.2 mg/kg/day after 3 days	40-60 mg/day (1.4 mg/kg or 100 mg/day, whichever is less)
	>70kg: 40 mg once daily	40 mg/day after 3 days (may ↑ to total of 100 mg/day after 2-3 weeks)	40-80 mg/day divided once or twice daily (100 mg/day)
Clonidine (Catapres) **(Kapvay)****	0.05 mg once daily 0.1 mg at bedtime	0.05 mg/day every 3-7 days 0.1 mg/day in weekly intervals	0.1 mg 1-4 times daily 0.1-0.2 mg twice daily (0.4 mg/day)
Guanfacine (Tenex) **(Intuniv)****	0.5 mg at bedtime 1 mg once daily	0.5 mg every 3-14 days No more than 1 gm/week	1.5-3mg/day divided into 2-3 doses (4 mg/day) 1-4 mg daily (4 mg/day)
Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL)	3 mg/kg/day for 7 days	3 mg/kg/day in weekly intervals	6 mg/kg/day or 400 mg/day whichever is smaller

**Approved by FDA for treatment of ADHD in age ≥6 years

Table adapted from: Cleveland KW, Erramouspe J. Cleveland K.W., Erramouspe J Cleveland, Kevin W., and John Erramouspe.Attention-Deficit/Hyperactivity Disorder. In: Chisholm-Burns MA, Schwinghammer TL, Wells BG, Malone PM, Kolesar JM, DiPiro JT. Chisholm-Burns M.A., Schwinghammer T.L., Wells B.G., Malone P.M., Kolesar J.M., DiPiro J.T. Eds. Marie A. Chisholm-Burns, et al.eds. *Pharmacotherapy Principles & Practice, 4e* New York, NY: McGraw-Hill; . http://ppp.mhmedical.com.cowles-proxy.drake.edu/content.aspx?bookid=1793&sectionid=120653043. Accessed August 21, 2017.

Non-stimulant Dosage Forms

Drug/Dosage Form	Strengths Available (mg)
Atomoxetine (Strattera) Capsule	10*, 18*, 25*, 40*, 60*, 80*, 100*
Clonidine (Catapres) Tablet	0.1*, 0.2*, 0.3*
Clonidine (Kapvay) ER 12 hour Tablet	0.1*
Guanfacine (Tenex) Tablet	1*, 2*
Guanfacine (Intuniv) ER 24 hour Tablet	1*, 2*, 3*, 4*
Bupropion (Wellbutrin) ER 12 Hour Tablet	100*, 150*, 200*
Bupropion (Wellbutrin XR, Forfivo XL, Aplenzin) ER 24 hour Tablet	150*, 174, 300*, 348, 450, 522

*denotes strength available in generic

Treatment-Pricing Considerations-30 Day-Supply

Nonstimulants		
Atomoxetine		
Strattera (brand & generics)	10-, 18-, 25-, 40-, 60-, 80-, or 100-mg capsule daily	$$$$
Clonidine		
Generic	0.1-, 0.2-, or 0.3-mg tablet twice daily	$
Kapvay (brand & generics)	0.1- ER tablet twice daily	$$$$

$, less than $40; $$, $40–$79; $$$, $80–$120; $$$$, greater than $120

Table adapted from: Cleveland KW, Erramouspe J. Cleveland K.W., Erramouspe J Cleveland, Kevin W., and John Erramouspe.Attention-Deficit/Hyperactivity Disorder. In: Chisholm-Burns MA, Schwinghammer TL, Wells BG, Malone PM, Kolesar JM, DiPiro JT. Chisholm-Burns M.A., Schwinghammer T.L., Wells B.G., Malone P.M., Kolesar J.M., DiPiro J.T. Eds. Marie A. Chisholm-Burns, et al.eds. *Pharmacotherapy Principles & Practice, 4e* New York, NY: McGraw-Hill; . http://ppp.mhmedical.com.cowles-proxy.drake.edu/content.aspx?bookid=1793&sectionid=120653043. Accessed August 21, 2017.

