MEDICATION MANAGEMENT OF ADHD
WHY? WHAT? HOW?

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Disclaimer

"As is standard procedure for these kind of presentations, what I'm talking about today is for educational purposes only and should not be taken as medical advice. Nothing presented here is a substitute for an established doctor/patient relationship.

The views I express here are my own and are not necessarily representative of the organizers of the International ADHD Conference."

Part #1

Why Do We Use Medications in Neuro-Psychiatry?

Recurring Themes

1 **“If you know one person with ADHD, you know one person with ADHD.”**

- Each person with ADHD is unique. There is no “typical” anything. You are going to have to think about each unique patient.

2 The ADHD medications are remarkably safe and effective.

- They remain “scary” due to an almost complete failure of Medical Education.

Setting Reasonable Expectations

"I'm writing a prescription that will give you a new freedom and a new happiness. You will not regret the past nor wish to shut the door on it. You will comprehend the word serenity and you will know peace."

Reasonable Expectations

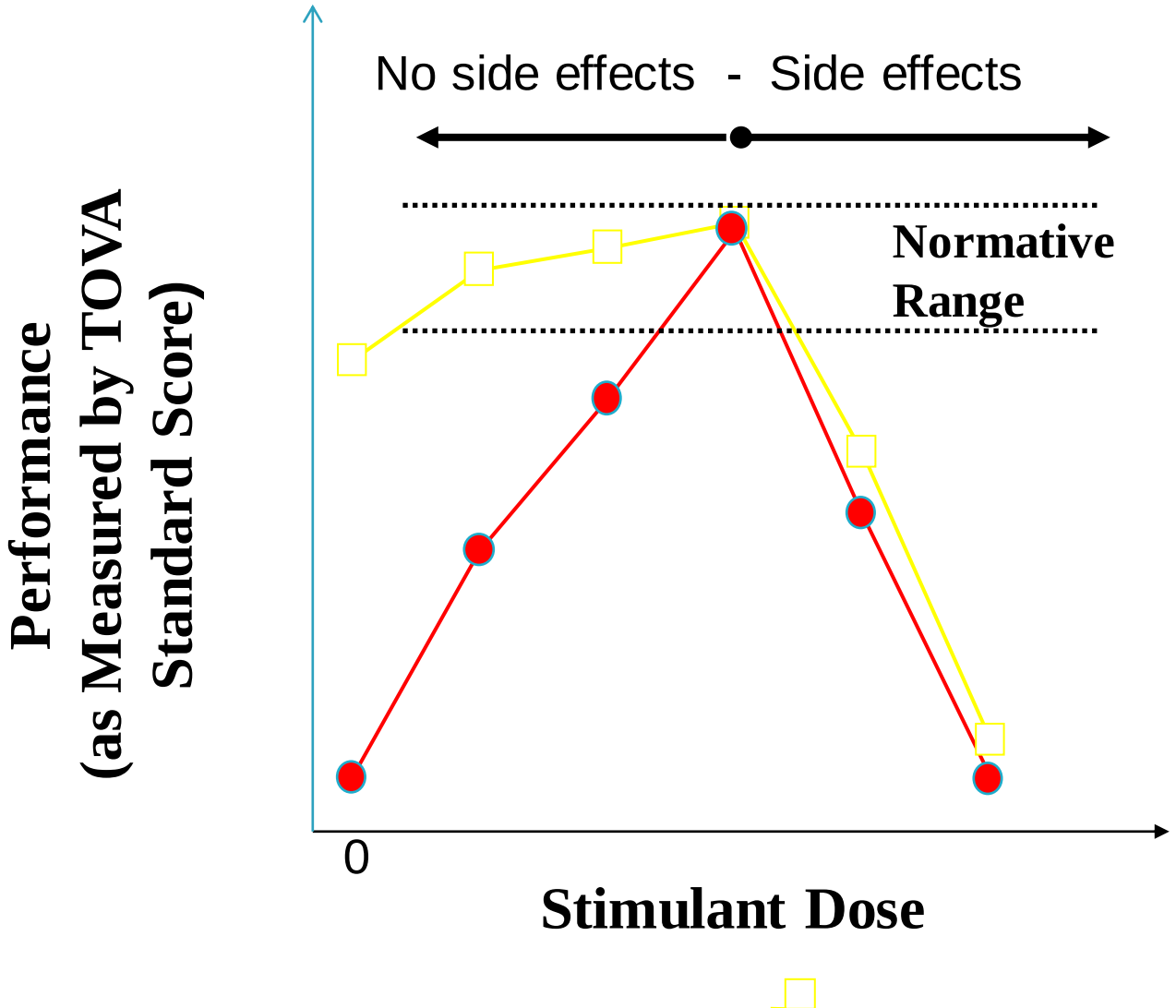
The goal of medication treatment is to attain

The Best Version of You

Reasonable Expectations – cont.

- On the right medications for you and at the right dose of that medication you should not "Feel" anything!
- What you will have to look for is the absence of ADHD impairments … things that are no longer happening.
- If you feel like a different person or have side effects that do not resolve quickly, the molecule may not be right for you or the dose may be too high.

Dose-Response of Stimulant Class Medications



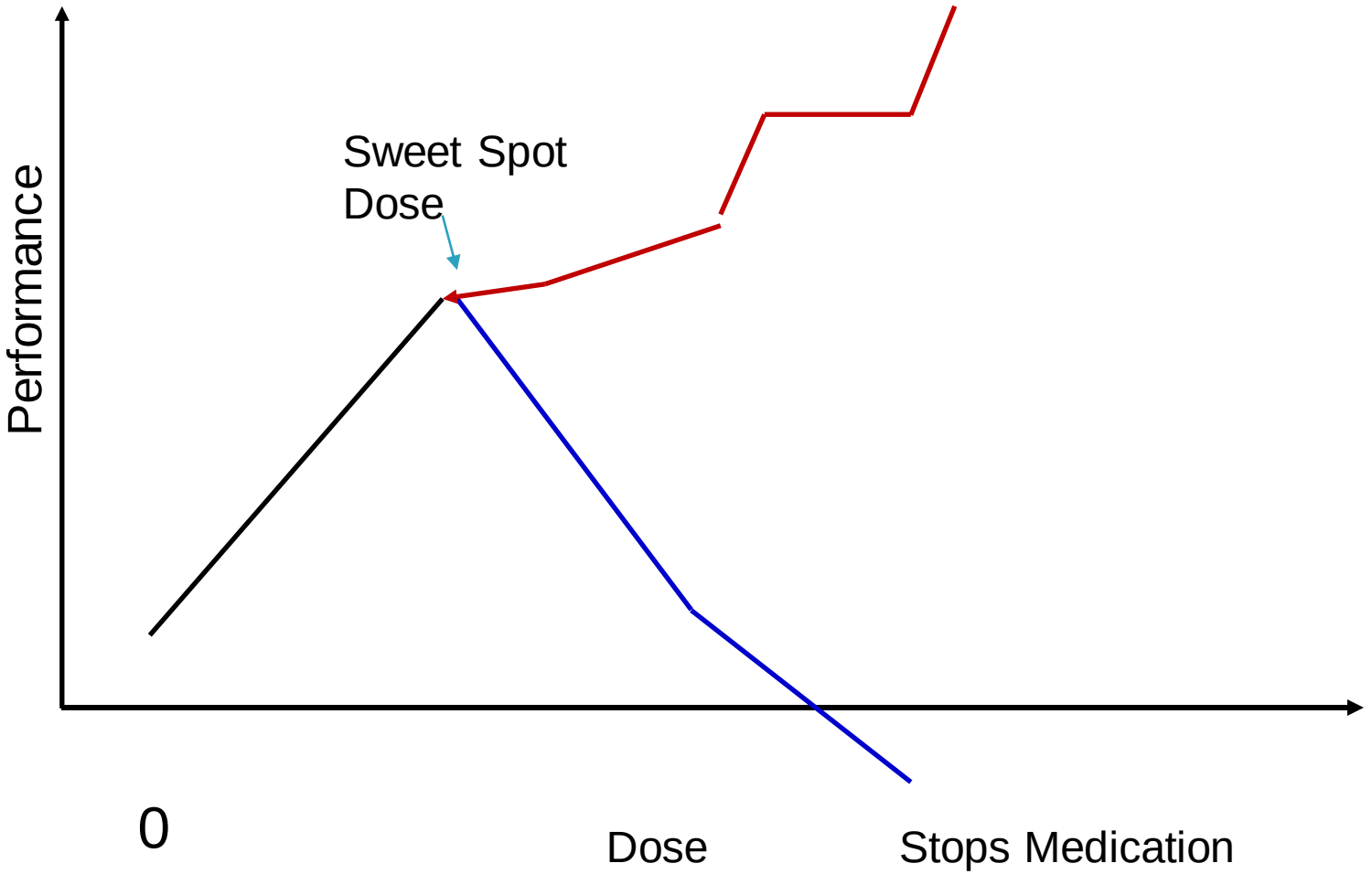
Magical Expectations Are The Most Common Cause of Treatment Failure

- The expectation that you ought to “feel something!”
- At the optimal dose of your optimal medication you should ***perform*** at the level of a NT person and have no side effects.
- No better but also no worse.
- ADHD medications remove symptoms and impairments but you should feel the same person as you were before.

Magical Expectations Are The Most Common Cause of Treatment Failure

- The relative lack of self-appraisal abilities is at the heart of the problem.
- The only way many people can tell for themselves that the medication is there is to have side effects. They start from the beginning over-dosing themselves.
- They develop tolerance to the side effects and tell the clinician “My med stopped working so I doubled the dose and it worked again.”
- Rinse and repeat until the medications is intolerable and blood pressure is very high.

Self-Sabotage



Magical Expectations Are The Most Common Cause of Treatment Failure

- There is an almost universal belief that more is better.
- Once you have found your “sweet spot dose” increasing the dose loses benefits and increases side effects that will ultimately cause the person to stop taking the medication.
- Tolerance develops to the side effects but not to the benefits of medication.
- ONCE YOU FIND YOUR SWEET SPOT, IT DOES NOT CHANGE FOR THE REST OF YOUR LIFE (if you are older than 16)

Two Types of Side Effects

The Zombie Syndrome

- A manifestation of the "Paradoxical Effect" – With ADHD people only, stimulant medications calm and slow people down.
- This is the basis of "I don't like how it changed his personality." "I don't feel myself."

The Starbucks Syndrome – like 3 double espressos.

- Fast pulse, jittery, hand tremor, agitated, IRRITABLE.

More Magical/Wishful Thinking

1. "I only need to take medication every once in a while when I need it." Ask your friends and employer about that one.
2. YOU ARE NEVER GOING TO BE NEUROTYPICAL
3. Medications are only the first step of managing ADHD.
4. Medications get you in the game on a level playing field for the first time in your life.

ADHD Medications Work Better Than Just About Anything Else in Medicine

- How do we measure how well treatments work?

