ADHD –הטיפול התרופתי
אפשרויות וקשיים

ד"ר איתי ברגר

המרכז הנוירו-קוגניטיבי

והיחידה לנוירולוגיה של הילד

הדסה והאוניברסיטה העברית

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- **All fees were paid to Hadassit (The technology transfer company of Hadassah University Hospitals)**

BETTER DIAGNOSIS

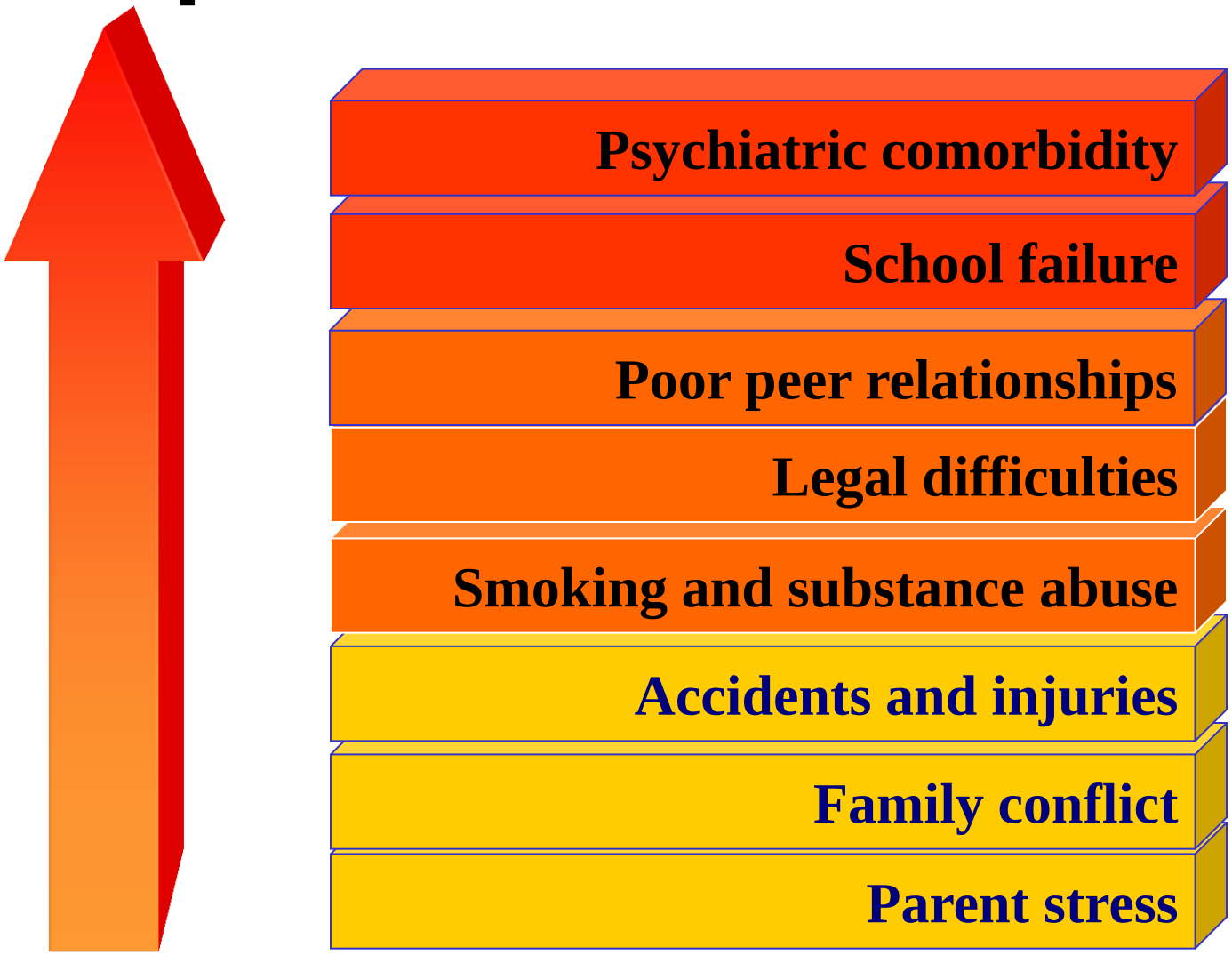
Primary Prejudice about ADHD

"It's essentially a simple problem, a matter of willpower"

"It's just being too hyper and not listening"

"Everyone with ADHD can pay attention very well for certain specific activities"

ADHD:
Impairment in ADHD



מדוע לטפל בהפרעת קשב?

Shaw *et al. BMC Medicine* 2012, **10**:99
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BMC Medicine

RESEARCH ARTICLE Open Access

A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment

Monica Shaw[1†], Paul Hodgkins[2*†], Hervé Caci[3], Susan Young[4], Jennifer Kahle[5], Alisa G Woods[6] and L Eugene Arnold[7]

Abstract

Background: In childhood, attention deficit/hyperactivity disorder (ADHD) is characterized by age-inappropriate levels of inattentiveness/disorganization, hyperactivity/impulsiveness, or a combination thereof. Although the criteria for ADHD are well defined, the long-term consequences in adults and children need to be more comprehensively understood and quantified. We conducted a systematic review evaluating the long-term outcomes (defined as 2 years or more) of ADHD with the goal of identifying long-term outcomes and the impact that any treatment (pharmacological, non-pharmacological, or multimodal) has on ADHD long-term outcomes.

Methods: Studies were identified using predefined search criteria and 12 databases. Studies included were peer-reviewed, primary studies of ADHD long-term outcomes published between January 1980 to December 2010. Inclusion was agreed on by two independent researchers on review of abstracts or full text. Published statistical comparison of outcome results were summarized as poorer than, similar to, or improved versus comparators, and quantified as percentage comparisons of these categories.

Results: Outcomes from 351 studies were grouped into 9 major categories: academic, antisocial behavior, driving, non-medicinal drug use/addictive behavior, obesity, occupation, services use, self-esteem, and social function outcomes. The following broad trends emerged: (1) without treatment, people with ADHD had poorer long-term outcomes in all categories compared with people without ADHD, and (2) treatment for ADHD improved long-term outcomes compared with untreated ADHD, although not usually to normal levels. Only English-language papers were searched and databases may have omitted relevant studies.

Conclusions: This systematic review provides a synthesis of studies of ADHD long-term outcomes. Current treatments may reduce the negative impact that untreated ADHD has on life functioning, but does not usually 'normalize' the recipients.

Keywords: ADHD, adult, childhood, outcomes, psychiatry, systematic

מדוע לטפל בהפרעת קשב?

- ירידה באיכות החיים
- התפתחות תחלואה נלווית במשך הזמן
- השפעה על תופעות עתידיות

Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study

Søren Dalsgaard, Søren Dinesen Østergaard, James F Leckman, Preben Bo Mortensen, Marianne Giørtz Pedersen

Summary

Background Attention deficit hyperactivity disorder (ADHD) is a common mental disorder associated with factors that are likely to increase mortality, such as oppositional defiant disorder or conduct disorder, criminality, accidents, and substance misuse. However, whether ADHD itself is associated with increased mortality remains unknown. We aimed to assess ADHD-related mortality in a large cohort of Danish individuals.

Methods By use of the Danish national registers, we followed up 1·92 million individuals, including 32 061 with ADHD, from their first birthday through to 2013. We estimated mortality rate ratios (MRRs), adjusted for calendar year, age, sex, family history of psychiatric disorders, maternal and paternal age, and parental educational and employment status, by Poisson regression, to compare individuals with and without ADHD.

Findings During follow-up (24·9 million person-years), 5580 cohort members died. The mortality rate per 10 000 person-years was 5·85 among individuals with ADHD compared with 2·21 in those without (corresponding to a fully adjusted MRR of 2·07, 95% CI 1·70–2·50; p<0·0001). Accidents were the most common cause of death. Compared with individuals without ADHD, the fully adjusted MRR for individuals diagnosed with ADHD at ages younger than 6 years was 1·86 (95% CI 0·93–3·27), and it was 1·58 (1·21–2·03) for those aged 6–17 years, and 4·25 (3·05–5·78) for those aged 18 years or older. After exclusion of individuals with oppositional defiant disorder, conduct disorder, and substance use disorder, ADHD remained associated with increased mortality (fully adjusted MRR 1·50, 1·11–1·98), and was higher in girls and women (2·85, 1·56–4·71) than in boys and men (1·27, 0·89–1·76).

Interpretation ADHD was associated with significantly increased mortality rates. People diagnosed with ADHD in adulthood had a higher MRR than did those diagnosed in childhood and adolescence. Comorbid oppositional defiant disorder, conduct disorder, and substance use disorder increased the MRR even further. However, when adjusted for these comorbidities, ADHD remained associated with excess mortality, with higher MRRs in girls and women with ADHD than in boys and men with ADHD. The excess mortality in ADHD was mainly driven by deaths from unnatural causes, especially accidents.

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הטיפול התרופתי

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ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents

Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management

Pediatrics 2011;128;1007; originally published online October 16, 2011;
DOI: 10.1542/peds.2011-2654

RECOMMENDATION 3:
The clinician should recommend stimulant medication in children with ADHD

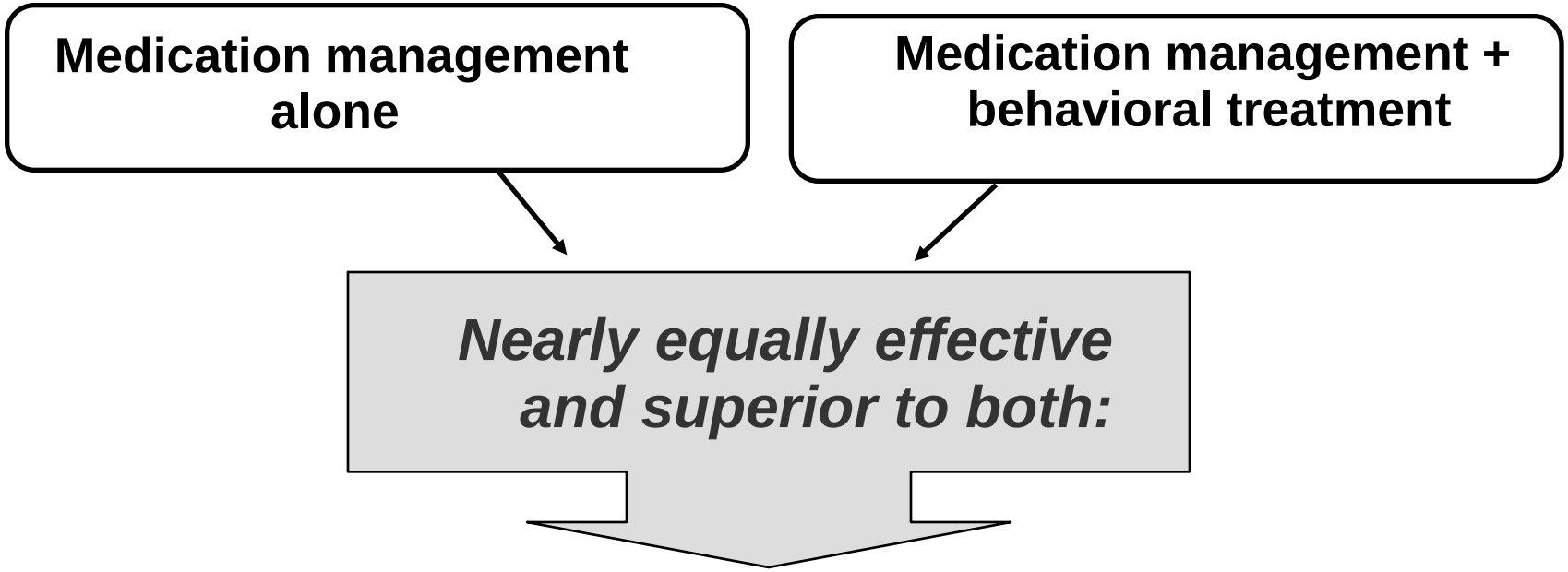
- For most children, stimulant medication is highly effective in the management of the core symptoms of ADHD
- For many, behavioral interventions are valuable as primary treatment or as an adjunct in the management of ADHD, based on the nature of coexisting conditions, specific target outcomes, and family circumstances