Treatment-Pricing Considerations-30 Day-Supply

Nonstimulants		
Guanfacine		
Generic	1- or 2-mg tablet twice daily	$
Intuniv (brand & generics)	1-, 2-, 3-, or 4-mg ER tablet once daily	$$$$
Bupropion		
Generic	75-mg tablet twice daily	$
Generic	150-mg SR tablet twice daily	$
Generic	200-mg SR tablet twice daily	$$
Generic	150-mg XL tablet daily	$

$, less than $40; $$, $40–$79; $$$, $80–$120; $$$$, greater than $120

Table adapted from: Cleveland KW, Erramouspe J. Cleveland K.W., Erramouspe J Cleveland, Kevin W., and John Erramouspe.Attention-Deficit/Hyperactivity Disorder. In: Chisholm-Burns MA, Schwinghammer TL, Wells BG, Malone PM, Kolesar JM, DiPiro JT. Chisholm-Burns M.A., Schwinghammer T.L., Wells B.G., Malone P.M., Kolesar J.M., DiPiro J.T. Eds. Marie A. Chisholm-Burns, et al.eds. *Pharmacotherapy Principles & Practice, 4e* New York, NY: McGraw-Hill; . http://ppp.mhmedical.com.cowles-proxy.drake.edu/content.aspx?bookid=1793&sectionid=120653043. Accessed August 21, 2017.

Treatment-Non-stimulants Adverse Reactions & Management

Drug	Adverse Effects	Management	Monitoring
Atomoxetine	Increased BP & pulse, N/V, fatigue and insomnia	Decrease dose or change to another medication (ex guanfacine or buproprion)	Height, weight, blood pressure, pulse ECG if warranted Eating and sleeping patterns Evaluate every 2–4 weeks until stable dose is achieved; then evaluate every 3 months Baseline and routine LFTs for hepatotoxicity
	Hepatotoxicity, suicidal thoughts	Discontinue or change to another medication	
Clonidine & Guanfacine	Sedation	Decrease dose Administer closer to bedtime	Same as above besides LFTs
Bupropion	GI upset, restlessness, sleep disturbances, tremor, tics, rash, seizures	Decrease dose or change to another medication (ex guanfacine) Discontinue medication	Height, weight, blood pressure, pulse every month Eating and sleeping patterns

Table adapted from: Cleveland KW, Erramouspe J. Cleveland K.W., Erramouspe J Cleveland, Kevin W., and John Erramouspe.Attention-Deficit/Hyperactivity Disorder. In: Chisholm-Burns MA, Schwinghammer TL, Wells BG, Malone PM, Kolesar JM, DiPiro JT. Chisholm-Burns M.A., Schwinghammer T.L., Wells B.G., Malone P.M., Kolesar J.M., DiPiro J.T. Eds. Marie A. Chisholm-Burns, et al.eds. *Pharmacotherapy Principles & Practice, 4e* New York, NY: McGraw-Hill; . http://ppp.mhmedical.com.cowles-proxy.drake.edu/content.aspx?bookid=1793&sectionid=120653043. Accessed August 21, 2017.

Patient Case

- A pediatrician comes to you asking your opinion on a treatment option for one of his patients. The patient is a 7-year-old child who was recently diagnosed with ADHD. The patient does not have any pertinent medical history or allergies. Which of the following would be the most appropriate initial therapy?
    A. Non-pharmacologic (behavioral) therapy
    B. Clonidine ER (Kapvay) 0.2 mg in the morning
    C. Dextroamphetamine/Amphetamine ER (Adderall XR) 20 mg twice daily
    D. Methylphenidate (Ritalin LA) 20 mg in the morning

Patient Case

- A pediatrician comes to you asking your opinion on a treatment option for one of his patients. The patient is a 7-year-old child who was recently diagnosed with ADHD. The patient does not have any pertinent medical history or allergies. Which of the following would be the most appropriate initial therapy?