  Effect Size. (0.4 barely detectable; 1.0 very robust)

- 1st Line Stimulants [1] (MPH and AMPH)

Research studies - force dosed; blinded	0.95
Fine-tuned/dose optimized	>1.80

- Atomoxetine (Strattera) (children < 12 y/o) 0.62
- Atomoxetine [2] (2 adult studies) 0.44
- Viloxazine[3] (Qelbree) (Children and adults) 0.62
- SSRI's for Major Depression 0.50
- SSRI's for anxiety disorders 0.39

[1]Faraone SV. Using a meta-analysis to draw conclusions about ADHD medication effects. Program and abstracts of the 156th Annual Meeting of the APA ; May 21, 2003;.
[2]Michaelson et al. *Biol Psychiatry* 2003. [3]FDA Novel drug Approvals for 2021

Why Do We Use Medications?

- I think we can all agree that ADHD is primarily genetic, biological, and neurological.
- While bad and inconsistent parenting can make anything worse, it does not cause ADHD.
- ADHD runs in families…. It is genetic.
- At least one parent will have ADHD as well.
- The risk of any one child having ADHD is 50% if one parent is ADHD.

Genetic/Neurological Implications

- Genetic disorders don't go away with time, growth, or development.
- We do not outgrow ADHD. We mature past the child-based diagnostic criteria.
- Multimodal Therapy was dropped by the AACAP Guidelines 16 years ago.
- But we have got to stop sending mixed messages that medication and behavioral therapies are equal and mutually exclusive. (Either/or)

Genetic/Neurological Implications

- Biological and neurological conditions are impossible to change with behavioral therapies or different ways of thinking. ADHD is neurologically hardwired.
- Behavioral therapies can help people compensate for ADHD impairments but the impairments are still there.
- Conversely, non-genetic mental conditions that happen to us (ex. PTSD, pain syndromes, head injuries) do not respond at a detectable level to any medication.

Genetic and Neurological –cont.

- We do not try to lower a fever with behavioral or talking techniques. Why do we do that as a 1st treatment with children with ADHD?

Non-medication-based therapies have not been shown to be significantly effective for the

CORE FEATURES OF ADHD

Let me be clear….

- Behavioral therapies do work and are helpful for virtually every one with an ADHD nervous systems.
- The medications level the neurological playing field so that then the behavioral therapies help repair the damage that happened while not being treated for so long.
- IT IS NOT A CHOICE OF ONE OR THE OTHER (it is not “therapy” OR medications)

It Is Not Meds or "Therapies;" It Needs to Be Both

- The stimulants do one thing spectacularly well:

If you are already engaged with a task, the stimulants help you stay engaged and not be distracted.

But we are still missing the 3rd indispensable piece:

- How do you get engaged in the first place?

But Here We Need To Take a Digression or The Rest Won't Make Much Sense

What Does It Mean To Be a Core Feature?

- A defining features of any condition.
- Without that feature it would not be the same condition.

For example:

If you do not have impairment from distractibility, you don't have ADHD.

If you have a good time sense, you can still have the diagnosis of ADHD.

CORE FEATURES OF ADHD

- Historically, Hyperactivity was the first feature – nobody could miss it (disruptive everywhere)
- - everyone could agree on it being an impairment
- Impulsivity was included in the diagnosis of Hyperactive Reaction of Childhood
- ADD: By 1980 and the DSM-3 Distractibility and Inattention became the primary symptom and disrupted behavior was seen as secondary.

Core Features – cont.

- 1990 and the DSM -4 - - Hyperactivity was reintroduced as an option:

  ADD with hyperactivity or

  ADD without hyperactivity
- 1994 and the DSM – 4 TR (Text revision) simplified to ADHD.
- 2013 and the DSM -5 tried to include adults without actually changing the childhood criteria. An almost complete failure.

A new CORE feature added in 2018 by the European Union

Emotional Dysregulation (ED)

- Mood lability
- Low frustration tolerance
- Emotional impulsivity
- Irritability
- Anger outbursts
- Worsens with menstrual flow

Kooij J.J.S., Bijlenga D, Salerno L, Jaeschke R,, et al. . (2019) Updated European Consensus Statement on diagnosis and treatment of adult ADHD European Psychiatry 56: 14–34. see page 19

Loss of Emotional Control Can Be a Part of Many Conditions

- ADHD – Chronic, excessive positive (+) emotion
- Autism spectrum disorder- Chronic, excess + emotion
- Bipolar disorder, manic – Episodic, excess + emotion
- Borderline PD- Chronic, impulsive aggression, *empty*
- Oppositional defiant disorder – Chronic, argumentative
- Disruptive mood dysregulation disorder (DMDD) – Chronic, irritability, and anger/uncontrollable rage
- Intermittent explosive disorder – Episodic, anger
- Generalized anxiety disorder- Chronic, excessive fear
- Depressive mood disorder –Episodic, excessive sadness

Summary

- "Emotional symptoms are currently considered to be *associated* features of ADHD – much like learning problems or executive dysfunction."

- "They are not, however, *diagnostic* for the disorder." *i.e.* emotional dysregulation is found in so many other conditions.

Faraone SV, et al. Practitioner Review: Emotional Dysregulation in ADHD – Implications for clinical recognition and intervention. Journal of Child Psychology and Psychiatry 60:2 (2019), pp 133–150.

Medication Treatment of ED When Part of ADHD

- The few studies (11 by 2019) that specifically looked at the response of emotional dysregulation to medication found significant improvements:
- Methylphenidate: 2/3 had remission[1]
- Lis-dextroamfetamine (Vyvanse): 60% no longer had "emotional control impairments" [2]
- Atomoxetine: "Small but positive effects."
- Alpha agonists: No published studies but described as "promising."

1 Katic et al. (2013) Journal of Child and Adolescent Psychopharmacology, 23, 386–393.

2 Blader et al. (2016) Journal of Child and Adolescent Psychopharmacology, 26, 164–173.

We Still Have to Understand Why the Non-Pharmacologic Therapies Failed So Consistently

Multimodal Treatment of ADHD (MTA)

All treatments in the MTA led to improvement in core ADHD symptoms

Optimized Medication Management alone

Medication management + Behavioral Treatment

Equal in effectiveness and superior to both:

"Maximum dose" Behavioral Treatment alone

Community-based treatment

MTA Cooperative Study Group. Arch Gen Psychiatry 1999;56:1073.

NYU-McGill Study

In medication responsive children there was "no support for or advantage from adding:"

- Long-term (2 yrs) psycho-social intervention
- Long-term O.D.D. prevention interventions
- Academic remediation and tutoring
- Organizational skills training
- Social skills training
- "Attention control training"
- Parental practices training

Klein RG, Abikoff H, Hechtman L, et.al., JAACAP 43:7. 792-838

Virtually No Interventions Were Effective.

- Neurofeedback: (The Neurofeedback Collaborative Group. Double-Blind Placebo-Controlled Randomized Clinical Trial of Neurofeedback for Attention-Deficit/Hyperactivity Disorder With 13-Month Follow-up (2021) *J American Academy of Child & Adolescent Psychiatry* 60 (7) 841-855
- Diet and Nutrition: Rucklidge, JJ , Mairin R. Taylor MR, , Johnstone, JM. Do Diet and Nutrition Affect ADHD? Facts and Clinical Considerations (2018) Psychiatric Times, 35 (9). " If there are benefits, they are small (ES-0.29)."

Virtually No Interventions Were Effective.

- Working Memory Training Monica Melby-Lervåg [1], Charles Hulme. Is working memory training effective? A meta-analytic review (2013) Developmental Psychology 49(2):270-91. "Current findings cast doubt on both the clinical relevance of working memory training programs."
- Cognitive Behavioral Therapy (CBT) Rajeh A, Amanullah S, Shivakumar K, Cole, J. Interventions in ADHD: A comparative review of stimulant medications and behavioral therapies, (2017) Asian Journal of Psychiatry, 25: 131-135. "Behavioral interventions play a key role for long-term improvement of executive functioning and organizational skills. There is a paucity of long-term RPC studies and current literature is inconclusive on what is the preferred intervention."

Galanter C. Limited Support for the Efficacy of Nonpharmacological Treatments for the Core Symptoms of ADHD (2013) Am J Psychiatry 170:3, 241-4.

One Only Treatment Modality Worked Well

Aerobic Exercise:

- Robustly effective (i.e. equal to medications) for about 8-10% of people with ADHD.
- The trade off is one hour of aerobic exercise for four hours of concentration and calmness that can be as good as a simulant medication.
- Come in for more conventional treatments when they get an injury that prevents exercise.

Qin XN, YihXH C, Hwei WC, Zheng BJY, Yeo WS. (2017) Managing childhood and adolescent attention-deficit/hyperactivity disorder (ADHD) with exercise: A systematic review. Complementary Therapies in Medicine 34: 123-128.

Sources

- Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. AACAP Official Action. (2007). *Journal of the American Academy of Child and Adolescent Psychiatry*. 46 (7):894-921. Children and adolescents (no longer includes adults).

  http://www.aacap.org/galleries/PracticeParameters/JAACAP_ADHD_2007.pdf

- Kooij Sandra JJ, et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. (2010), *BioMedCentral - Psychiatry* 10:67. Pages 1-24. http://www.biomedcentral.com/1471-244X/10/67

- Kooij J.J.S., Bijlenga D, Salerno L, Jaeschke R, Bitter I, Balázs J, Thome J, Dom G, Kasper S, Nunes C, Filipe S.Stes. Mohr P, Leppämäki S, Casas M, Bobes J, McCarthy JM, Richarte V, Philipsen AK, et al. Updated European Consensus Statement on diagnosis and treatment of adult ADHD. (2019) *European Psychiatry* 56: 14–34. http://dx.doi.org/10.1016/j.eurpsy.2018.11.001

- Graham J, Banaschewski T, Buitelaar J, Coghill D, *et al*. (for the European Guidelines Group). European guidelines on managing adverse effects of medication for ADHD. (2011) *European Child and Adolescent Psychiatry* 20:17–37. DOI 10.1007/s00787-010-0140-6

Everyone Wanted and Expected the Non-Medication Therapies to Work Robustly

We Weren't Asking the Right Questions

- **"Look back over your entire life; if you have been able to get engaged and stay engaged with literally any task of your life, have you ever found something you couldn't do?"**
- *A person with ADHD will usually answer, "No. If I can get started and stay in the flow, I can do anything."*
- *There are situations when people with ADHD hyperfocus and have super-human engagement.*

Executive Function Deficit Theory

- This makes EFD Theory almost completely invalid.
- EFD Theory has dominated the field of ADHD for more than 20 years.
- EFD Theory assumed that people with ADHD were the same as Neurotypical people, just broken or damaged.
- This theory assumed that executive dysfunction was the *cause* of ADHD as opposed to the *result* of an ADHD nervous system.
- "EF weaknesses are neither necessary nor sufficient to cause all cases of ADHD." *(Willcutt 2005)*

Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the Executive Function Theory of Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review. Biological Psychiatry 2005;57:1336–1346.