Stimulant Medication

- **In many cases, stimulant medication also improves child's ability, and decreases emotional over-reactivity, thereby leading to improved relationships with peers and parents**

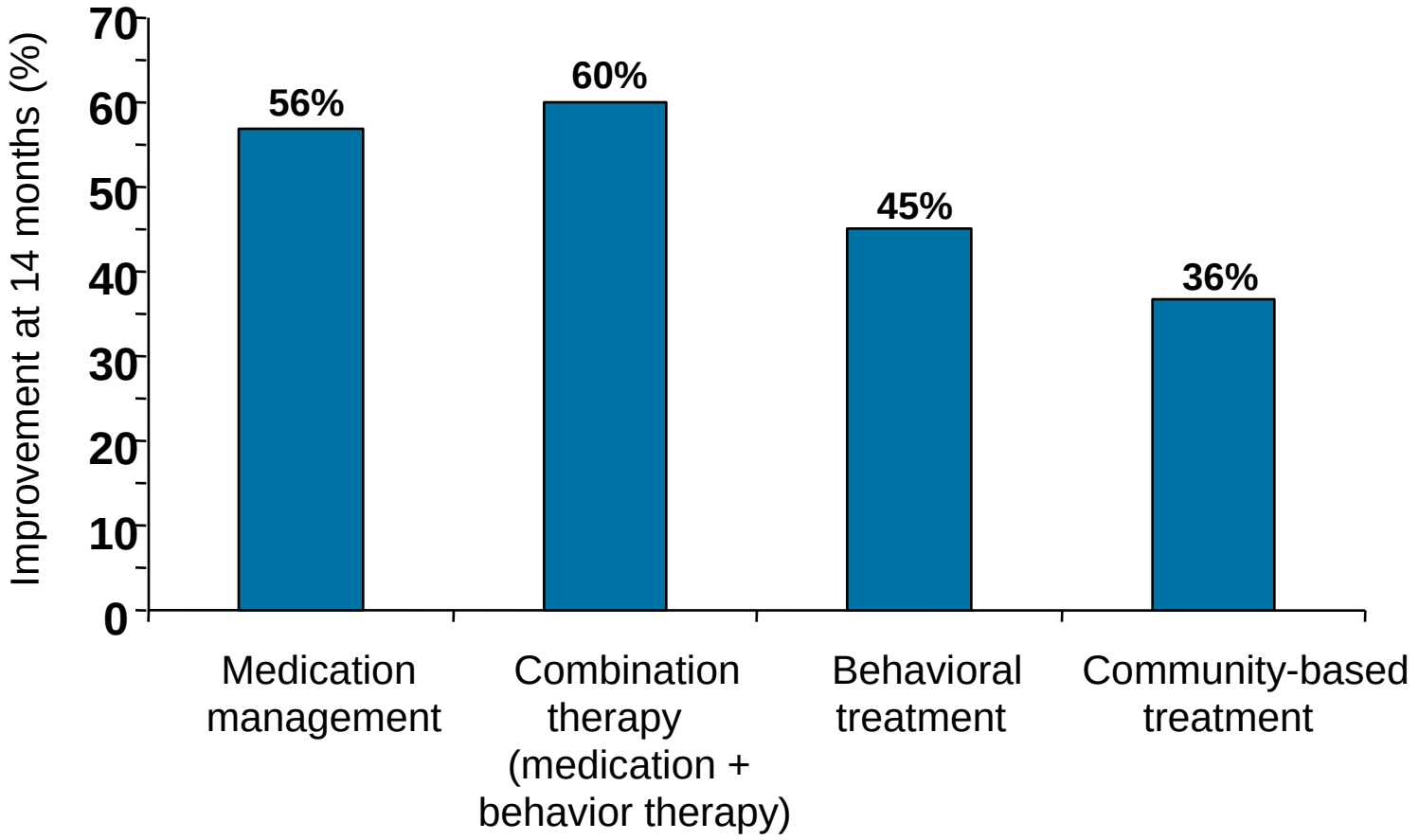
ADHD: MTA Results

All treatment arms found to be effective on an absolute basis



MTA Study Group, *Arch Gen Psych*, 1999 Dec;56(12):1073-86

Long-Term Outcomes of Therapies for ADHD in the MTA Study



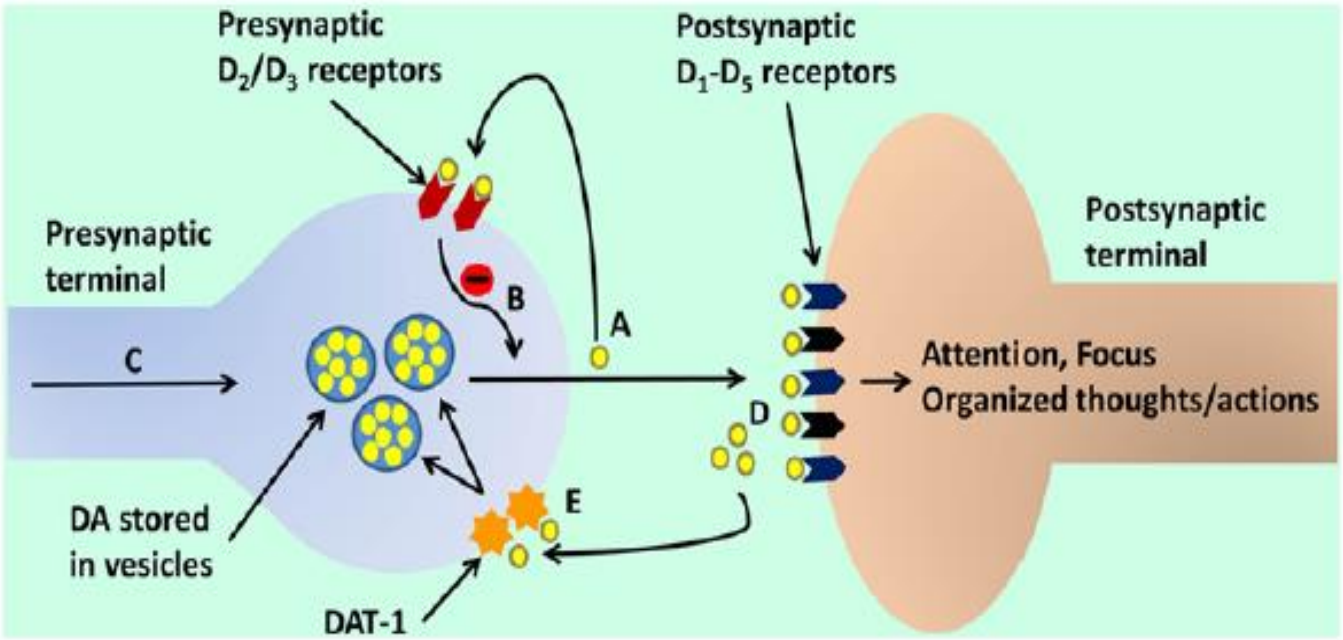
A Chemical Problem

- **ADHD is fundamentally a chemical problem**
- **Most effective treatment is to change the chemistry with medication**
- **Unless the problematic chemistry is changed, other interventions are not likely to be very effective**

ADHD: Targets of Pharmacotherapy

- **Core symptoms:**
  - **Inattentive ± hyperactive, impulsive**
- **Associated impairment:**
  - **occupational failure, social and academic deficits**
- **Pattern of comorbid disorders:**
  - **oppositional, antisocial, substance use, mood and anxiety disorders**

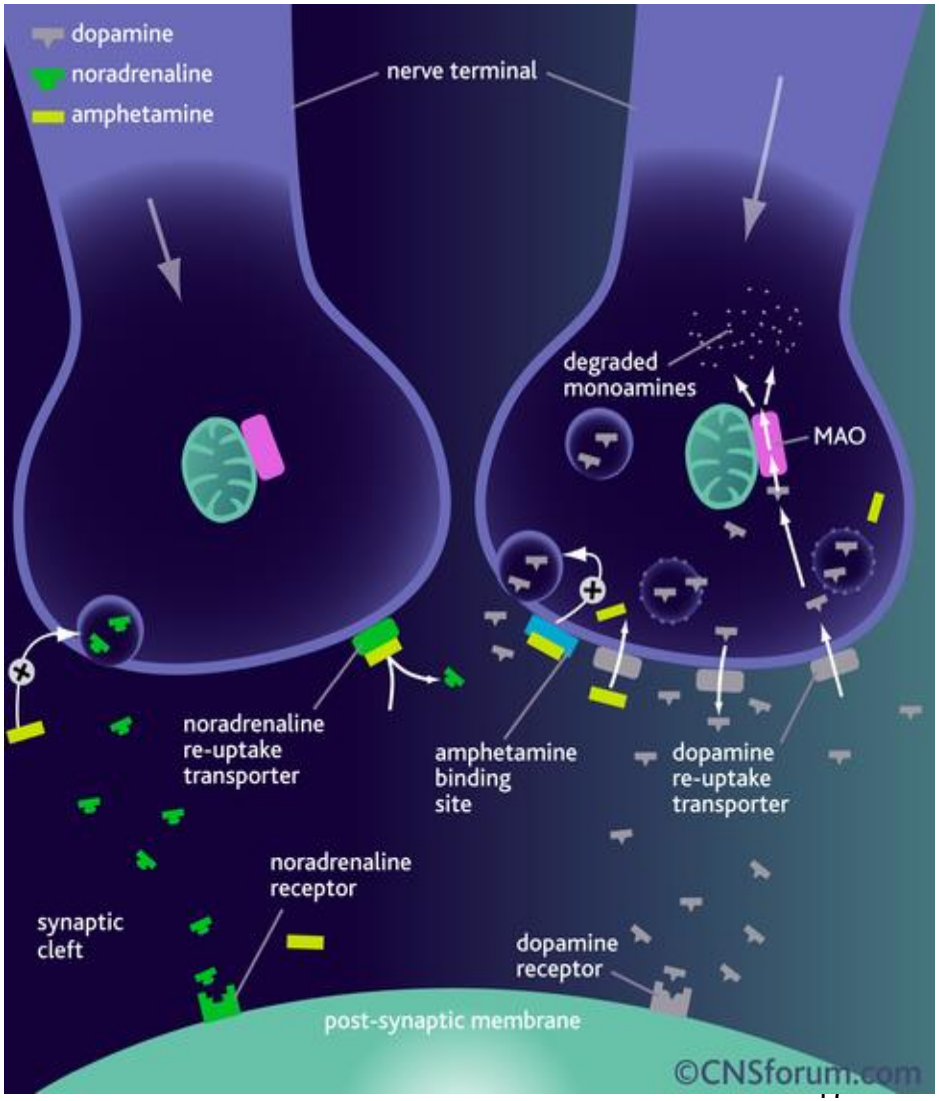
הטיפול בסטימולנטים



- **Amphetamines and Methylphenidate based therapies are approved by the FDA for all age groups**
- **The therapeutic effects elicited primarily through inhibition of the pre-synaptic dopamine transporter, with a lesser effect on the nor-epinephrine transporter**

הטיפול בסטימולנטים

- **The net effect is (inhibit DAT-1 and NET) = inhibiting the reuptake of DA and NE**
- **However, amphetamine also gains access into the pre-synaptic terminal via DAT-1 and NET to release the stored NTs**
- **Both stimulants inhibit monoamine oxidase, the enzyme that metabolizes these catecholamines; however, amphetamine is the more potent of the two (Volkow et al, *Arch Gen Psychiatry 1995;* Pliszka et al, *Neuropsychol Rev 2007)***