A. Non-pharmacologic (behavioral) therapy
B. Clonidine ER (Kapvay) 0.2 mg in the morning
C. Dextroamphetamine/Amphetamine ER (Adderall XR) 20 mg twice daily
D. **Methylphenidate (Ritalin LA) 20 mg in the morning**

Patient Case

- The same doctor also has another medication question for you. He received a phone call from one of his patient's mother, stating that her daughter was getting very agitated and irritable in the morning while at school. Her daughter takes methylphenidate IR 30mg in the morning. What adjustment would be most appropriate to help alleviate the patient's agitation and irritability?
    A. Increase the patient's dose of methylphenidate (Ritalin SR)
    B. Switch the patient to a long-acting methylphenidate formulation
    C. Add clonidine 0.05 mg once daily
    D. Discontinue stimulants in this patient

Patient Case

- The same doctor also has another medication question for you. He received a phone call from one of his patient's mother, stating that her daughter was getting very agitated and irritable in the morning while at school. Her daughter takes methylphenidate IR 30mg in the morning. What adjustment would be most appropriate to help alleviate the patient's agitation and irritability?
    A. Increase the patient's dose of methylphenidate (Ritalin SR)
    B. **Switch the patient to a long-acting methylphenidate formulation**
    C. Add clonidine 0.05 mg once daily
    D. Discontinue stimulants in this patient

Treatment

Other adjunctive therapies

Treatment- Other Adjunctive Therapies

- Tricyclic Antidepressants
- Anxiolytics
- Anticonvulsants
- Antipsychotics
- Mineral Supplements

Pharmacoeconomic and Treatment Adherence Concerns

- Annual healthcare costs of patients with ADHD are more than double those without ADHD
- Should not be based solely on cost, but also on efficacy and safety along with adherence to the prescribed regimen

Matza LS, Paramore C, Prasad M. A review of the economic burden of ADHD. Cost Eff Resour Alloc. 2005;3:5. [PubMed: 15946385]

In-patient Considerations

- Do not need to restart stimulants
- May consider restarting adjunctive therapies
- Formulary concerns

Objectives

- Describe the pathophysiology of ADHD
- List the DSM-5 diagnostic criteria for pediatric ADHD
- Identify first-line treatment options for pediatric ADHD
- Identify second-line and adjunctive treatment options for pediatric ADHD

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Supplementary Slide- Treatment vs. Behavioral Intervention

A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD

Background: Previous studies have demonstrated the short-term efficacy of pharmacotherapy and behavior therapy for attention-deficit/hyperactivity disorder (ADHD), but no longer-term (i.e., >4 months) investigations have compared these 2 treatments or their combination.

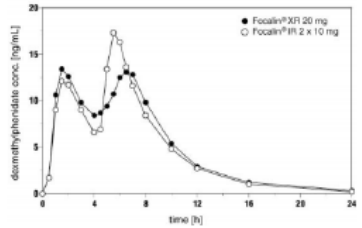
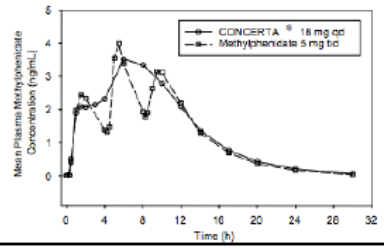
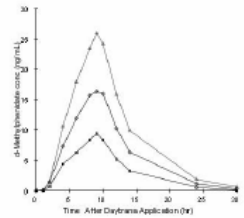
Methods: A group of 579 children with ADHD Combined Type, aged 7 to 9.9 years, were assigned to 14 months of medication management (titration followed by monthly visits); intensive behavioral treatment (parent, school, and child components, with therapist involvement gradually reduced over time); the two combined; or standard community care (treatments by community providers). Outcomes were assessed in multiple domains before and during treatment and at treatment end point (with the combined treatment and medication management groups continuing medication at all assessment points). Data were analyzed through intent-to-treat random-effects regression procedures.

Results: All 4 groups showed sizable reductions in symptoms over time, with significant differences among them in degrees of change. For most ADHD symptoms, children in the combined treatment and medication management groups showed significantly greater improvement than those given intensive behavioral treatment and community care. Combined and medication management treatments did not differ significantly on any direct comparisons, but in several instances (oppositional/aggressive symptoms, internalizing symptoms, teacher-rated social skills, parent-child relations, and reading achievement) combined treatment proved superior to intensive behavioral treatment and/or community care while medication management did not. Study medication strategies were superior to community care treatments, despite the fact that two thirds of community-treated subjects received medication during the study period.