ADHD is Not a Deficit of:

- Effort
- Character
- Willpower
- Brain activity
- Brain size
- Brain integrity
- Structure
- Parenting skills
- Intelligence
- Self-control
- Neurotransmitters
- Executive function

Deficit models have not produced therapies that have shown detectable, lasting benefits

Jadad AR, Boyle M, Cunningham C, Kim M, Schachar R. (1999),. Evid Rep Technological Assessment Summary. November : i-viii, 1-341.

ADHD Has Been at a Theoretical Dead End for 20 Years.

- Asking the right question: Can you name a completely new concept or treatment in ADHD in this century that has actually worked?

- 52 non-pharmacologic therapeutic approaches in a row have failed to show any benefits for the **core features** of ADHD.
- It is obvious that we have been missing something that is both huge and fundamental about the very nature of ADHD.

The Importance of Engagement

Orban, S.A., Rapport, M.D., Friedman, L.M. *et al.* Inattentive Behavior in Boys with ADHD during Classroom Instruction: the Mediating Role of Working Memory Processes. (2018) *J Abnormal Child Psychol* **46,** 713–727

We Must Look at ADHD in a Totally Different Way

- The impairments of ADHD depend on the situation.
- The Executive Functions can often be there but the person does not have access to them quickly enough.
- ADHD is a problem of consistent Access to your abilities *On Demand*.
- If you can do anything under the right circumstances, it is NOT a DISORDER.
- It is a 2nd nervous system that functions perfectly well but by its own set of rules, principals, and methods.

The Fundamental Question

If I can do anything so long as I can stay engaged in the task,

How do I get engaged and stay “in the Zone”?

NICUP – How to get in the ZONE

- Novelty (Creativity)
- Interest, (Fascination)
- Challenge or competitiveness,
- Urgency (Substitute for Importance)
- Passion (Where do we invest our emotions?)

The Neurotypical Nervous System

The majority of people in the world - 90%.

Works on the basis of two factors:

- The Importance of the task.
- The Reward for doing it or the consequences of not doing it.
- Novelty, interest, challenge, urgency and passion (NICUP) help but are not required.

Advantages of an Importance-Based Nervous System

- You can prioritize.
- You can use 2nd hand Importance – *i.e.* your teacher or your boss think the task is important.
- It does not have to be Important right now.
- You can use deferred gratification; Do not need immediate rewards.
- A neurotypical person can share their partner's sense of importance. The inability to be motivated by a partner's priorities is a major source of strife in ADHD relationships.

Multimodal Therapy is No Longer the Standard of Care

- Recommendation 10: "If a patient has a robust response to psychopharmacological treatment,…then psychopharmacological treatment alone is satisfactory." [1]
- At best, behavioral therapies have only provided "non-specific benefits" that are situation bound and literally disappear as soon as the subject leaves the highly structured setting.
- No one is happy about this.

Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. AACAP Official Action. (2007). Journal *of the American Academy of Child and Adolescent Psychiatry*; 46 (7):894-921.

We Need All Three Parts

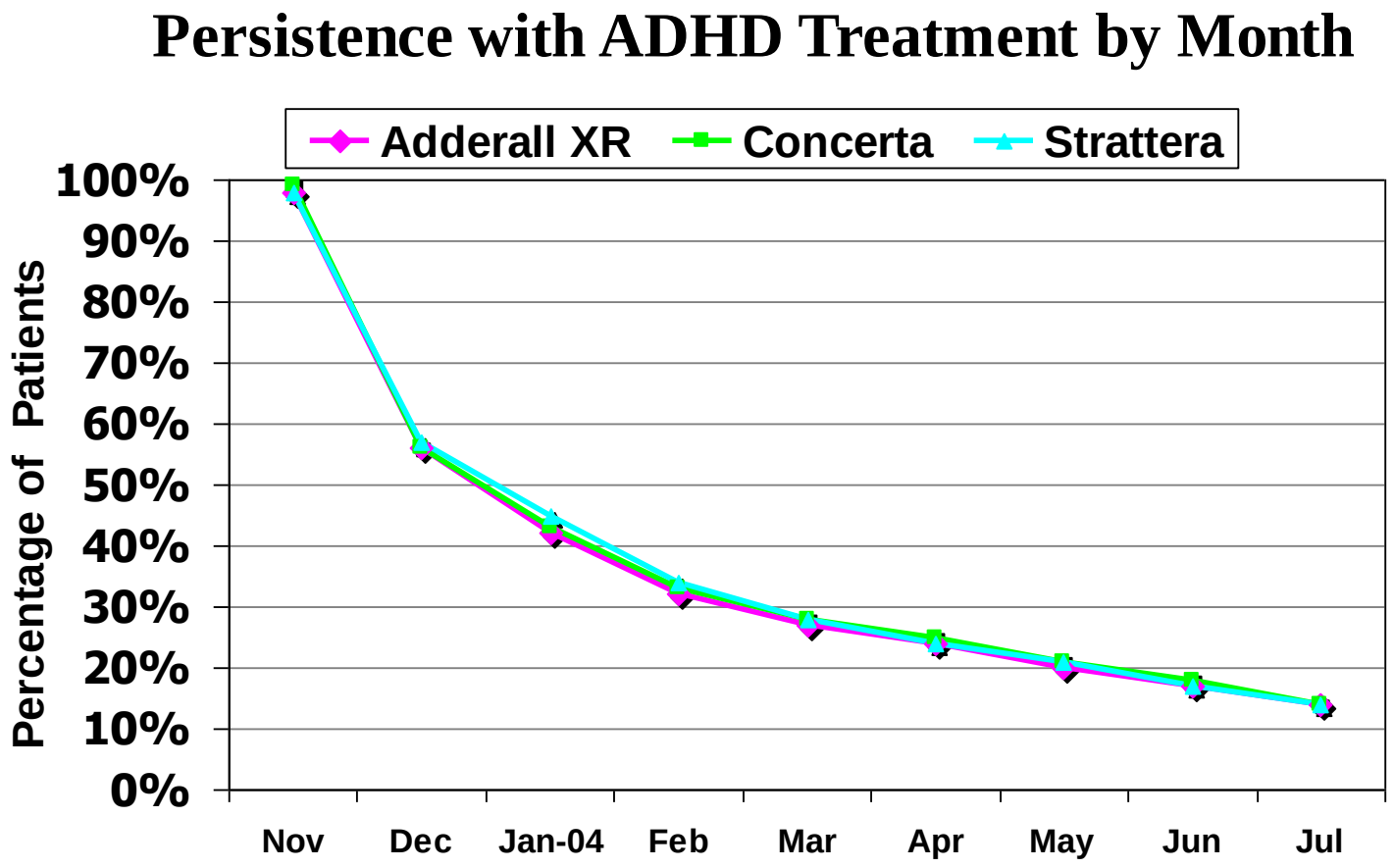
1. Learn the special ways people with ADHD get engaged in the task they want to do.

2. Let the 1st line stimulants keep us from being distracted.

3. Then use the therapies and coaching to reverse the IMPAIRMENTS from ADHD.

Currently all we are doing is step 2 and it is not working very well.

Persistence with ADHD Therapy is Poor Across Brands



Hodgkins P, Boken M, Capone NM, DeLeon A. 19th U.S. Psychiatric Congress; Nov. 15-19, 2006; New Orleans, LA. Abstracts 123 and 124.

Why Not Just Medication?

- “Pills don’t give skills.”
- Medications reduce symptoms.
- Improved functioning requires the acquisition of new skills.

But not just any skills will work.

Traditional importance-based approaches have not been successful.

WHAT TO DO AT EVALUATION

Work Up

- ADHD cannot be diagnosed by neuro-psychological testing. Psychological and/or neuropsychological evaluation is not mandatory unless the patient has significantly low achievement relative to IQ.
- AACAP "strongly recommends" that ADHD medications be optimized prior to LD evaluation.
- "ADHD can only be diagnosed by a carefully taken clinical history that is rarely reimbursed by payor sources.

Work Up

- If Medical History is unremarkable, Laboratory and Neurological workups are not indicated. (AACAP Rec. 3 and 4)
- EEG, qEEG, MRI, fMRI have not been shown to be of value in diagnosis or monitoring.
- "PET and SPECT are to be avoided due to exposure to ionizing radiation." (http://www.psych.org/psych_pract/clin/populations/children/SPECT.pdf)

AACAP Practice Parameter. *JAACAP* (2007);46(7):894-921

What to Do at an Evaluation (AHA Guidelines[1])

- Medical history (essentially screening for SUUD risk)
  - Personal congenital or acquired cardiac disease
  - Palpitations, chest pain, syncope, murmurs, post-exercise symptoms
  - Family Hx of early cardiac disease (<30 y/o)
  - Other meds (including stimulating OTC's)
- BP/heart rate: baseline and at every follow up
- Adults: workup only as indicated; No routine or screening ECG, ECHO, Holter, or treadmill [1,2]

[1]Gutgesell H, et al. Circulation. 1999; 99:979-982.

[2]AACAP Practice Parameter. *JAACAP* (2007);46(7):894-921.

ADHD medications do not have cardiovascular risks

"Based on 19 observational studies with more than 3.9 million participants suggested that there was no statistically significant association between ADHD medications and the risk of cardiovascular events among children and adolescents, early and middle-aged adults and older adults."

Le Zhang, MPH; Honghui Yaoetal, et al. Risk of Cardiovascular Diseases Associated With Medications Used in Attention-Deficit/Hyperactivity Disorder. (2022) JAMA Network Open. 5(11) e. 2243597

Treatment is Based on Future Risks

- Untreated ADHD decreases life expectancy by 13 years. Mostly due to accidents and substance use disorders.

- This is the same impact on life expectancy as all Heart Disease or all Diabetes

Barkley Russell , How ADHD Affects Life Expectancy. ADDitude Webinar updated Sept 20, 2022

Non-Treatment – Impairments Persist But Consequences Get Much Worse

Childhood	▶ ▶ ▶	Adulthood
School failure / under-achievement	Becomes	Job failure or under-employment
Multiple injuries	Becomes	Fatal car wrecks / risk taking
Drug experimentation	Becomes	Drug dependence
ODD / CD	Becomes	ASPD, criminal involvement
Impulsivity and carelessness	Becomes	Unplanned pregnancy, STDs.
Repetitive failure	Becomes	Hopelessness, frustration, giving up

NEW UNDERSTANDINGS ABOUT TREAMENT

What is the mechanism of action?

Virtually no reason to think it is stimulation or neurotransmitter-based:

- Tolerance develops to the stimulation side effects in a matter of days.
- But tolerance rarely if ever develops to the benefits.
- Just having stimulant (dopaminergic or adrenergic) neurotransmitter effects means nothing. 47 PDR medications stimulate by the same mechanism but only 3 have benefit for ADHD.