STIMULANTS

- **Thus, the net effect with either stimulant is to rectify the level of NTs such as DA and NE in the synapse**
- **The slightly different mechanism of action between methylphenidate and amphetamine explains why some patients failing to respond to one stimulant show a better response with the other**
- **Methylphenidate and amphetamines are considered as equally efficacious for long-term treatment**
- **Both immediate and extended-release forms are available and have shown equal efficacy in clinical trials**

ADHD

Pharmacologic Treatments

Approved by FDA for ADHD

Stimulants

- Methylphenidate
- Amphetamine compounds
- Dextroamphetamine
- Lisdexamfetamine

Nonstimulant

- Atomoxetine

Not Approved by FDA for ADHD

Antidepressants

- Tricyclics
- Bupropion

Antihypertensives

- Clonidine
- Guanfacine

Miscellaneous

- Combined pharmacotherapy
- Modafinil
- Neuroleptics (only in severe cases with monitoring)

Wilens TE, et al. *Annu Rev Med.* 2002; Greenhill LL. Nathan PE, Gorman J, *Treatments That Work. 2008*

Stimulant Medications

- **Amphetamine**
  - **- dextroamphetamine (Dexedrine): 4-6 hours**
  - **d, l amphetamine (Adderall): 4-6 hours**
  - **Extended release (Adderall-XR) 8-10 hours**
  - **Lisdexamfetamine (Vyvance) 10-12 hours**

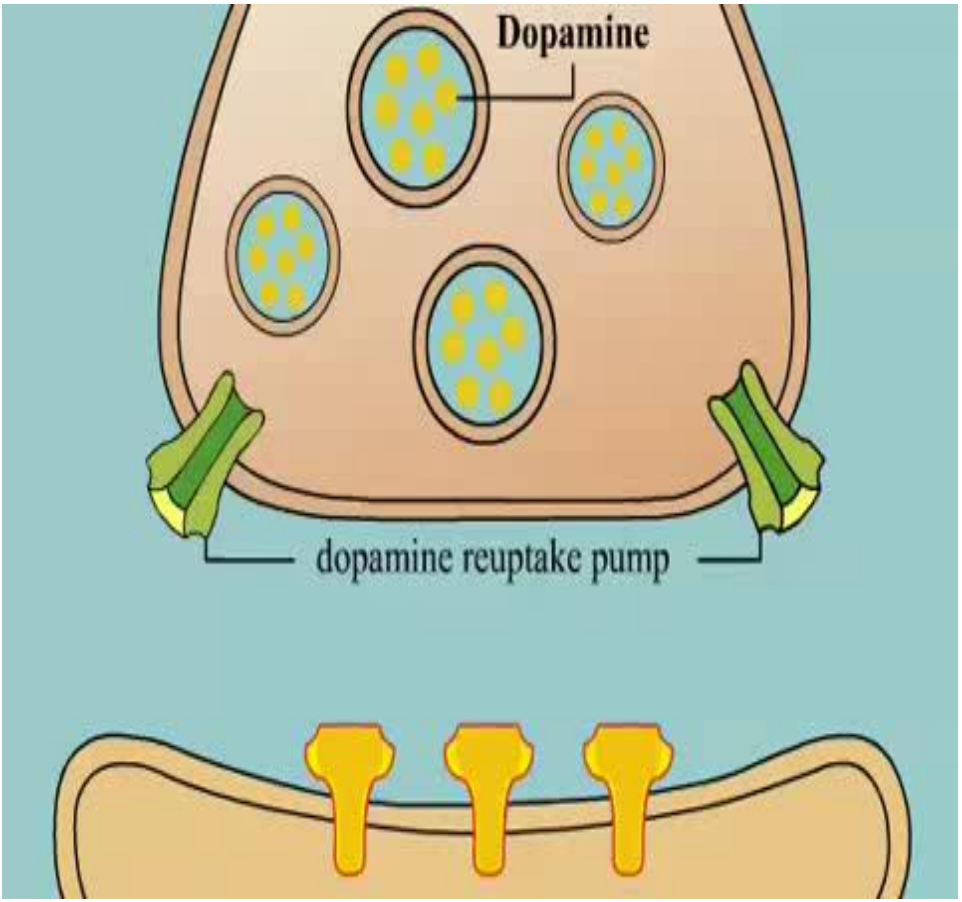
- **Methylphenidate**
  - **Ritalin: 4 hours**
  - **Concerta: triphasic, 10-12 hours**
  - **Ritalin-LA (biphasic) 6-8 hours**
  - **Focalin (d -isomer) 4 hours**
  - **Focalin-XR 8 hours**

STIMULANTS

- **Stimulant medications currently available include short, intermediate, and long-acting methylphenidate, or dextroamphetamine**
- **Each stimulant improved core symptoms equally**
- **Individual children, however, may respond to one of the stimulants but not to another (Pediatrics, 2001)**

Pharmacodynamics

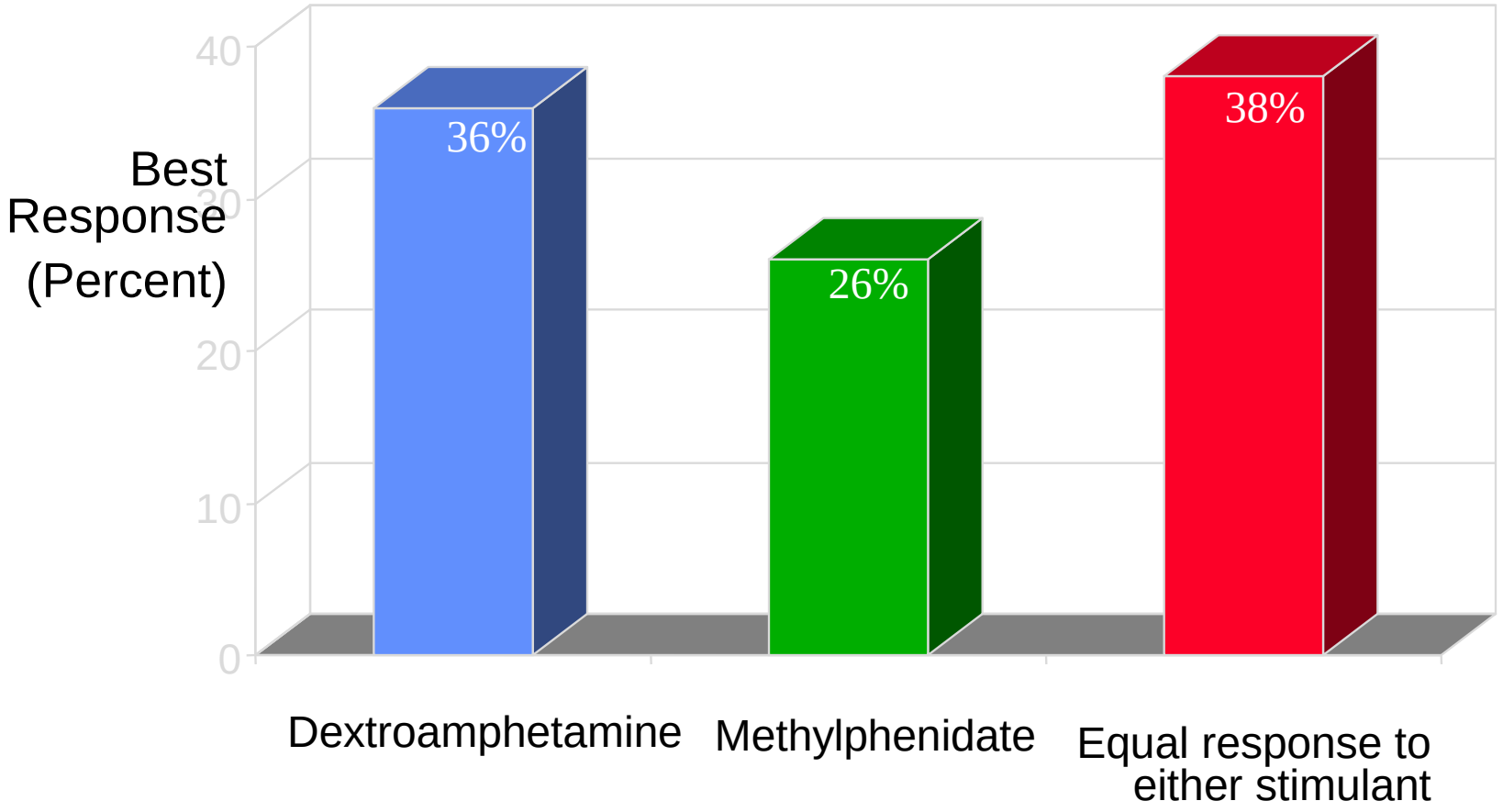
Methylphenidate - pure uptake inhibitor without other presynaptic activity



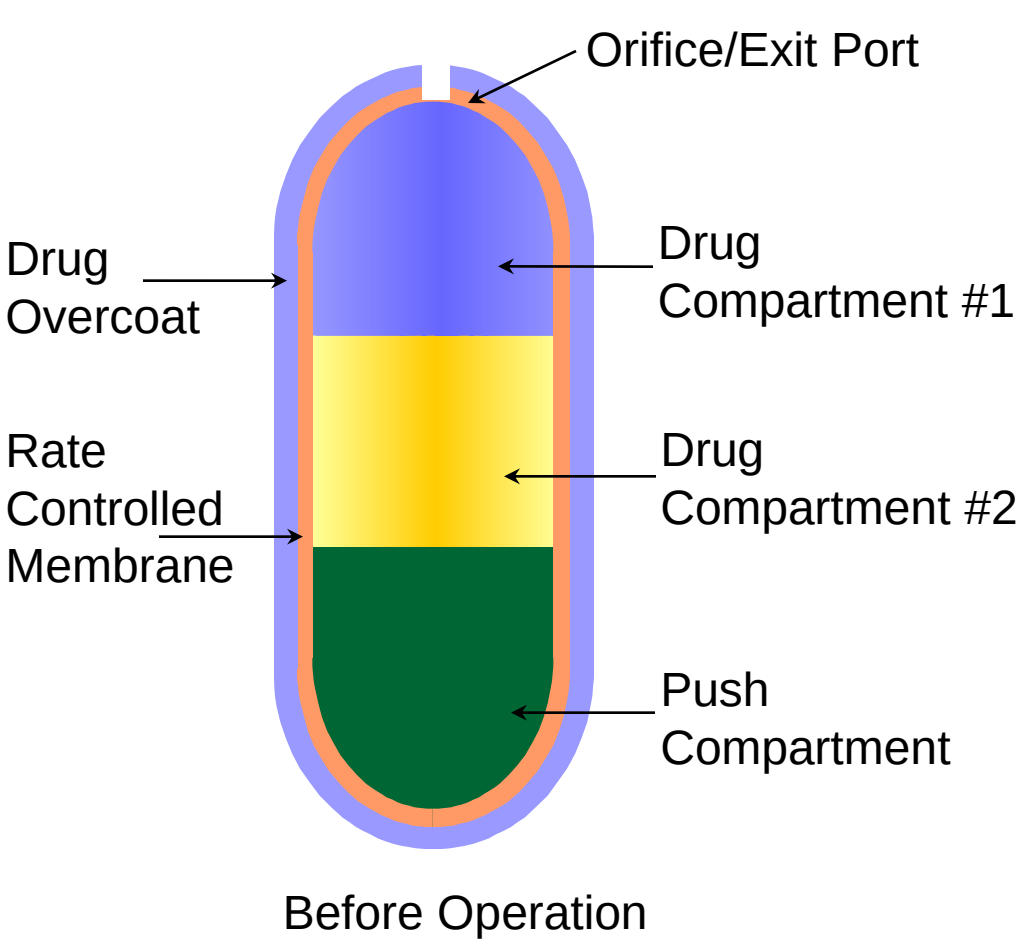
- **MPH acts by blocking the reuptake of dopamine and norepinephrine.**
- **As a result, the natural effect of dopamine and norepinephrine on the post-synaptic neurons is amplified.**
- **Minimal to no-effect on Serotonin**