Conclusions: For ADHD symptoms, our carefully crafted medication management was superior to behavioral treatment and to routine community care that included medication. Our combined treatment did not yield significantly greater benefits than medication management for core ADHD symptoms, but may have provided modest advantages for non-ADHD symptom and positive functioning outcomes.

A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. Arch Gen Psychiatry. 1999;56(12):1073-86.

Supplementary Slide- Stimulant Dose Equivalence

Name	Dose	Comments
methylphenidate (Ritalin)	10 mg (BID or TID)	•Short acting (3-4h): Ritalin, Methylin •Intermediate-acting (6-8h): Ritalin-SR, Methylin ER, Metadate ER. •Long-acting (8-10h): Ritalin LA, Metadate CD, Daytrana (patch) •Longest-acting (10-13h): Concerta
D-methylphenidate (Focalin)	5 mg (BID or TID)	
Focalin XR	10 mg *Equal to TDD of Focalin IR	Similar distribution and elimination to twice daily IR dosing You see a similar bimodal peak with Adderall XR 
Concerta	36 mg Other doses: (Ritalin = Concerta) 5 mg = 18 mg 15 mg = 54 mg	Novel in its distribution without bimodal peaks 
methylphenidate patch (Daytrana)	10 mg	"Nominal" or goal dose, since the actual amount of MPH in the patch reflects TDD rather than sustained concentration. *See chart below 

Nominal Dose Delivered (mg) Over 9 Hours*	Dosage Rate* (mg/hr)	Patch Size (cm^2)	Methylphenidate Content per Patch (mg)
10	1.1	12.5	27.5
15	1.6	18.75	41.3
20	2.2	25	55
30	3.3	37.5	82.5

*Nominal *in vivo* delivery rate in children and adolescents when applied to the hip, based on a 9-hour wear period.

Developed by Matt Swenson, MD, Utah Academy of Child & Adolescent Psychiatry. Available at: http://www.uacap.org/uploads/3/2/5/0/3250432/stimulant_equivalency. Accessed September 06 2017.

Supplementary Slide- Stimulant Dose Equivalence

mixed amphetamine salts (Adderall)	5 mg BID (10 mg Adderall XR)	Probably twice as potent and lasts 4-5 hrs rather than Ritalin's 3-4 hrs. If Adderall lasts 5 hours, expect Adderall XR to last about 10 hours (or double). However, see caveat below.
dextroamphetamine (Dextrostat or Dexedrine)	3.75 mg BID	*75% of Adderall dose since "mixed" amphetamines are 3:1 Dextro- verses Levo-enantiomer Similar pharmacokinetics to Adderall. Note that elimination is variable because rates of excretion and absorption are sensitive to gastric and bladder pH. Acidic = low absorption & fast excretion /Alkaline = high absorption & low excretion •Diet high in citrus fruits, vegetables, or dairy products increase urine pH •Diet high in meat products or cranberries can decrease urine pH
Dexadrine Spansules	7.5 mg	Probably lasts 8-10 hours but can be quite variable. Equal to TDD of Dexadrine IR.
Lisdexamfetamine (Vyvanse)	25 mg	A bit tricky: A prodrug that is converted to dextroamphetamine by the hydrolytic activity of red blood cells. The "conversion rate" is measured at 0.2948, meaning 30mg Vyvanse is equal to 8.85 mg dextroamphetamine, or 11.8 mg Adderall.

Developed by Matt Swenson, MD, Utah Academy of Child & Adolescent Psychiatry. Available at: http://www.uacap.org/uploads/3/2/5/0/3250432/stimulant_equivalency. Accessed September 06 2017.

Supplementary Slide- Desipramine

A double-blind comparison of desipramine and placebo in children and adolescents with chronic tic disorder and comorbid attention-deficit/hyperactivity disorder.