ADHD People Do Not Respond to Stimulants the Same As Neurotypicals

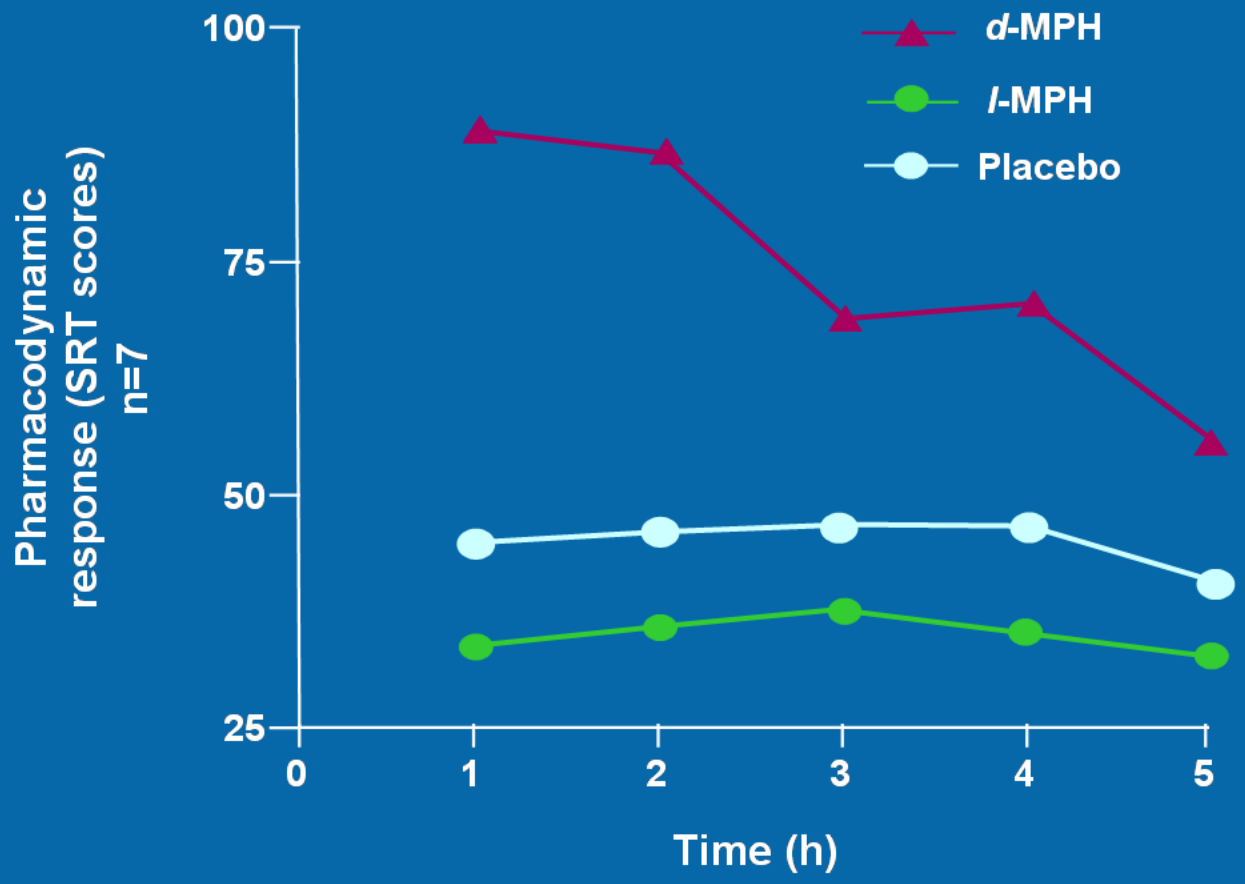
- There is no DA/NE explanation for the "Paradoxical Response" seen only in people with an ADHD style nervous system.

- The Ramp Effect (The blood level of the stimulant must be changing in order to get an effect) is only true for side effects, NOT for the benefits of ADHD medications.

Isomers of methylphenidate

- There are four different ways that the methylphenidate (Ritalin) molecule can be bent in 3 dimensions.
- Right and left erythro-methylphenidate
- Right and left threo-methylphenidate
- Only one of these isomers of methylphenidate has benefits for ADHD. The other 3 isomers make the impairments of ADHD much worse.
- Just having that structure and being a stimulating molecule means nothing.

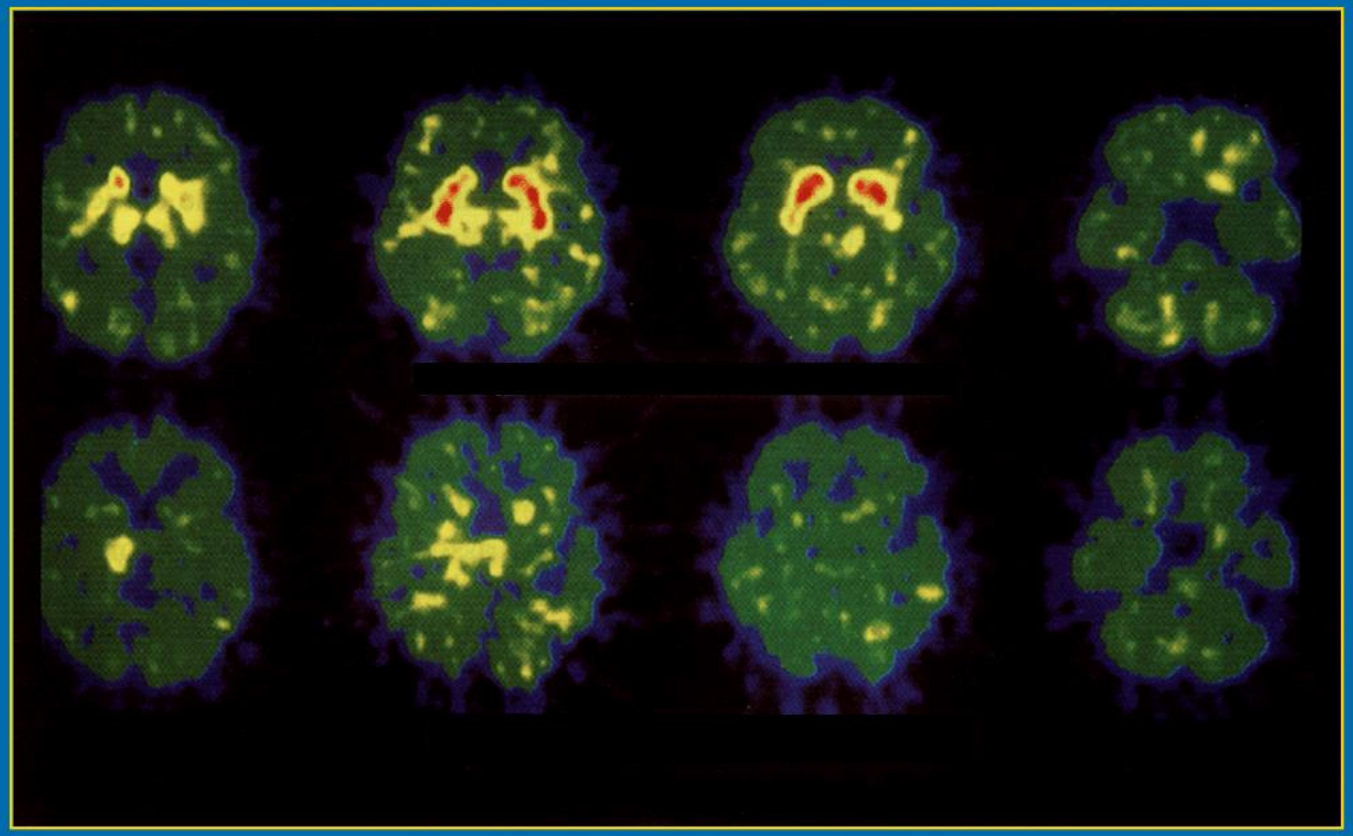
Pharmacodynamic Activity Lies Primarily in *d*-MPH



SRT=scanning reaction time.

Srinivas N, et al. *Clin Pharmacol Ther.* 1992;52:561-568.
Srinivas NR, et al. *J Pharm Sci.* 2001;90:1205-1215.

Rapid and Selective Distribution of *d*-MPH to the Striatum

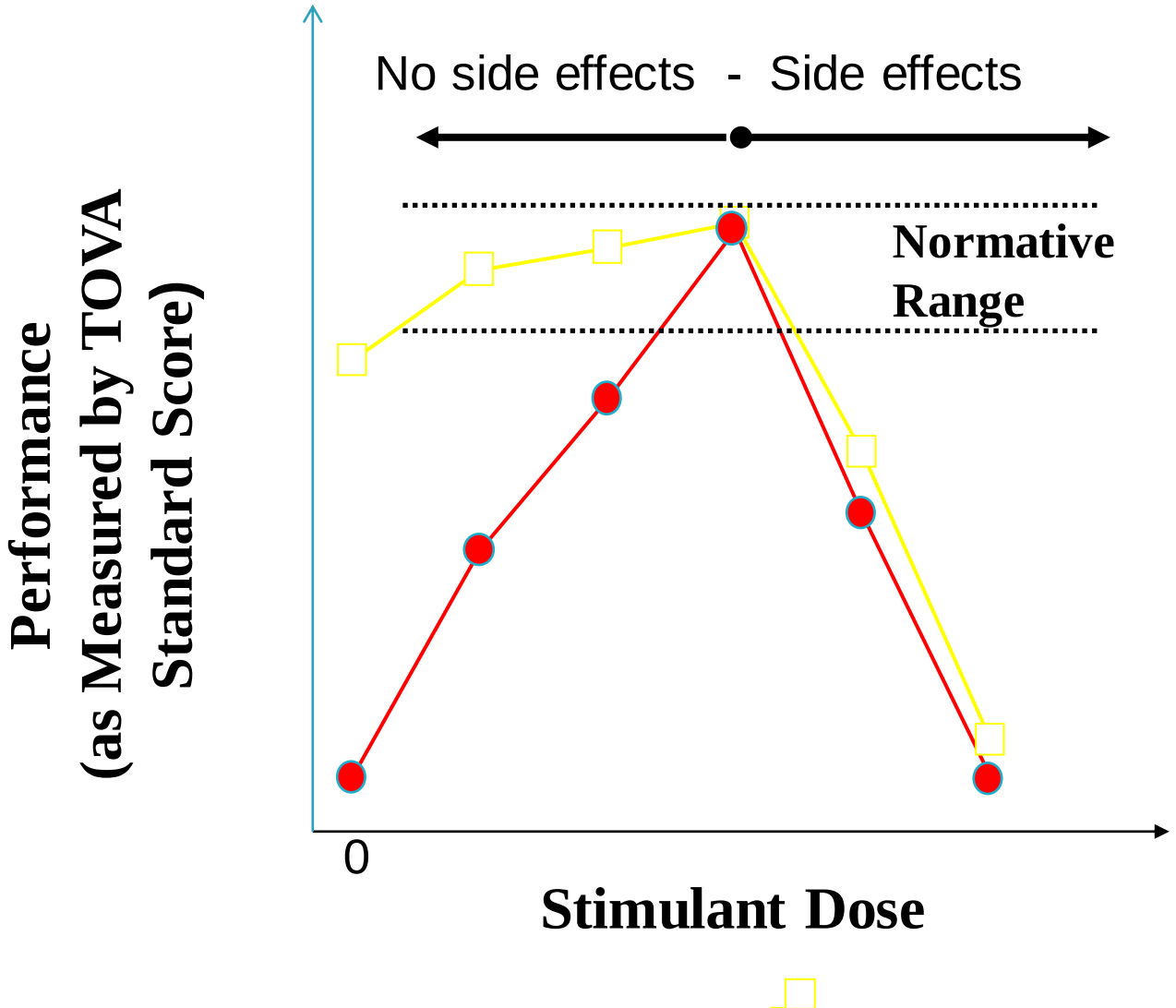


d-threo-methylphenidate

l-threo-methylphenidate

*Transaxial PET images from one healthy volunteer after IV administration.
Ding YS, et al. *Psychopharmacol Berl.* 1997;131:71-78.