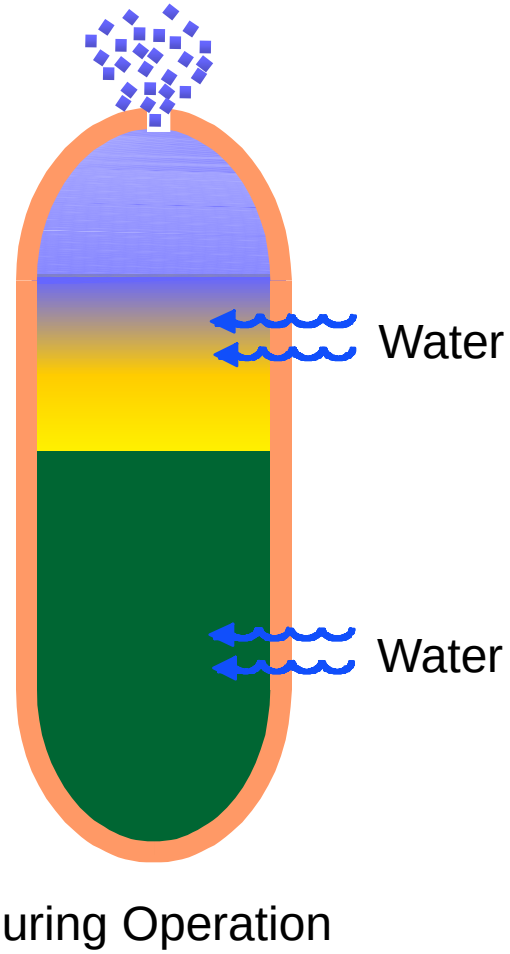
ADHD
Response to Stimulants

Meta-analysis of within-subject comparative trials evaluating response to stimulant medications



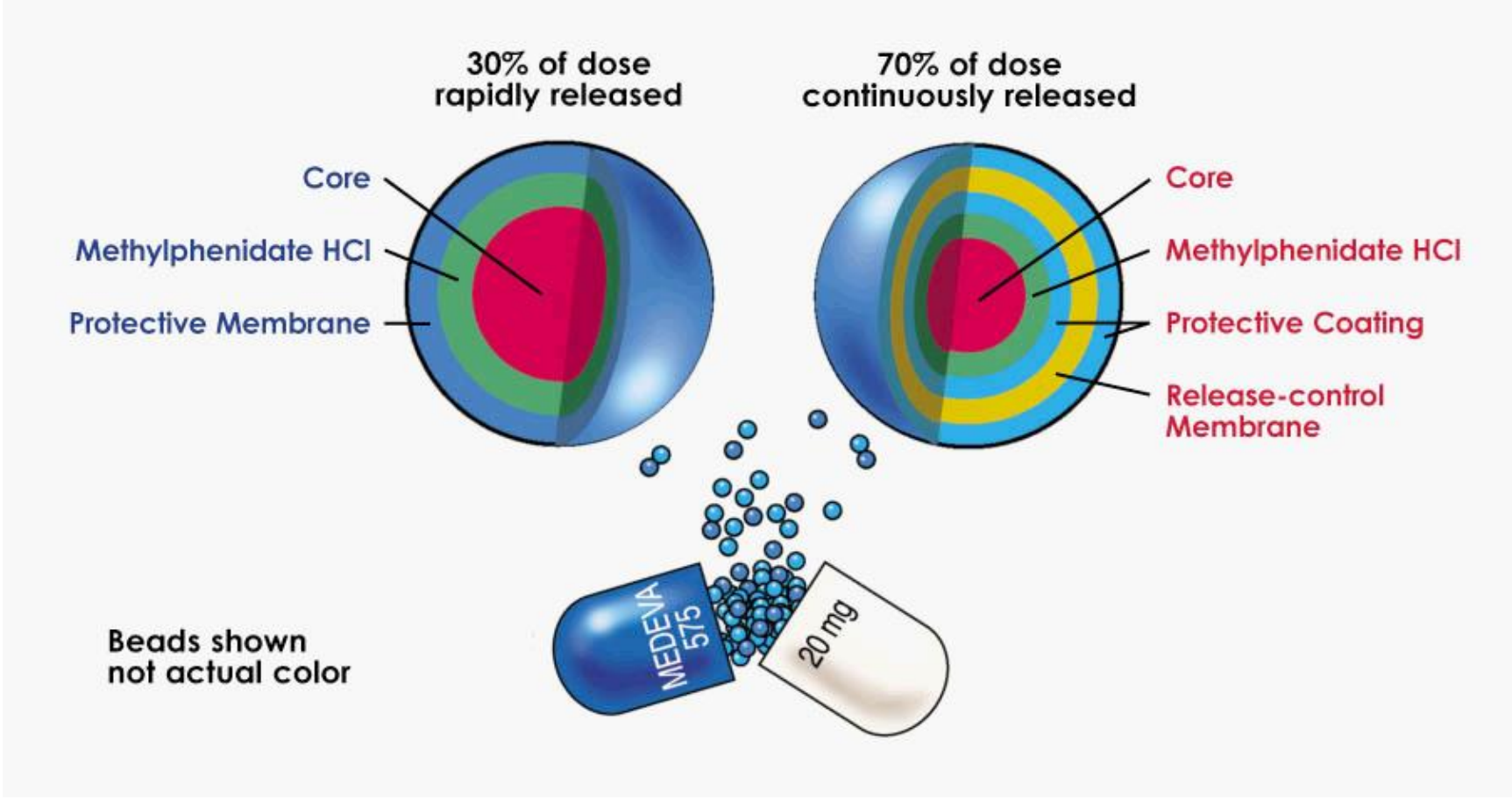
OROS (methylphenidate HCl)-
Concerta
Capsule-Shaped Tablet





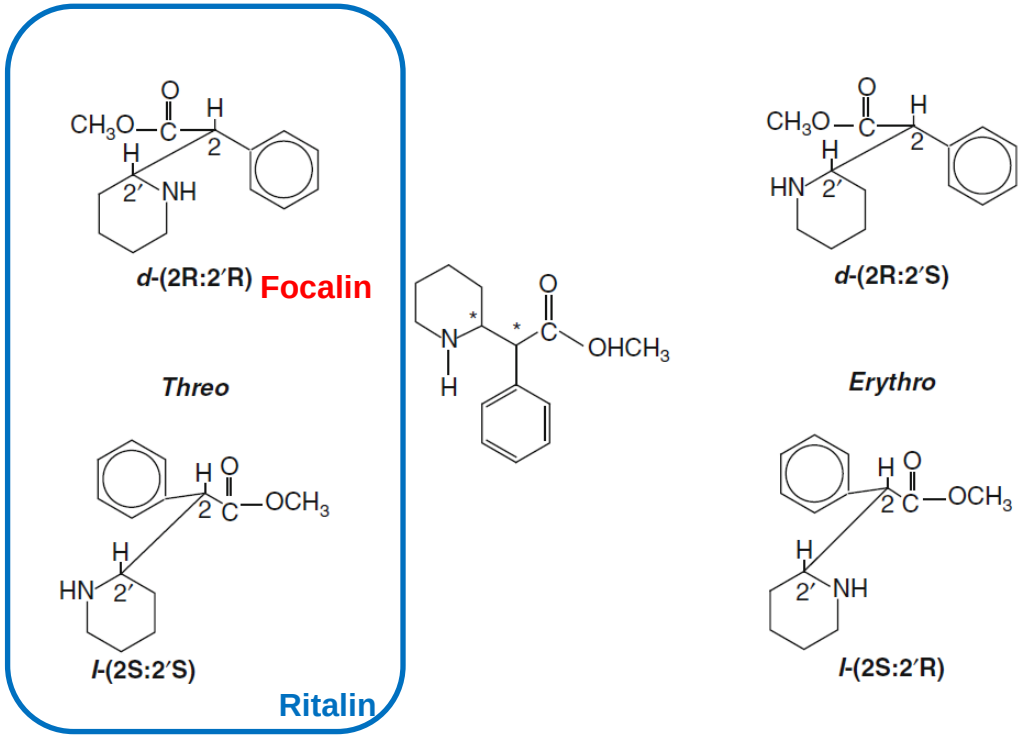
Ritalin LA (methylphenidate)

Biphasic Release: Bead-Delivery System



Centedrin → Ritalin → Focalin

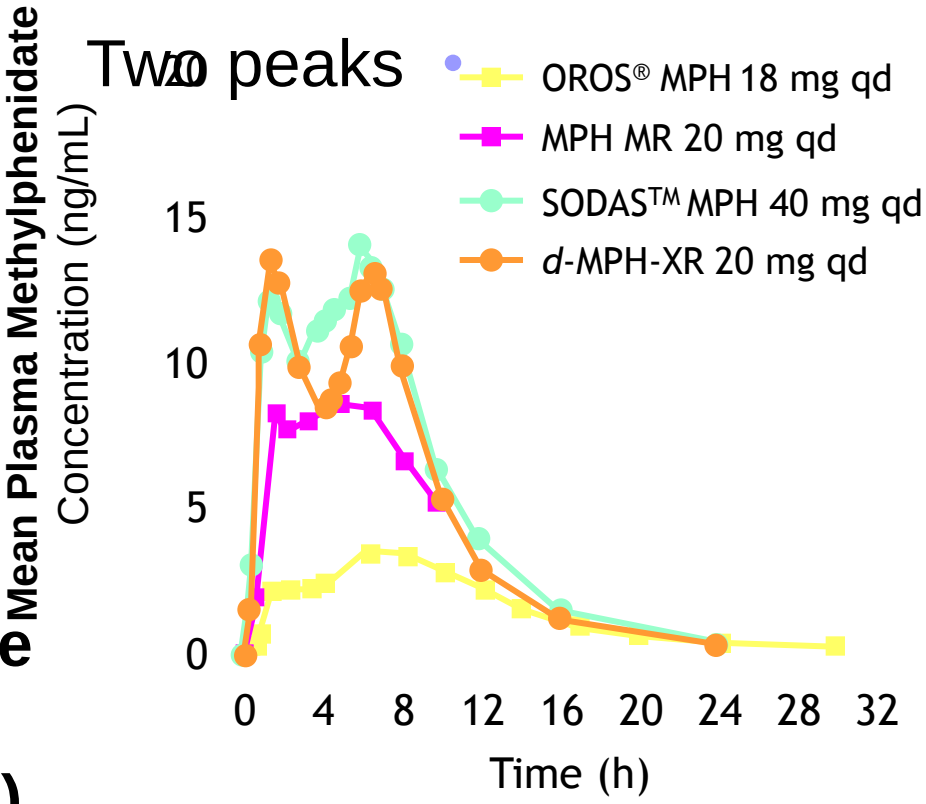
d/l-threo/erythro → d/l-threo → d-threo



d-MPH-XR (Focalin XR™)

- SODAS™ release system
  - 50% IR *d*-MPH beads and 50% ER *d*-MPH beads covered by polymer overcoat
  - Can be sprinkled on food
- Single isomer technology
  - Composed of only the *d*-MPH stereoisomer (dexmethylphenidate)