Background: Currently, there is no consensus on the best therapeutic approach to chronic tic disorders and comorbid attention-deficit/hyperactivity disorder (ADHD). To address this issue, we evaluated the tolerability and efficacy of the noradrenergic tricyclic antidepressant desipramine hydrochloride in the treatment of children and adolescents with chronic tic disorders and comorbid ADHD

Methods: Forty-one children and adolescents with chronic tic disorders, including Tourette disorder and comorbid ADHD, were studied in a 6-week, double-blind, placebo-controlled, parallel trial. Desipramine was titrated weekly up to 3.5 mg/kg per day. We rated ADHD and tic symptoms weekly and monitored adverse effects, laboratory findings, and cardiovascular parameters.

Results: Treatment with desipramine (mean total daily dose, 3.4 mg/kg per day) was well tolerated without meaningful adverse effects. Desipramine significantly reduced core symptoms of ADHD (ADHD Rating Scale; 42% decrease from baseline relative to placebo, P<.001), with equal response in inattentive symptoms and hyperactive/impulsive symptoms (P<.001 for both). The ADHD response rate was robust (71% vs 0%; desipramine vs placebo, P<.001). Likewise, desipramine significantly reduced tic symptoms (Yale Global Tic Severity Scale; 30% decrease from baseline relative to placebo, P<.001), with equal response in motor and phonic tic symptoms (P<.01 for both). The tic response rate was substantial (58% vs 5%; desipramine vs placebo, P<.001). There were small but statistically significant differences between desipramine and placebo in heart rate and blood pressure.

Conclusions: Treatment with desipramine was well tolerated and was associated with robust clinically significant reductions in tic and ADHD symptoms in children and adolescents with chronic tic disorders and ADHD diagnoses.

Spencer T, Biederman J, Coffey B, et al. A double-blind comparison of desipramine and placebo in children and adolescents with chronic tic disorder and comorbid attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 2002;59(7):649-56.

Supplementary Slide- Atomoxetine + Olanzapine

Combination use of atomoxetine hydrochloride and olanzapine in the treatment of attention-deficit/hyperactivity disorder with comorbid disruptive behavior disorder in children and adolescents 10-18 years of age.

Objective**:** The aim of this study was to assess the use of atomoxetine and olanzapine in combination to treat attention-deficit/hyperactivity disorder (ADHD) and comorbid disruptive behaviors in children and adolescents 10-18 years of age.

Methods: Eleven subjects ages 10-18 received open-label atomoxetine and olanzapine for a 10 week treatment period. Patients were assessed at baseline, 2 weeks, 4 weeks, 6 weeks, and 10 weeks (posttreatment). ADHD improvement was measured through the ADHD Rating Scale (ADHD-RS) (Investigator and Parent ratings). Aggression was measured through the Modified Overt Aggression Scale (MOAS).

Results: The combined use of atomoxetine and olanzapine resulted in statistically significant improvement in ADHD symptoms and overt aggression from baseline to posttreatment. As evidenced by a 33% reduction in symptoms on the ADHD-RS-I and the MOAS, 73% of patients were considered responders to ADHD treatment, whereas 55% responded to treatment for aggression. Both medications were generally well tolerated. Olanzapine treatment was associated with significant weight gain. Patients gained, on average, 3.9 kg. throughout the treatment period.

Conclusions: These data provide initial evidence that combination use of atomoxetine and olanzapine for the treatment of ADHD and comorbid disruptive behaviors was effective in reducing ADHD symptoms and aggressive behavior in a 10 week treatment period.

Holzer B, Lopes V, Lehman R. Combination use of atomoxetine hydrochloride and olanzapine in the treatment of attention-deficit/hyperactivity disorder with comorbid disruptive behavior disorder in children and adolescents 10-18 years of age. J Child Adolesc Psychopharmacol. 2013;23(6):415-8.

Supplementary Slide- Risperidone

Risperidone for attention-deficit hyperactivity disorder in people with intellectual disabilities.

Objective**:** To examine the effectiveness of risperidone for the treatment of attention deficit hyperactivity disorder in people with intellectual disabilities.

Methods: Eleven studies were considered but none were suitable for inclusion.

Conclusions: There is no evidence from RCTs that risperidone is effective for the treatment of ADHD in people with ID. Prescribing in this population can only be based on open-label studies or extrapolation from research in people with autism and disruptive behavior disorders; however these studies have not investigated people with ID separately so there are reservations regarding the applicability of these findings. Research into effectiveness and tolerability is urgently needed.