Dose-Response of Stimulant Class Medications



What is the Mechanism of Action?

- The dose-response curve suggests a replacement model.
- A stimulant mechanism would give a straight line in which the higher the dose, the greater the effect.
- “Look-alike molecule” the occurs only in the ventral striatum that is necessary for membrane stability.

Choosing and Fine-Tuning a 1st Line Stimulant

The Stimulants are the TREATMENT OF CHOICE.

All three sets of guidelines recommend trying both AMPH and MPH first before going to 2nd and 3rd line agents [1,2] unless there is a reason recorded in the chart…

- Patient/parent request
- Recent or unstable substance abuse
- Uncontrolled glaucoma
- Uncontrolled seizures
- Untreated cardiovascular disease

1 Dulcan M. et al. *JAACAP*. 1997;36(suppl 10):85S-121S.
2 American Academy of Pediatrics. *Pediatrics*. 2001;108:1033-1044

Is One Molecule Better than the Other?

In large groups:

- Effect size is the same[1,2] (0.95 in research; 1.8 when fine tuned)
- Response rates are the same (70-75% to either one; 80-85% when both are tried)[3]
- Side effect profiles are the same.[3]

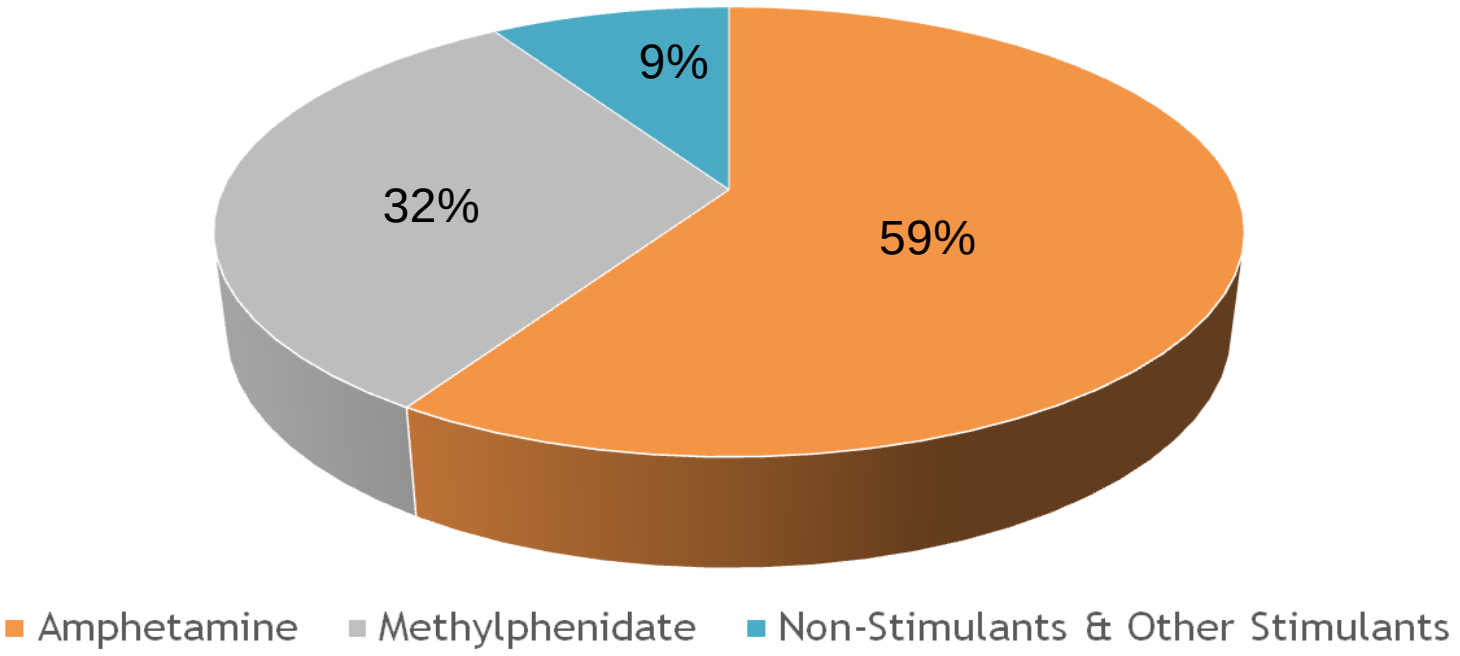
In clinical practice, however, individuals usually have clear preferences for one agent over the other.

- Nothing predicts optimal molecule. [3]
- Does not appear to run in families.

1 Dulcan M. et al. *JAACAP*. 1997;36(suppl 10):85S-121S.
2 American Academy of Pediatrics. *Pediatrics*. 2001;108:1033-1044
3 Greenhill LL, et al. Medication Tx strategies in the MTA study.(1996) JAACAP 35; 1304-1313.

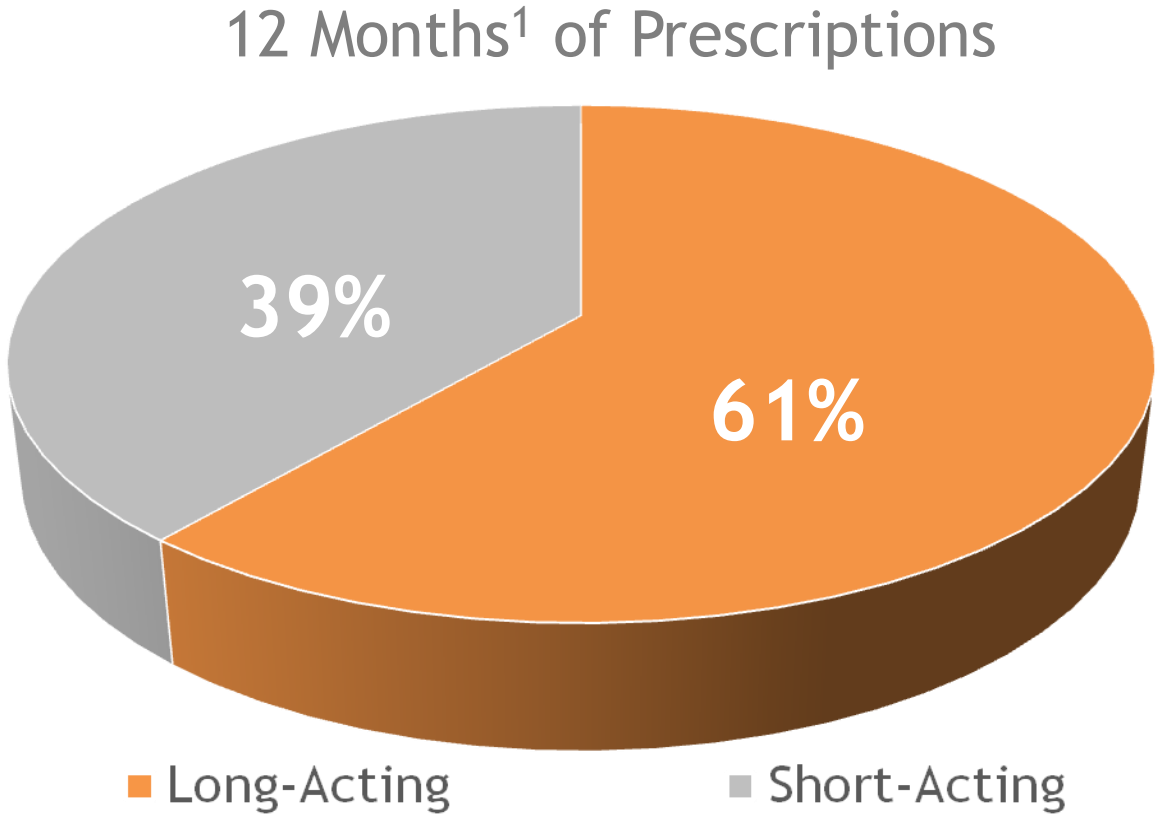
Choice of Molecule by Adulthood

- 12 Months[3] of Filled Prescriptions (USA)



1. Wolraich M, et al. *Pediatrics*. 2011;128(5):1007-1022.
2. Post RE, et al. *Am. Fam. Physician*. 2012;85(9):890-896.
3. Symphony Health Solutions, PHAST Prescription Data –12/2004

Long Acting Formulations are More Common



1. IMS National Prescription Audit, 12 month end Dec 2015.

Seven Advantages of Extended Release Delivery Systems

1. **Convenience**.
2. More consistent and **stable benefits**. The goal of treatment is stability of performance, mood, impulse control, engagement…
3. By definition, people with ADHD are **forgetful**, likely to lose things, disorganized, poorly structured, easily distracted from activities.
4. Smoothes out **rebound** at the end of the dose; more tolerable.
5. Poor **sense of time/ Time Blindness**; 85% of adults/95% of late adolescents with ADHD do not own a watch. How can we expect meds to be taken on time?
6. Extremely sensitive to embarrassment and teasing. Only time release formulations allow for **privacy and confidentiality.**

7. Time released formulations are least likely to be abused

- In the US, 90% of misuse and abuse are with the immediate released formulations (and by college students.)
- The Ramp Effect is directly proportional to the speed of change of blood concentration. The faster the rate of change, the greater the "Pop."
- Most clinicians in the US do not prescribe IR formulations to college students.

Misuse and Abuse

- Does it occur? Yes, it does. About 1/3 of college students report trying ADHD stimulants…. Once or twice, to cram for a test.
- Long-term abuse is by a narrow demographic: White, Male, fraternity member, who was already alcoholic when they came to college, who use stimulants so they can drink more.
- Extended abuse is almost unheard of in women, Blacks, Asians, or Hispanics.
- No study has shown better academic performance.