♦ Mean plasma concentrations over time



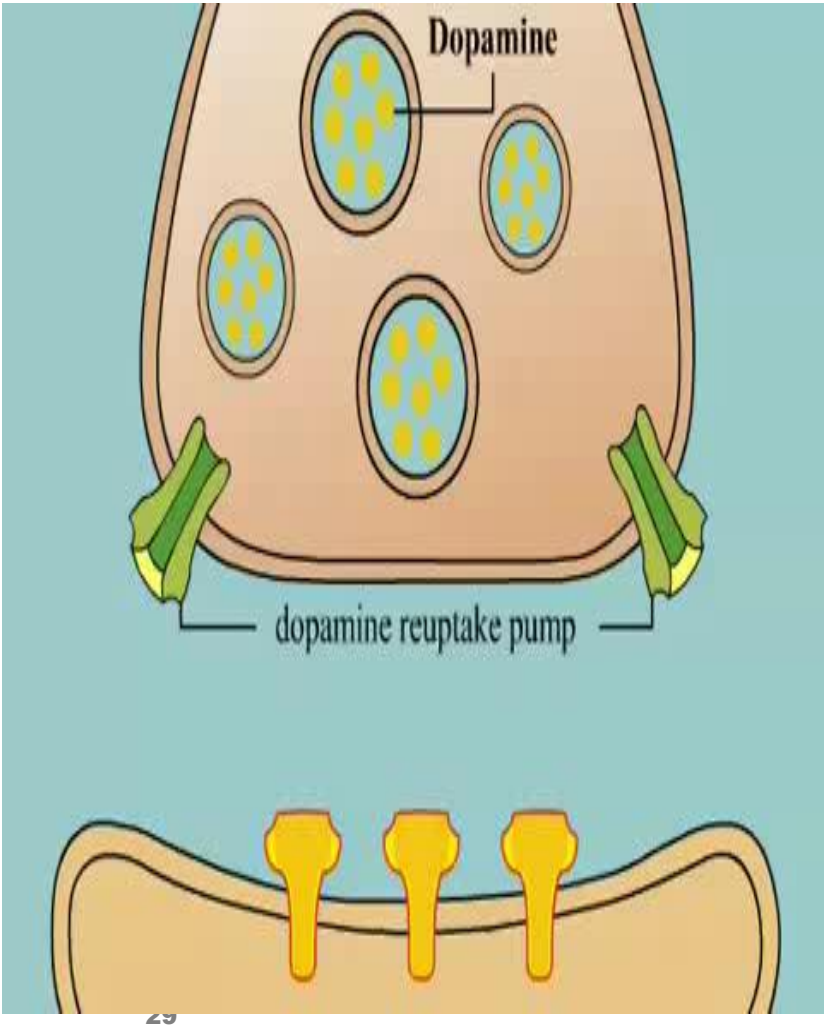
Source: Focalin XR™ [package insert], Novartis Pharmaceuticals Corporation.

טיפול בסטימולנטים

- **The efficacy and tolerability of had significantly greater improvements on both the teacher parent rating components**
- **Overall, the treatments were well tolerated, and most adverse events were mild**

(Wolraich, Pediatrics, 2001)

Pharmacodynamics
Amphetamines



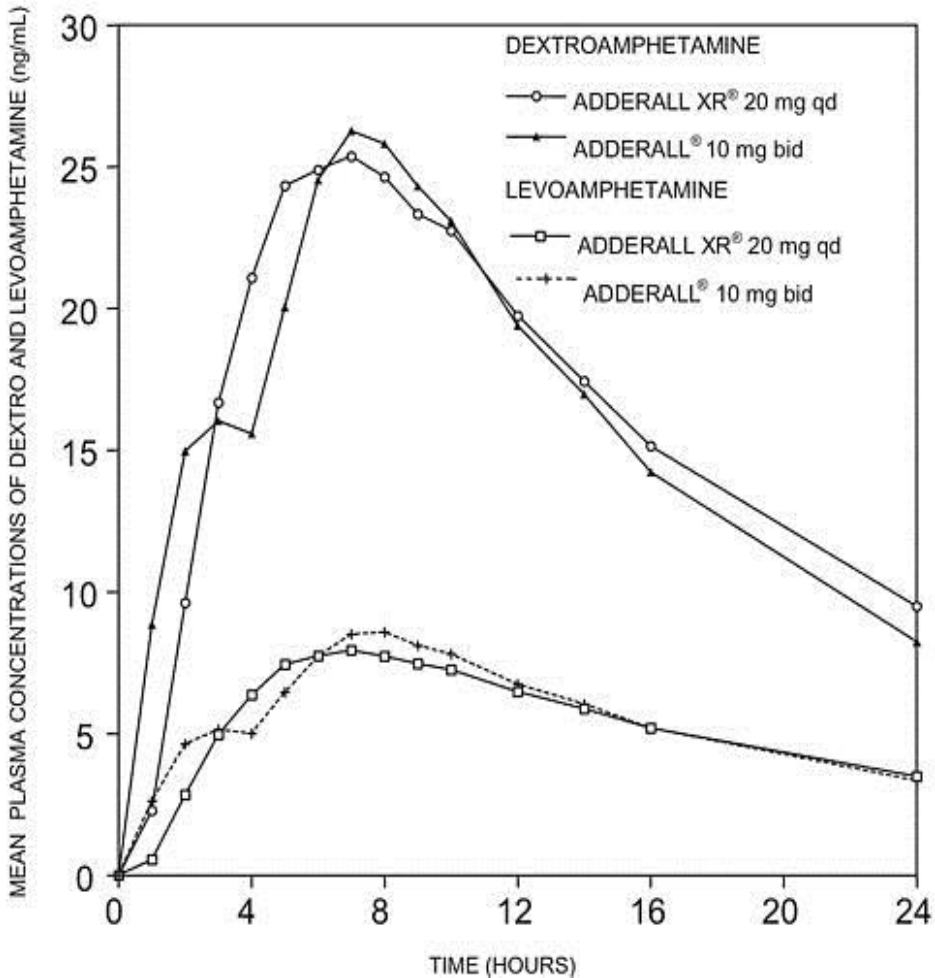
- **Amphetamines – similar to dopamine, and can enter the presynaptic neuron via its dopamine transporters as well as by diffusing through the neural membrane directly**
- **Once inside the presynaptic neuron, amphetamines force the dopamine molecules out of their storage vesicles and expel them into the synaptic gap**
- **Amphetamines also seem to reduce the reuptake of dopamine.**
- **Amphetamines remove the inhibiting effect of glutamate receptors thus releasing this "natural brake", making the dopaminergic neurons more readily excitable**

ADDERALL

- **Amphetamine combination**
- **Racemic stereoisomers; dextro isomer of amphetamine saccharate and d, & l-amphetamine asperate salts mixed in 3:1 ratio**

Pharmacokinetics - Adderall XR (2001)

- Bead filled (mixed amphetamine combination) capsule that upon administration mimics twice daily dosing
- Half of the beads immediate release while the other half are extended release
- Adderall XR reaches its peak plasma concentration in approximately 7 hours



Prodrug Stimulants

- **The prodrug concept – a pharmacologically inactive chemical that might be used to alter the physiochemical properties of drugs to increase their usefulness or reduce their toxicity**
- **The International Union of Pure and Applied Chemistry definition - “any compound that undergoes biotransformation before exhibiting its pharmacological effects”**
- **Inactive until metabolized by enzymes into an active pharmacologic moiety**
- **Designed to overcome pharmaceutical and pharmacokinetic barriers to the clinical application of drugs - low oral absorption, lack of site specificity, chemical instability, toxicity, and poor patient acceptability (Stanczak, Pharm Rep 2006)**

Lisdexamfetamine Dimesylate

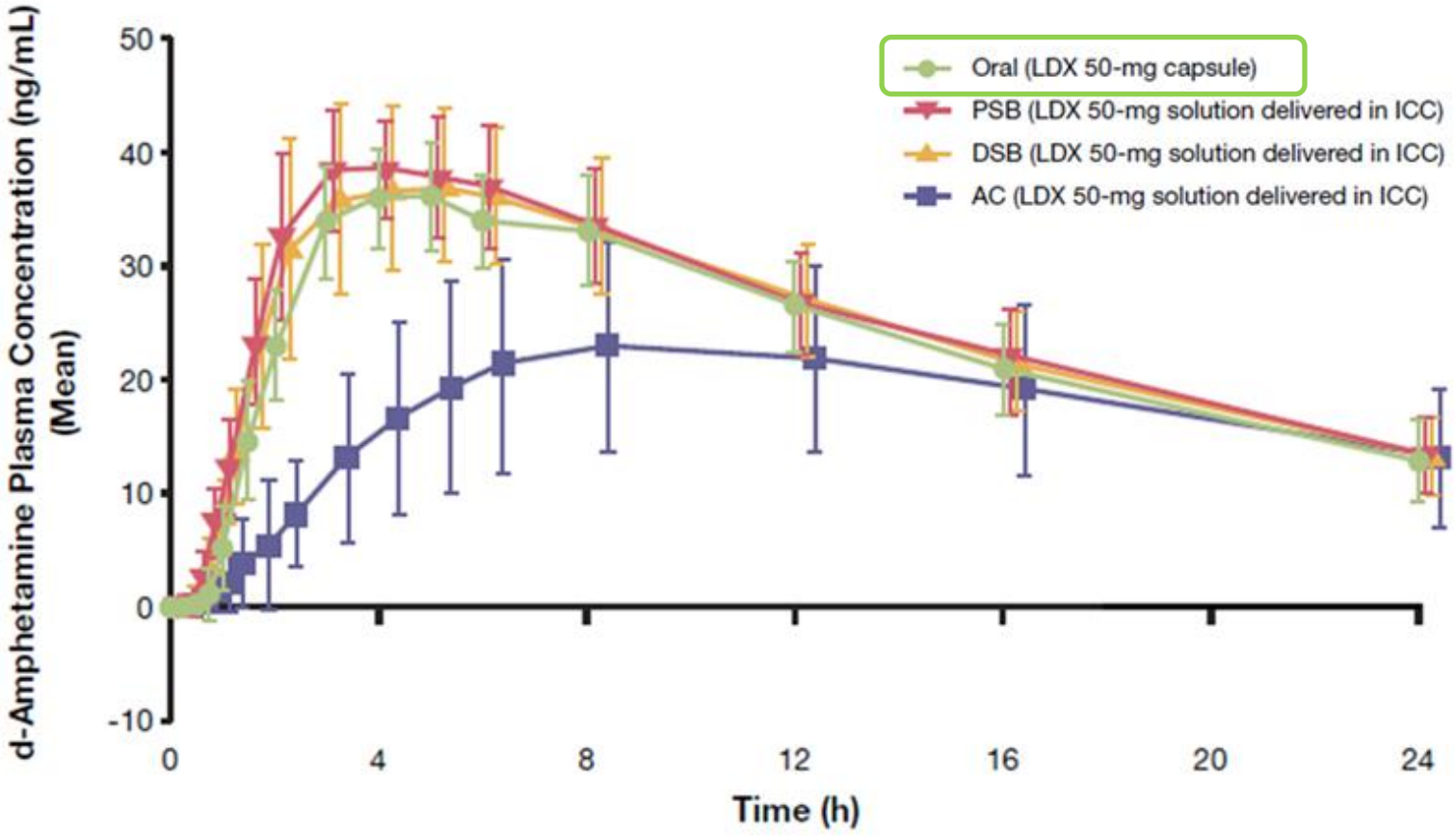
- After oral ingestion, LDX is converted to l-lysine, a naturally occurring essential amino acid, and active d-amphetamine, which is responsible for its activity
- The conversion of LDX to d-amphetamine is not affected by gastrointestinal pH and is unlikely to be affected by alterations in normal gastrointestinal transit times
- LDX was designed to provide a long duration of effect that is consistent throughout the day **(Shojaei, APA 2007)**

Lis-dex-amfetamine (LDX)

Pharmacokinetics - Vyvanse (2007)

- **When a Vyvanse pill is swallowed, enzymes in the gut (trypsinogen) and on the red blood cell split the lysine away from the dextoramphetamine, which then becomes active**
- **An unexpected benefit of this system is that the dextroamphetamine is released into the blood stream very steadily and works smoothly during a period up to ten hours or so after it is taken**
- **Even when snorted or injected, lisdexamfetamine exhibits notably reduced addiction potentials, when compared to other amphetamine-based stimulants**

Pharmacokinetics - Vyvanse



Stimulant Dosing

Medication	Starting Dose	Maximum Dose*	Usual Dosing
Ritalin®	5 mg QD/BID	2 mg/kg/day	TID (4 h)
Focalin®	2.5 mg	1 mg/kg/day	BID (5-6h?)
Concerta®	18 mg QD	2 mg/kg/day	QD (12 h)
Ritalin LA	10 mg QD	2 mg/kg/day	QD (6-8 h)
Focalin XR	5 mg QD	2 mg/kg/day	QD (8-10h?12)
Adderall®	2.5 to 5 mg QD	1.0 mg/kg/d	BID (6 h)
AdderallXR®	5-10 mg	1.0 mg/kg/d	QD (12 h)
Vyvanse	30 mg	30 to 70 qd	QD (13 hr)

*Maximum dosing may exceed FDA approved dose limits

Wilens, et al. *Annu Rev Med.* 2002;53:113-131; updated 2005.