Thomson A, Maltezos S, Paliokosta E, Xenitidis K. Risperidone for attention-deficit hyperactivity disorder in people with intellectual disabilities. Cochrane Database Syst Rev. 2009;(2):CD007011

Supplementary Slide- Zinc Sulfate

Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: a double blind and randomized trial

Background: Attention-deficit hyperactivity disorder is an early-onset, clinically heterogeneous disorder of inattention, hyperactivity, and impulsiveness. The diagnosis and treatment of attention-deficit hyperactivity disorder continues to raise controversy, and, there is also an increase in treatment options. In this 6-week double blind, placebo controlled-trial, we assessed the effects of zinc plus methylphenidate in the treatment of children with attention deficit hyperactivity disorder. To the best of our knowledge, this study is the first double blind and placebo controlled clinical trial assessing the adjunctive role of zinc in ADHD.

Methods: Our subjects were 44 outpatient children (26 boys and 18 girls) between the ages of 5-11 (mean +/- SD was 7.88 +/- 1.67) who clearly met the DSM IV diagnostic criteria for attention-deficit hyperactivity disorder and they were randomized to methylphenidate 1 mg/kg/day + zinc sulfate 55 mg/day (with approximately 15 mg zinc element) (group 1) and methylphenidate 1 mg/kg/day + placebo (sucrose 55 mg) (group 2) for a 6 week double blind clinical trial. The principal measure of the outcome was the Teacher and Parent ADHD Rating Scale. Patients were assessed by a child psychiatrist at baseline, 14, 28 and 42 days after the medication started.

Results: The present study shows the Parent and Teacher Rating Scale scores improved with zinc sulfate over this 6-week, double blind and placebo controlled trial. The behavior of the two treatments was not homogeneous across the time. The difference between the two protocols was significant as indicated by the effect on the group, the between-subjects factor ($F = 4.15$, d.f. = 1, $P = 0.04$; $F = 4.50$, d.f. = 1, $P = 0.04$ respectively). The difference between the two groups in the frequency of side effects was not significant.

Conclusions: This double-blind, placebo-controlled study demonstrated that zinc as a supplementary medication might be beneficial in the treatment of children with attention-deficit hyperactivity disorder. However, further investigations and different doses of zinc are required to replicate these findings in children with ADHD.

Akhondzadeh S, Mohammadi MR, Khademi M. Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: a double blind and randomized trial [ISRCTN64132371]. BMC Psychiatry. 2004;4:9.

Supplementary Slide- Iron Supplementation

Effects of iron supplementation on attention deficit hyperactivity disorder in children

Background: Iron deficiency has been suggested as a possible contributing cause of attention deficit hyperactivity disorder (ADHD) in children. This present study examined the effects of iron supplementation on ADHD in children.

Methods: Twenty-three nonanemic children (aged 5-8 years) with serum ferritin levels <30 ng/mL who met DSM-IV criteria for ADHD were randomized (3:1 ratio) to either oral iron (ferrous sulfate, 80 mg/day, n = 18) or placebo (n = 5) for 12 weeks. There was a progressive significant decrease in the ADHD Rating Scale after 12 weeks on iron (-11.0 +/- 13.9; P < 0.008), but not on placebo (3.0 +/- 5.7; P = 0.308).

Results: Improvement on Conners' Parent Rating Scale (P = 0.055) and Conners' Teacher Rating Scale (P = 0.076) with iron supplementation therapy failed to reach significance. The mean Clinical Global Impression-Severity significantly decreased at 12 weeks (P < 0.01) with iron, without change in the placebo group.

Conclusions: Iron supplementation (80 mg/day) appeared to improve ADHD symptoms in children with low serum ferritin levels suggesting a need for future investigations with larger controlled trials. Iron therapy was well tolerated and effectiveness is comparable to stimulants.

Konofal E, Lecendreux M, Deron J, et al. Effects of iron supplementation on attention deficit hyperactivity disorder in children. Pediatr Neurol. 2008;38(1):20-6.