Where is the Greater Harm?

- " The majority of Non-Medical Use (NMU) is associated with no, or minor, medical effects."
- Only harm was with non-oral use; ie. Already deeply into drug abuse.[1]
- International drug rehab recommendations encourage the continued use of ADHD stimulant during rehab and recovery[2]

Faraone SV, et al Systemic Review: Nonmedical use of prescription stimulants: Risk Factors, outcomes, risk reduction strategies (2020) AACAP 59(1) 100-1121
2 Hozgen H, et al International Consensus Statement for the Screening, Diagnosis, and Treatment of Adolescents with Concurrent ADHD and SUD European Addiction Research 2020;26:223–232

Where is the Greater Harm?

- The research does not use terms in any consistent way so much remains unclear.
- Does not distinguish between nonmedical use, misuse, and abuse.
- What is rarely acknowledged is that adolescents are going to self-medicate at the same time they refuse supervised medical care.
- ADHD hyperarousal is by far the most common target symptom for self medication-> Marijuana, alcohol, “downers”, Xanax, etc.

Drugs of Abuse vs Meds for ADHD

Drugs of Abuse

- Are taken to "feel good" or get high
- Creates craving in users
- Appeal to a large and ready market
- Involve a "struggle" to get people to stop taking them

ADHD Medications

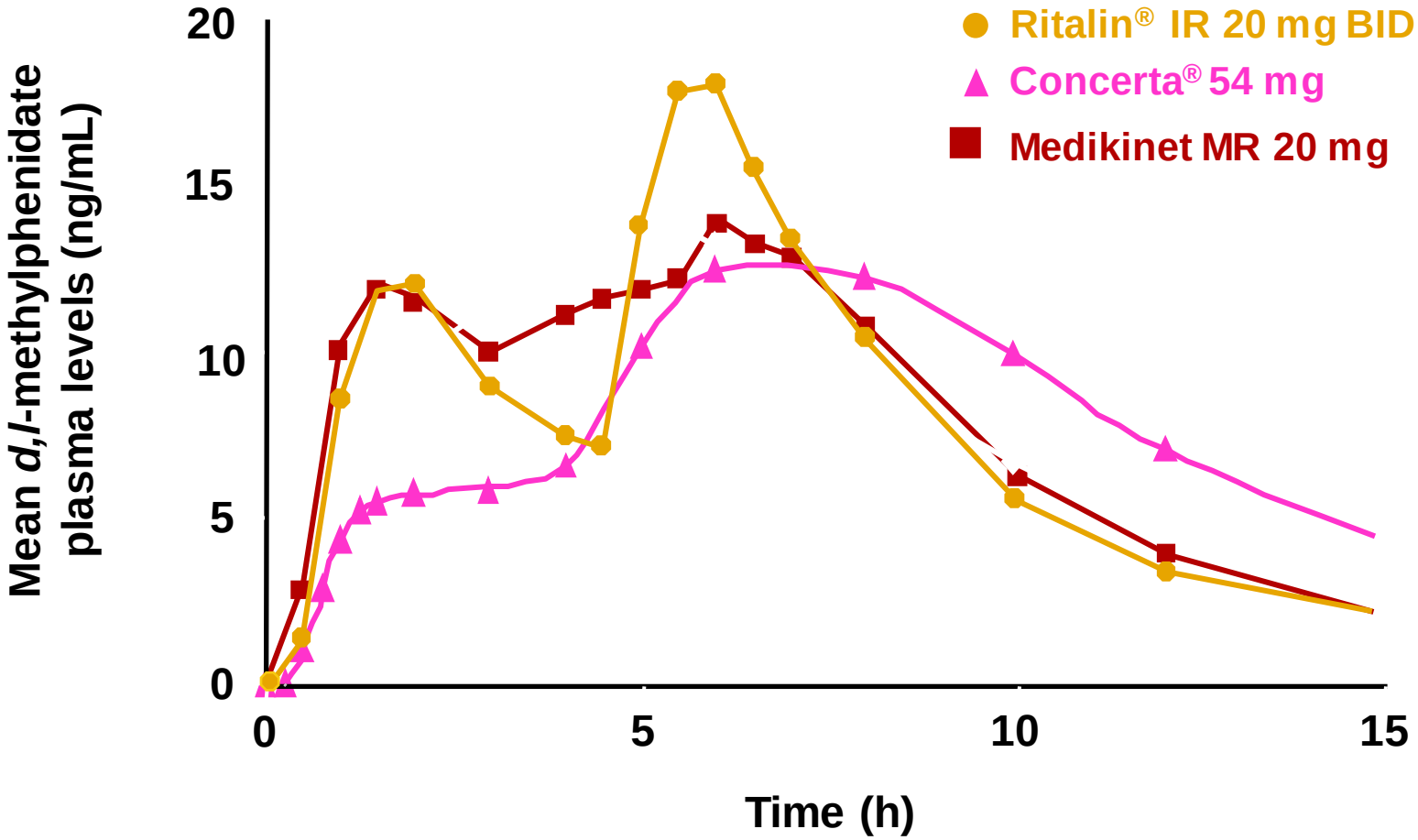
- Unpleasant if over-dosed; Adolescents complain about taking them
- Are commonly forgotten by patients
- Are readily available, but long-term abuse is rare
- Involve a "struggle" to get people to take them,
- Prevent the development of later drug abuse

Effects of DEA Controlled Substance Status

- Tremendously increases price.
- Creates an unwarranted patient stigma.
- Discourages starting medications in the 1st place; creates false fear of addiction.
- Erects administrative barriers to continued care:
  - Monthly trips to the pharmacy
  - Forget to renew prescription and stop taking medication
  - Artificially created medication shortages

Choosing Among the 47 Formulations on the Market

Stimulant Formulations Are Not Interchangeable



Gonzalez MA, et al. *Int J Clin Pharmacol Ther.* 2002;40:175-184.
Data on file, Novartis Pharmaceuticals.

Tremendous Variability Between Amphetamine Formulations

- Vyvanse 20 mg is only 30% AMPH = 6 mg
- Adderall XR 20 mg is 63% AMPH = 12.5 mg
- Dextro-AMPH 20 mg is 87% AMPH = 17.4 mg

- Many pharmacists and clinicians don't stop to think about the actual amount that is delivered and freely substitute one formulation for another causing lots of problems for the patient.
- You must be the policeman.

Choosing a Formulation

- Two molecules – AMPH and MPH

BUT….

- 47 way of extending the duration of action and deterring misuse.
- To make matters more difficult many generics have the same name but are vastly different formulations (Ex. Methylphenidate ER 18, 27, 36 and 54 mg can be any of 7 different formulations)

Six Groups of Extended Release Mechanisms

- Failed or "Not Good Enough"

  Ritalin SR ®; Metadate ER ® ; Dexedrine Spansule ®

- Back Loaded

  Concerta ® (22/78); Metadate CD ® (30/70); Aptensio (40/60); Biphentin (in Canada 40/60)

- 50-50 Beaded

  Adderall XR ®; Ritalin LA ® /Focalin XR ®

- Transdermal

  Daytrana ® Xelstrym®

- Prodrug

  Vyvanse ®, Astarzys®

- Ion Exchange Resin

  Quillivant XR® , Adzenys OTC ®, Dynavel XR ®

Back-loaded Delivery Systems

- Based on the early observation of the Ramp Effect in which all stimulant medications had to have a constantly rising blood level in order to produce stimulation ***but not the beneficial effects for ADHD.***
- This is why all but 1 side effect (appetite suppression) occur when blood levels are rising or falling.

Do "Back-Loaded" Delivery Systems Make Sense?

- Based on Swanson's finding of "acute daily tolerance."[1] Product designed to constantly change the dose.
- Findings not repeated by others.
- Tolerance rarely develops in a lifetime, why should it in a mere 10-12 hours?
- Does not match clinical practice and patient behavior. No clinician has ever seen a patient back-load their medication.
- Back-loaded delivery systems are least likely to support the goal of "Consistency and Stability" since dose and blood level are designed to constantly change.

[1] Swanson J, et al. Clinical Pharmacology Ther, 66, 295-305.

50-50 Beaded Systems

ex, Adderall XR or Focalin XR

- According to the ramp theory, these 50/50 products should not work because the blood level is relatively stable. But they work very well.
- Half of the dose is short-acting. The other half has a coating that dissolves at a predetermined pH of about 6.8 (that is about 4 hours down the GI tract.)
- Assures that the 2nd dose gets taken. Other-wise there is a 90% failure to remember the subsequent dose.

Transdermal

Ex: Daytrana or Xelstrym

- Manufactured by the same company (Noven).
- Medication and adhesive in microspheres mixed on plastic backing.
- Slow onset. Takes 2 hours to see benefits, peak blood level takes 5-6 hours.
- FDA approves only 9 hour wear (because that is all they tested.)
- Designed to deliver medication for 24 hours.
- Expensive, rarely covered by insurance without multiple failed oral trials.

Prodrug

Ex:Vyvanse or Azstarys

- Inert combination of AMPH and lysine. Must be absorbed, get to the inside of a RBC where the lysine is clipped off leaving active amphetamine.
- "Goldilocks Enzyme."
- Most reliable and versatile delivery system.
- Only 30% of nominal weight is AMPH. (ex. Vyvanse 70 mg contains only 21 mg of amphetamine.) Generally under-dosed.
- Passed the FDA and DEA tests to no longer be a controlled substance but were still denied.