Medications for ADHD

- Demonstrated safe and effective
- Often do not follow mg/kg rules
- Effective dose not based on age, wt or severity of sx
- Require titration and monitoring to "fine tune" to:
  - individual sensitivity
  - time frames for schedule and tasks

DOSE and SCHEDULE basic principles

- Unlike most other medications, stimulant dosages usually are not weight dependent
- Clinicians should begin with a low dose of medication and titrate upward because of the marked individual variability in the dose-response relationship (Pediatrics, 2011)

DOSE and SCHEDULE basic principles

- The first dose that a child's symptoms respond to may not be the best dose to improve function
- Clinicians should continue to use higher doses to achieve better responses
- This strategy may require reducing the dose when a higher dose produces side effects or no further improvement

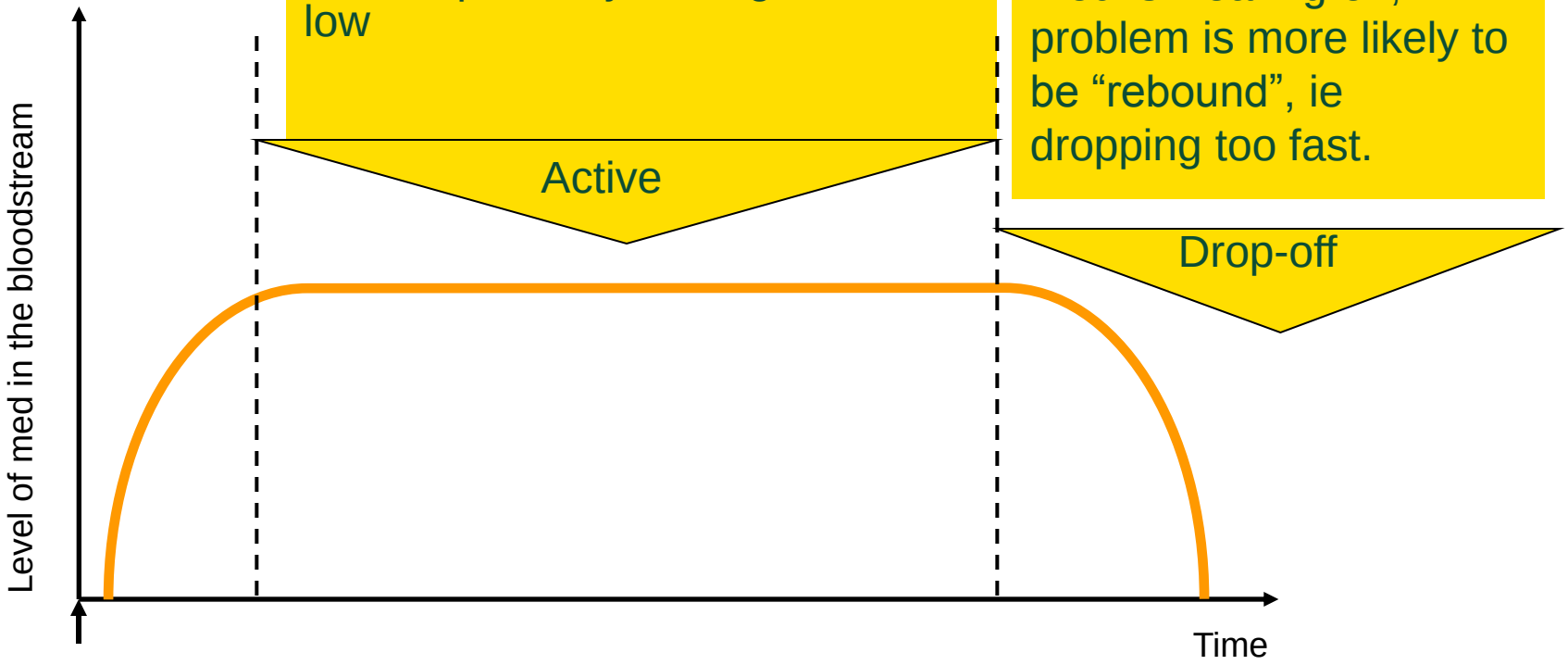
Time Frames and Rebound

If sustained feeling/acting excessively:

- "wired" or racy
- irritable
- serious, loss of "sparkle"

during the time dose is active, dose is probably too high or too low

If these effects occur as med is wearing off, problem is more likely to be "rebound", ie dropping too fast.



TE Brown, 2002

Advantages of Extended-Release Formulations of Stimulants

- Provides sustained medication levels throughout the day
- Smoother: minimizes ups and downs during day
- No mid-day dose required, eliminating trips to the school nurse, doses during workday
- Reduces stigma
- Enhances patient compliance
- May reduce illicit diversion and abuse

Methylphenidate Transdermal System

- **A transdermal formulation has been developed that contains MPH in a multipolymeric adhesive platform from which drug is released continuously over a wear time of 9 hours when applied to intact skin**
- **Based on the good results, MTS appeared to offer a useful strategy for once-daily administration of MPH in children with attention deficit hyperactivity disorder**
- **MTS can be adapted to individual duration-of-action needs by changing the patch wear time within the recommended 9 hours (McGough,J Att Dis, 2006)**

סטימולנטים –תופעות לוואי

- Stimulants are generally considered safe medications, with few contraindications to their use
- Side effects occur early in treatment and tend to be mild and short-lived
- The most common side effects are decreased appetite, stomachache or headache, delayed sleep onset, jitteriness, or social withdrawal
- Most of these symptoms can be successfully managed through adjustments in the dosage or schedule of medication (Pediatrics, 2001)

DOSE and SCHEDULE basic principles

- The best dose of medication for a given child is the one that leads to optimal effects with minimal side effects
- The dosing schedules vary depending on target outcomes
- No consistent controlled studies compare different dosing schedules

(Pediatrics, 2005)

סטימולנטים וטיקים

- The effects of medication on tics are unpredictable and transient
- The presence of tics before or during medical management of ADHD is not an absolute contraindication to the use of stimulant medications (Pediatrics, 2005)

סטימולנטים ואפילפסיה

- **Although MPH appears to be effective for children with epilepsy the issue of whether it may "lower seizure threshold" continues to be debated**
- **Studies of the use of MPH have not demonstrated an increase in seizure frequency or severity when it is added to appropriate anticonvulsant medications**
- **It was concluded that the efficacy of MPH in improving symptoms of ADHD was similar to reported rates in children with ADHD without epilepsy and MPH does not adversely affect the severity or frequency of seizures in the individuals with epilepsy, provided they are well controlled for epilepsy (Pediatrics, 2005, Epilepsy Behav 2011)**

סטימולנטים – חופשות

- Many clinicians recommend drug holidays during summers, although no controlled trials exist to indicate whether holidays have gains or risks

סטימולנטים –תופעות לוואי

- **Lack of response to treatment should lead clinicians to assess the accuracy of the diagnosis and the possibility of undiagnosed coexisting conditions**
- **Continuing lack of response to treatment may reflect:**
  - **unrealistic target symptoms**
  - **lack of information about the child's behavior**
  - **an incorrect diagnosis**
  - **a coexisting condition affecting the treatment of the attention deficit hyperactivity disorder**
  - **lack of adherence to the treatment regimen**
  - **a treatment failure**

Management Strategies for:

Severe Decrease In appetite

- Monitor weight
- Administer with or after meals
- Give high-calorie snacks
- Consider medication holidays

Headache/Stomachache, Irritability/Moodiness, or OCD Symptoms

- Decrease dose
- Switch to another stimulant
- Switch to 2nd line agent

Management Strategies for:

Delayed Sleep Latency

- **Sleep Hygiene/Bedtime rituals**
- **Change to shorter acting stimulant**
- **Consider adjunctive treatment (e.g., clonidine)**
- **Relaxation training**

Irritability

- **Evaluate when it occurs**
  - **Peak (too high dose)**
  - **Wear off (? rebound)**
- **Change dose**
- **Assess for comorbidity**
- **Consider adjunctive therapy**

Non-Stimulant options for ADHD

- **Specific noradrenergic agent approved for ADHD - Strattera (atomoxetine)**

- **Antidepressants (not approved for ADHD)**
  -Wellbutrin (buproprion)
  -Pamelor (nortriptyline)
  -Norpramin (desipramine)

- **Alpha-2 Agonists (Not Approved for ADHD)**
  -Catapres (clonidine)
  -Tenex (guanfacine)

NON STIMULANTS

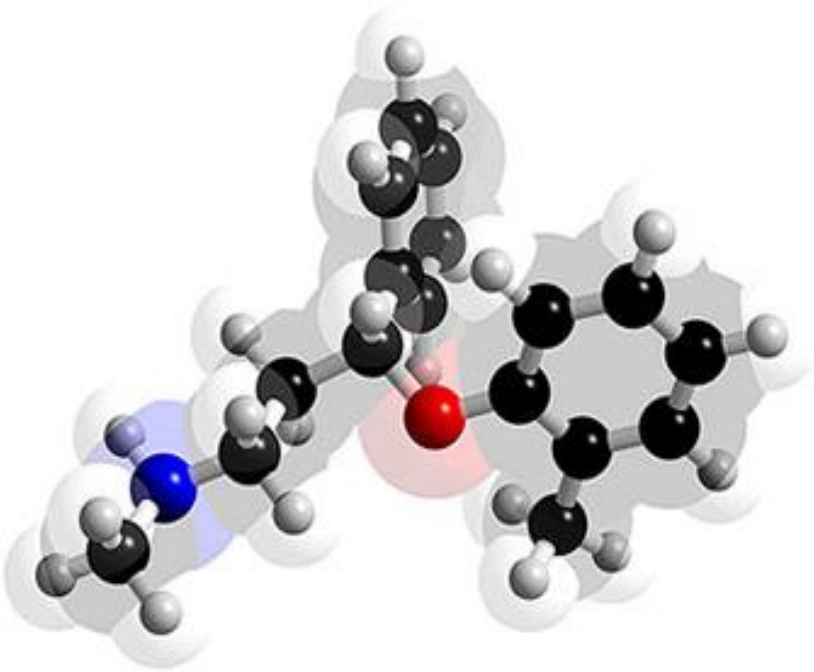
- **SNRI – Atomoxetine (FDA appr)**
- **Modafinil – non FDA appr**
- **Reboxetine - non FDA appr**
- **Clonidine - non FDA appr**
- **Guanfacine - non FDA appr**

Other Non-stimulant Meds for ADHD

- **Buproprion:**
  - **NE reuptake and DA reuptake inhibitor**
  - **Dosing is somewhat unclear in children; adults = mean 393mg/day of Wellbutrin XR**
- **Alpha$_2$ Adrenergic Agonists:**
  - **May strengthen working memory by improving functional connectivity in prefrontal cortex**
    - **Clonidine: less effective than stimulants, used as adjunct to manage tics, sleep problems and aggression**
      Adverse Effects include bradycardia and sedation
    - **Guanfacine: more selective for a_{2a} receptor**
      less sedation/dizziness than clonidine
      2-4 mg with effect between 2-4 weeks

Nonstimulant - Atomoxetine

- **A potent inhibitor of the presynaptic norepinephrine transporter, with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors**



Dosing of Atomoxetine in ADHD

- PDR Recommendations (Not a controlled substance)
  - Start ≈ 0.5 mg/kg/d
  - Target 1.2 mg/kg/d
  - Max of 1.4 mg/kg/d or 100 mg/d
- Example: 8 year old
  - Start 18 mg for 4-7 days in AM after food
  - 25 mg for 4-7 days then increase to 40 mg
- If already on stimulant, cross-taper, introduce ATMX then reevaluate need for stimulant
- Available in 10mg, 18mg, 25mg, 40mg, 60mg
- Sprinkling not formally tested and may irritate GI tract
- Full benefits often not seen until 4 to 6 weeks of treatment!

Physician Desk Reference®. Monvale, NJ:Thompson PDR;2005.

Atomoxetine

- **Showed symptom improvements even in lowest dose (0.5 mg/kg daily) compared with placebo**
- **All doses of atomoxetine were well tolerated**
- **The higher doses of atomoxetine (1.2 and 1.8 mg/kg daily) tended to be associated with anorexia (12% with both doses) and somnolence (7% and 11%, respectively)**
- **No significant differences in outcome were found in the 2 studies comparing IR-MPH and atomoxetine (Rappley, NEJM 2005)**

Atomoxetine

- Atomoxetine and other nonstimulants that are prescribed off-label in ADHD (bupropion) are less likely to be associated with abuse
- The 2007 treatment guidelines from the American Academy of Child and Adolescent Psychiatry suggest consideration of atomoxetine as the first medication for ADHD in persons with an active substance abuse problem, comorbid anxiety, or tics, or in patients who experience severe adverse effects when receiving stimulants

OTHER MEDICATIONS

- **Clonidine, occasionally used in the treatment of ADHD - limited studies of clonidine indicate that it is better than placebo in the treatment of core symptoms (although with effect sizes lower than those for stimulants)**
- **Its use has been documented mainly in children with ADHD and coexisting conditions, especially sleep disturbances and tics (Pediatrics 2005)**

OTHER MEDICATIONS

- **All studies which evaluated TAD indicated positive effects on ADHD symptoms**
- **Trials comparing tricyclic antidepressants with methylphenidate indicated either no differences in response or slightly better results with stimulant**
- **Clinicians should select tricyclic antidepressants after the failure of 2-3 stimulants and only if they are familiar with their use (Findling 2008)**

Safety of ADHD Medications

American Medical Assn. Report

- **"More than 170 studies involving >6,000 children using stimulant medications for ADHD…up to 90% will respond to at least 1 stimulant without major adverse events if drug titration is done carefully "**
- **Adverse effects from stimulants are generally mild, short-lived, & responsive to dosing or timing adjustments"** **(Goldman, et. al., 1998, pp 1103-1104)**

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POLICY STATEMENT

Cardiovascular Monitoring and Stimulant Drugs for Attention-Deficit/Hyperactivity Disorder

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of All Children

James M. Perrin, MD, Richard A. Friedman, MD, Timothy K. Knilans, MD, the Black Box Working Group, the Section on Cardiology and Cardiac Surgery

Cardiovascular Monitoring and Stimulant Drugs for Attention-Deficit/Hyperactivity Disorder

James M. Perrin, Richard A. Friedman, Timothy K. Knilans, the Black Box Working Group and the Section on Cardiology and Cardiac Surgery

Pediatrics 2008;122;451-453

Rates of Sudden Death in population vs. on stimulants

- **SD rates in General Population (Berger et al. Ped Clin N America, 2004)**
  - **0.6-6 / 100,000 children/ year**
  - **1 / 1000 adults/year**
- **Estimated SD rate on stimulants (based on Rx data)**
  - **0. 25/ 100,000 people/ year (calculated based on data)**
  - **0.50/ 100,000 people/ year (assuming 50% underreporting)**

(T.Wilens, 2006)

CARDIOVASCULAR MONITORING

SUMMARY

Although the sudden death of a child is a tragedy, there have been no studies or compelling clinical evidence to demonstrate that the likelihood of sudden death is higher in children receiving medications for ADHD than that in the general population. It has not been shown that screening ECGs before starting stimulants have an appropriate balance of benefit, risk, and cost-effectiveness for general use in identifying risk factors for sudden death. Until these questions can be answered, a recommendation to obtain routine ECGs for children receiving ADHD medications is not warranted.

FDA Pediatric Advisory Committee 2006

- **Reassessment by larger FDA Pediatric Advisory 2006**
  - **No additional CV risk in medically healthy kids**
  - **Risk with structural heart defects approximates that in child athletes**

(T. Wilens, 2006)

FDA Advisory Committee 2006 Recommendations

American Heart Association Guidelines

- **No need for ECG, Echo, Cardiac biopsy in routine cases**
- **But if:**
  - **Family history of SD (<30 yrs of age)**
    - **Hx of structural / congenital cardiac structural defects**
    - **Syncope**
    - **Chest pain**
    - **Palpitations**
    - **Hypertension**
- **Monitor during treatment**

(T. Wilens, 2006)

Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study

Søren Dalsgaard, Søren Dinesen Østergaard, James F Leckman, Preben Bo Mortensen, Marianne Giørtz Pedersen

Summary

Background Attention deficit hyperactivity disorder (ADHD) is a common mental disorder associated with factors that are likely to increase mortality, such as oppositional defiant disorder or conduct disorder, criminality, accidents, and substance misuse. However, whether ADHD itself is associated with increased mortality remains unknown. We aimed to assess ADHD-related mortality in a large cohort of Danish individuals.

Methods By use of the Danish national registers, we followed up 1·92 million individuals, including 32 061 with ADHD, from their first birthday through to 2013. We estimated mortality rate ratios (MRRs), adjusted for calendar year, age, sex, family history of psychiatric disorders, maternal and paternal age, and parental educational and employment status, by Poisson regression, to compare individuals with and without ADHD.

Findings During follow-up (24·9 million person-years), 5580 cohort members died. The mortality rate per 10 000 person-years was 5·85 among individuals with ADHD compared with 2·21 in those without (corresponding to a fully adjusted MRR of 2·07, 95% CI 1·70–2·50; p<0·0001). Accidents were the most common cause of death. Compared with individuals without ADHD, the fully adjusted MRR for individuals diagnosed with ADHD at ages younger than 6 years was 1·86 (95% CI 0·93–3·27), and it was 1·58 (1·21–2·03) for those aged 6–17 years, and 4·25 (3·05–5·78) for those aged 18 years or older. After exclusion of individuals with oppositional defiant disorder, conduct disorder, and substance use disorder, ADHD remained associated with increased mortality (fully adjusted MRR 1·50, 1·11–1·98), and was higher in girls and women (2·85, 1·56–4·71) than in boys and men (1·27, 0·89–1·76).

Interpretation ADHD was associated with significantly increased mortality rates. People diagnosed with ADHD in adulthood had a higher MRR than did those diagnosed in childhood and adolescence. Comorbid oppositional defiant disorder, conduct disorder, and substance use disorder increased the MRR even further. However, when adjusted for these comorbidities, ADHD remained associated with excess mortality, with higher MRRs in girls and women with ADHD than in boys and men with ADHD. The excess mortality in ADHD was mainly driven by deaths from unnatural causes, especially accidents.

Funding This study was supported by a grant from the Lundbeck Foundation.

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Hematologic and Blood Biochemistry Monitoring During Methylphenidate Treatment in Children With Attention-Deficit/Hyperactivity Disorder: 2-Year, Open-Label Study Results

Sharon B. Wigal, PhD[a], Timothy E. Wilens, MD[b], Mark Wolraich, MD[c], Marc Lerner, MD[a]

Hematologic and Blood Biochemistry Monitoring During Methylphenidate Treatment in Children With Attention-Deficit/Hyperactivity Disorder: 2-Year, Open-Label Study Results

Sharon B. Wigal, Timothy E. Wilens, Mark Wolraich and Marc Lerner

Pediatrics 2007;120;e120-e128; originally published online Jun 4, 2007;

- **These long-term data suggest that chronic therapy with MPH has no clinically significant impact on laboratory values, challenging the necessity of routine hematologic monitoring in otherwise healthy children with ADHD**

Patients' Fears of Medications for ADHD

- Change personality "zombie"?
- Slow growth? Start tics?
- Lose appetite? Sleep?
- Later drug or alcohol problems?
- Dependence on meds for lifetime?
- Being labeled, attribution problems?
- Reactions of family, teachers, peers?

Controversial Treatments for ADHD

- Dietary restrictions (food dyes, sugar)
- Diet supplements: anti-oxidants, algae
- optometric vision training
- EEG neuro-feedback

No scientific evidence for the safety or effectiveness of these treatments for ADHD, but NIMH is doing study on neurofeedback

Article

Nonpharmacological Interventions for ADHD: Systematic Review and Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments

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Joseph Sergeant, Ph.D.

European ADHD Guidelines Group

Objective: Nonpharmacological treatments are available for attention deficit hyperactivity disorder (ADHD), although their efficacy remains uncertain. The authors undertook meta-analyses of the efficacy of dietary (restricted elimination diets, artificial food color exclusions, and free fatty acid supplementation) and psychological (cognitive training, neurofeedback, and behavioral interventions) ADHD treatments.

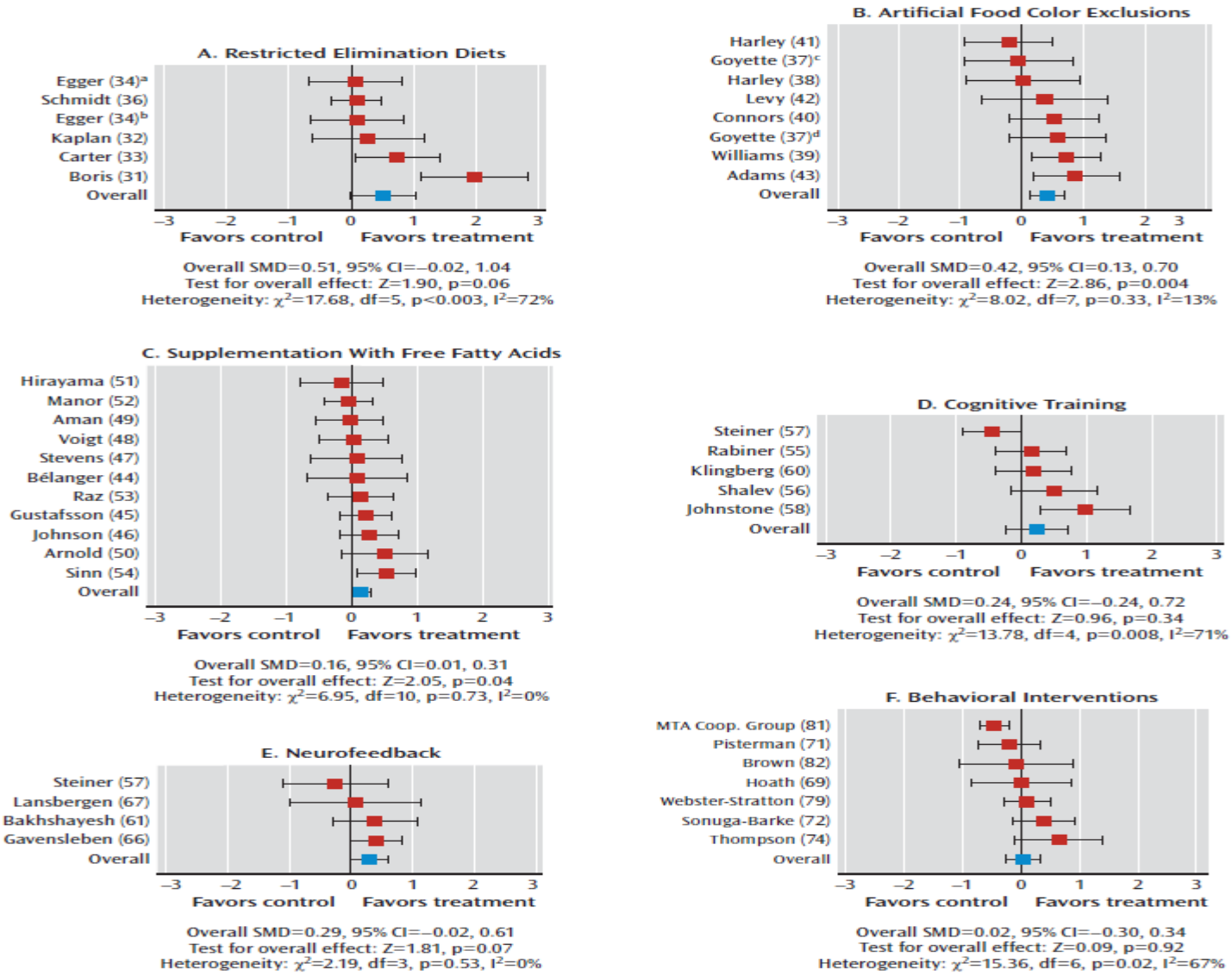
Method: Using a common systematic search and a rigorous coding and data extraction strategy across domains, the authors searched electronic databases to identify published randomized controlled trials that involved individuals who were diagnosed with ADHD (or who met a validated cutoff on a recognized rating scale) and that included an ADHD outcome.