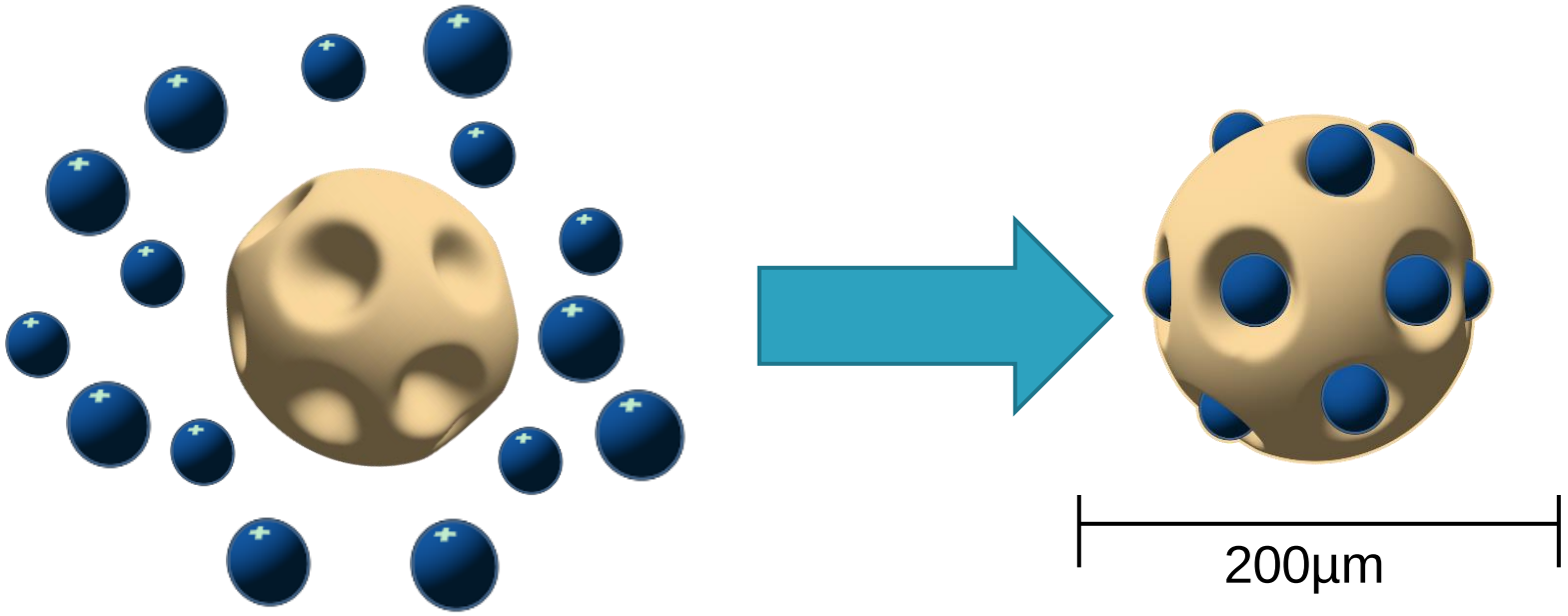
Prodrug – cont.

- “Smooth.”
- Only formulation not affected by food.
- Only formulation stable in water forever.
- Most convenient for low-dose responders.
- Most expensive formulation unless a low dose responder.
- Vyvanse went out of patent in August 2023. Azstarys (dexmethylphenidate) will be under patent for 10 more years

Ion Exchange Resin

Quillivant XR, Adzenys XR ODT, Dyanavel XR

- Stimulant base bound to resin that must be displaced by Chloride ions from the GI tract releasing stimulant to be absorbed.



HOW DO YOU DISCOVER THE OPTIMAL DOSE?

No Parameter Predicts Optimal Dose

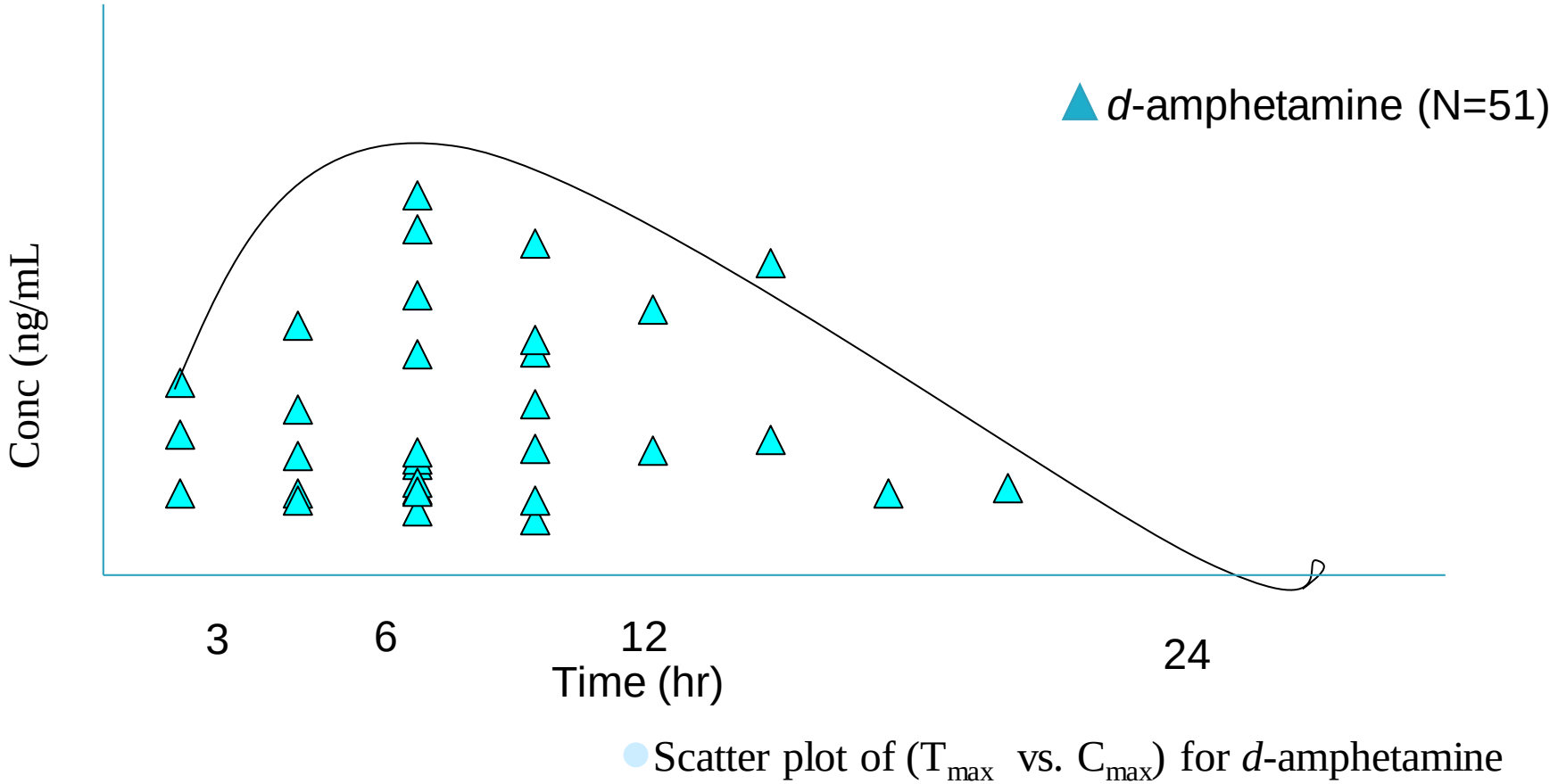
No parameter predicts the optimal dose for a given individual.

- Weight based nomograms have been used to protect the double blind in research. They do not work at all in clinical practice.
- Age: Children and adults take the same range of doses.
- There is no correlation with weight, height, gender, scale scores, or severity of impairment.

Greenhill LL, et al. (1996) Medication strategies in the MTA study: Relevance to clinicians and researchers. *JAACAP*. 35 (10):1304-1313.

There is Tremendous Variability in Efficiency of GI Absorption from Person to Person

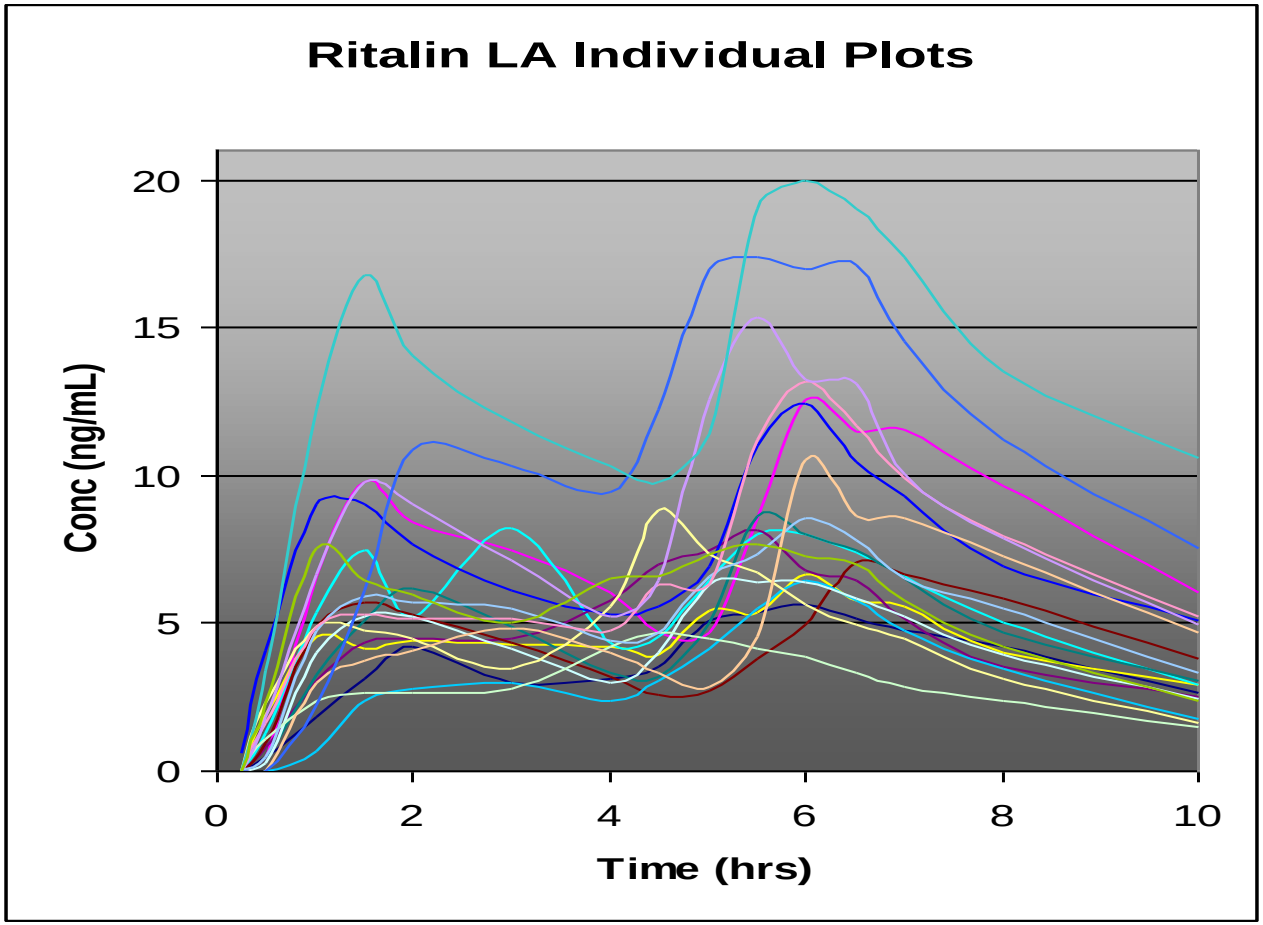
Time to Peak *d*-Amphetamine Plasma Concentration (for MAS XR 20 mg)



*One patient reached T_{max} at 24 hours but is not illustrated here.

Data on file, MAS XR 037. Shire US Inc

There Is High Individual Variability in Efficiency of Absorption from the GI Tract



Three Factors Determine Dose

1. The efficiency of absorption out of the GI tract.
2. The efficiency of metabolism (methylphenidate medications) or elimination in the urine (amphetamine).