Results: Fifty-four of the 2,904 nonduplicate screened records were included in the analyses. Two different analyses were performed. When the outcome measure was based on ADHD assessments by raters closest to the therapeutic setting, all dietary (standardized mean differences=0.21–0.48) and psychological (standardized mean differences=0.40–0.64) treatments produced statistically significant effects. However, when the best probably blinded assessment was employed, effects remained significant for free fatty acid supplementation (standardized mean difference=0.16) and artificial food color exclusion (standardized mean difference=0.42) but were substantially attenuated to nonsignificant levels for other treatments.

Conclusions: Free fatty acid supplementation produced small but significant reductions in ADHD symptoms even with probably blinded assessments, although the clinical significance of these effects remains to be determined. Artificial food color exclusion produced larger effects but often in individuals selected for food sensitivities. Better evidence for efficacy from blinded assessments is required for behavioral interventions, neurofeedback, cognitive training, and restricted elimination diets before they can be supported as treatments for core ADHD symptoms.

(Am J Psychiatry 2013; 170:275–289)

FIGURE 3. Forest Plots With Standardized Mean Difference (SMD), Effect Size, and Homogeneity Statistics for Meta-Analyses of the Six Domains Using Probably Blinded Assessments



[a] Younger group in Egger et al. (34).
[b] Older group in Egger et al. (34).
[c] Experiment 1 in Goyette (37).
[d] Experiment 2 in Goyette (37).

biases into analyses. Second, the included trials differed greatly with respect to several important treatment parameters. For instance, the largest standardized mean differences were observed with trials with preschool children—a finding consistent with the proposition that behavioral interventions may be most effective as part of early intervention strategies (84). Third, although not effective for ADHD symptoms themselves, behavioral interventions may result in other positive effects (e.g., reducing oppositional behavior [68]).

For both neurofeedback and cognitive training, effects were substantially lower for probably blinded than for most proximal assessments, despite attempts in some trials to blind parents to treatment allocation by using sham and/or active control conditions. However, the standardized mean differences for these still relatively novel approaches were higher than those for the more traditional behavioral interventions. Both sets of analyses included trials that used a range of different approaches to treatment. Cognitive training trials addressed either working memory or attention deficits, and neurofeedback trials targeted several different electrophysiological correlates of ADHD. Neither analysis had sufficient power to identify whether any approach was better than the others. Based on these results, the value of psychological approaches that directly target neuropsychological processes should be further investigated.

Artificial food color exclusion had statistically significant but modest effects on ADHD symptoms. The effects for free fatty acid supplementation were also significant but small. Restricting analyses to trials with probably blinded assessments did not change the results—probably because of the use of placebo-controlled designs, which meant that most proximal assessments were often blinded. Restricting the analyses to trials with no/low medication levels reduced the effects on ADHD of artificial food color exclusions but not of free fatty acid sup-

markedly to marginally nonsignificant levels when the analysis was restricted to probably blinded assessments. This change was largely due to the exclusion of two trials with very large effects from the analysis of probably blinded assessments—the first (35) because it was an open-label trial and the second (16) because the reported blind assessment by a pediatrician was based in part on unmasked parental accounts of behavior. Participants in restrictive elimination diets and the artificial food color exclusion trials were often preselected to be adverse responders before entering the controlled phase of the trial, so these effects may be limited to individuals with suspected food sensitivities.

Despite using a common search and selection protocol, our ability to directly compare different nonpharmacological approaches was hindered by methodological variations across domains linked to different research traditions in each area. There were also differences between domains in terms of ratings of reported study quality. The included trials used a range of different control conditions, and these varied considerably in the extent to which they allowed for control of extraneous and potentially biasing factors, such as the effects of nonspecific attention by therapists. While the use of strict placebo control was common only in dietary domains, the best-designed psychological trials included active, attention, or sham comparators. Trials also differed considerably in the intensity and duration of therapy. An analysis of these factors was not possible because of the limited number of trials in each treatment domain. Our exclusion of trials that included individuals with subclinical levels of ADHD and the fact that few trials included analyses of the predictors of treatment response meant that we were unable to test the hypothesis that patients with less severe ADHD are more responsive to psychological interventions (86).

Neurotherapeutics (2012) 9:588–598
DOI 10.1007/s13311-012-0136-7

Evidence-Based Information on the Clinical Use of Neurofeedback for ADHD

Tais S. Moriyama · Guilherme Polanczyk · Arthur Caye · Tobias Banaschewski · Daniel Brandeis · Luis A. Rohde

Published online: 25 August 2012
© The American Society for Experimental NeuroTherapeutics, Inc. 2012

- **….. there is not enough data to support the use of NF as a mono-therapy for ADHD**

Primary fears about ADHD medications

“This will make problems for me”

“make me too hyper or too slow”

“take away my personality”

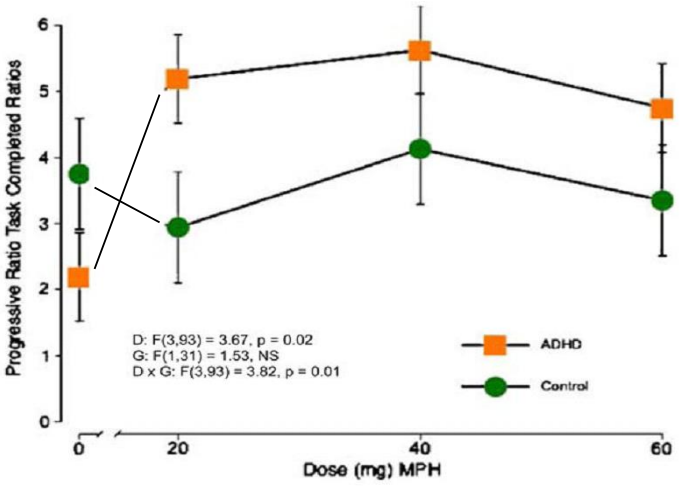
“get me dependent or addicted”

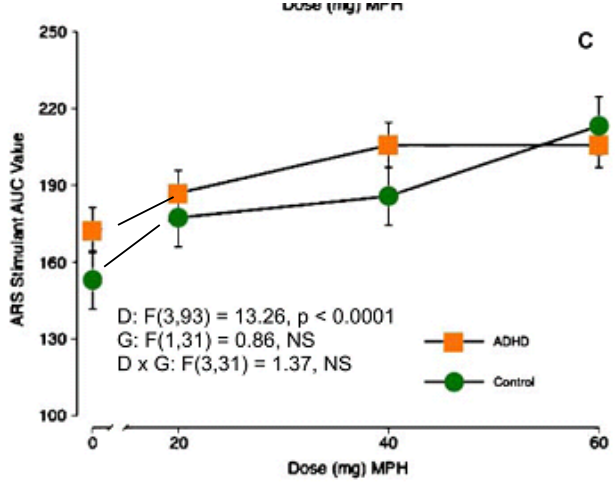
Patient Education is needed about medications

Need to be "fine-tuned" in collaboration with each patient

- **Set patient expectations to collaborate**
- **Adjust med, dose or timing to individual needs and body chemistry**
- **Prevent stimulant "rebound"**
- **Need to report any side effects**

מיתוס
ריטלין כ Cognitive Enhancer





- בעיה בסטונדנטים
  - Abuse, סחר וכו'
- הרבה מחקרים
- שורה תחתונה-
  - **סובייקטיבית**- תחושה טובה זהה בין ADHD לביקורת
  - בבריאים - <u>אין שיפור ביכולות **קוגניטיביות**</u> (במיוחד ביחס ל ADHD)
  - בבריאים פלצבו גורם לאותה תחושה **סובייקטיבית** כ MPH

Kollins, Psychopharmacology, 2009, 204(1)
(Looby, Exp Clin Psychopharmacol. 2011; 19)

Agency/Year	Guidelines/Recommendations/Algorithms	Notes
American Academy of Pediatrics (AAP), 2011	Preschool-aged children (4-5 years): parent- or teacher-administered behavior therapy; if not available or is not beneficial, methylphenidate may be used but only in moderate to severe dysfunction	Methylphenidate use in this population is off-label. Although dextroamphetamine is approved for use in this population, its use is not recommended because of lack of safety and efficacy data. Metabolism of stimulants in this population is slower; hence, a smaller initial dose and slower upward titration is recommended
	Elementary school-aged children (6-11 years): parent- or teacher-administered behavior therapy alone or in combination (preferable) with an FDA-approved medication	The evidence for use of FDA-approved medications is strongest for stimulants, followed by atomoxetine, extended-release guanfacine, and finally, extended-release clonidine; hence, most clinicians may use this sequential approach
	Adolescents (12-18 years): FDA-approved medication alone or in combination with behavior therapy (preferred)	If substance abuse or medication diversion is an issue in this age group, stimulants with less abuse potential (Vyvanse, Daytrana, or Concerta) or nonstimulants should be used

American Academy of Child and Adolescent Psychiatry (AACAP), 2007	For children (6-11 years) and adolescents (12-18 years): FDA-approved medication (stimulants or atomoxetine); if not beneficial, seek expert opinion for ADHD diagnosis; if diagnosis is confirmed, behavioral therapy alone or in combination with medications not approved by FDA should be used	Extended-release guanfacine and clonidine were approved by the FDA after these recommendations were published; hence, the recommendation for using an FDA-approved medication includes stimulants or atomoxetine only

ADHD TREAMENT

- **The following can be considered true treatment failure**
  - **1) lack of response to 2 or 3 stimulant medications at maximum dose without side effects or at any dose with intolerable side effects**
  - **2) inability of behavioral therapy or combination therapy to control the child's behaviors**
  - **3) the interference of a coexisting condition**

ADHD TREAMENT FOLLOW-UP

- **The clinician should periodically provide a systematic follow-up for the child with ADHD**
- **Monitoring should be directed to target outcomes and adverse effects by obtaining specific information from parents, teachers, and the child**

אז מה לעשות?

- **The evidence <u>strongly supports</u> the use of stimulant medications for treating the core symptoms of children with ADHD**
- **Behavior therapy alone has only limited effect**

(Brown and the Subcommittee on ADHD, *Pediatrics 2005)*


THANK YOU
FOR
YOUR
ATTENTION
ANY QUESTION ?
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