- MPH is metabolized down 6 different tracks. 50% of metabolism is in the lining of the gut.
- AMPH IS excreted in the urine. If the pH = 8 (basic), a single dose of AMPH lasts 28 hrs. If pH = 6 (acidic), the duration is 2 hrs.

Factors that Determine Dose

- But by far the biggest determinant is the Blood Brain Barrier (BBB).
- This is why we do not do blood levels for most medications that act in the Central Nervous System. Blood levels do not correlate with anything.
- Change in the permeability of the BBB is presumed to be the cause of rare cases of loss of efficacy.

TAKE HOME MESSAGES

#1 SINCE THESE ARE MEDICATIONS THAT THE PATIENT WILL POTENTIALLY TAKE ALL DAY, EVERY DAY, FOR THE REST OF THEIR LIFE, IT MAKES SENSE TO TAKE SOME TIME UP FRONT TO BE SURE THAT YOU HAVE THE ABSOLUTE BEST OUTCOME.

EVEN IF YOU GET A **GOOD** RESPONSE WITH THE FIRST MEDICATION TRIED, YOU MAY GET A **GREAT** RESPONSE WITH THE OTHER ONE.

TAKE HOME MESSAGES

#1 Every patient is unique. Nothing predicts which molecule will work best or what the optimal dose and duration of action will be.

#2 The only way to determine which stimulant molecule will work best for any given patient is to do separate trials on *each* molecule using the most reliable delivery systems available to you.

IF NOTHING PREDICTS OPTIMAL MEDICATION, DOSE, OR DURATION…

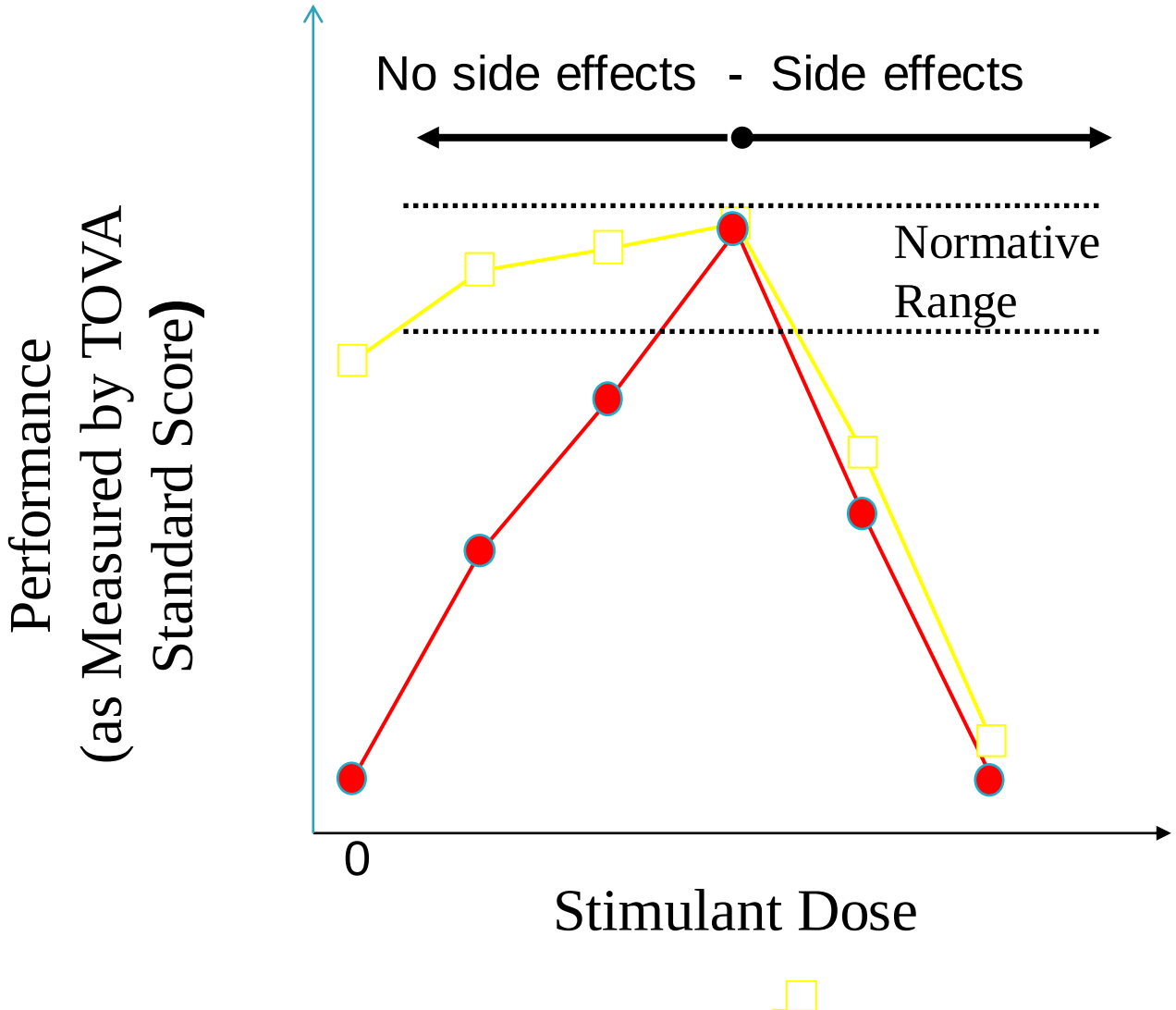
HOW DO YOU FINE-TUNE TO OPTIMAL RESULTS?

Optimize the 1st Line Agents

- Stimulant medications are fine-tuned to the **Target Symptoms** of the individual patient on the basis of 4 factors:
  1. Optimal **molecule**
  2. Optimal **delivery system**
  3. Optimal **dose**
  4. Optimal **timing of doses**

Greenhill LL, et al. Medication treatment strategies in the MTA.(1996) JAACAP 35; 1304-1313.

Dose-Response of Stimulant Class Medications



Target Symptoms That Respond Well to Stimulant Medications

- Reading speed, comprehension, and retention.
- Fidgeting, can't relax, tense, impatient.
- Interrupt others, blurt out.
- Hard to start tasks; procrastinate.
- Hard to stick with tasks; easily distracted. Jump from task to task. Mind wanders.
- Hot temper; easily irritated/frustrated.
- Misplace things; forgetful.

Target Symptoms That Do Not Respond Well to Stimulant Medication

- Poor organization (this is a lack of specialized skills, not a symptom).
- Being on time; punctuality.
- Mood lability; overly sensitive to slights.
- Listening to people; awareness of the feelings and emotions of others.
- Self-awareness; self-appraisal; ability to learn from experience.
- Quarrelsome, argumentative behaviors.

Target Symptom Titration Methodology

1. List patient's target symptoms.
2. Adjust stimulant medications in the smallest dosage increments available of the most reliable delivery systems of both medications (ex. 10 mg of dex MPH ER; 10 mg Vyvanse).
3. Continue to increase dose as long as the patient continues to see improvement in target symptoms without side effects.
4. Stop increasing the dose when the patient no longer sees further improvement in target symptom relief or develops side effects.
5. Take a "no risk" nap while on medication.

Fine-tuning Instructions for Adderall XR

What follows is a standardized way of determining the right dose of medication and the right timing of that dose. To determine the best dose of Adderall XR for you, increase the amount of medicine by a 5 mg capsule each day. With each increase in the dose of just one capsule you should notice a clear improvement in your concentration, productivity, calmness and impulse control. At some point you will increase the dose but the two doses will seem the same in their ability to relieve the symptoms of ADHD. At this point your dose will be the ***lower*** of the two doses.
*****Stop increasing the dose when you develop side effects (either sleepy or over stimulated) or when you increase the dose and do not see a clear improvement in your ability to function.** ***

Target Symptoms:

1) _____ 3)_____

2) _____ 4) _____

And so on until you discover the lowest dose that gives you optimal performance and no side effects.

STEP #2: Once you have found your optimal dose and how long it lasts you should try to take a nap after lunch one day to demonstrate in a "no risk trial" that this medication at optimal dose does not interfere with sleep. You can then add a second dose overlapping the doses by 30 minutes so the new dose gets in as the first dose is wearing off. This allows full coverage for your entire day.
If you have any problems, call _____and leave your name and telephone numbers where you can be contacted during the day and evening.

STEP # 1: Find your optimal dose and duration of action.

1st Day 1 capsule in the morning; Time taken: _____ Time wore off: _____ Please note any benefits or side effects: _____

2nd Day 2 capsules in the morning; Time taken: _____ Time wore off: _____ Please note any benefits or side effects: _____

3rd Day 3 capsules in the morning; Time taken: _____ Time wore off: _____ Please note any benefits or side effects: _____

4th Day 4 capsules in the morning; Time taken: _____ Time wore off: _____ Please note any benefits or side effects: _____

5th Day 5 capsules in the morning; Time taken: _____ Time wore off: _____ Please note any benefits or side effects: _____

And so on until you discover the lowest dose that gives you optimal performance and no side effects.

STEP #2: Once you have found your optimal dose and how long it lasts you should try to take a nap after lunch one day to demonstrate in a "no risk trial" that this medication at optimal dose does not interfere with sleep. You can then add a second dose overlapping the doses by 30 minutes so the new dose gets in as the first dose is wearing off. This allows full coverage for your entire day. If you have any problems, call _____and leave your name and telephone numbers where you can be contacted during the day and evening.

All of these Patient Forms are Free Online

www.DodsonADHDtreatment.com

No cookies, no advertising, no registering, no industry sponsorship. Share them with colleagues and students.

There is one catch: The forms and handouts are for clinicians only. We do not want patients to direct their own care.

When is the Dose Optimal?

- When you increase the dose and the patient does not see further improvement in target symptoms, ***the previous dose is the lowest dose that gives optimal benefits***.

OR

When you increase the dose and the ***diastolic blood pressure*** goes up by more than 10 mmHg, the previous dose is the highest dose that does not produce autonomic nervous system hyper-arousal.

What is good enough? – cont.

- Continuous performance tests (TOVA, Qbtech, Quotient) can provide very objective data about the effect of medication on getting things done. Expensive. Rarely covered by insurance.

OR

- "Please rate your medication and dose on a scale of 1 to 10 with 1 being awful, nothing but side effects and 10 being the best response you can imagine".

  8-10 = very good;

  7 = barely acceptable;

  <6 = medication failure; experience tells us that we can get a better outcome.

Questions and Comments So Far

Second Half

ADHD medications:
Why, What, and How?

The Problem of Generics

- Quality control – generics can vary in potency 80% to 125%; ex. A Generic 20 mg pill can be any amount from 16 to 25 mg from pill to pill.
- Many people can tell the difference of 2-3 mg.
- Some are just fraudulent. *ex.* Mallinckrodt, Teva, and Kudco "Concerta" are really cheaper, failed" formulations. Shorter duration, different kinetics.
- For more information go to: www.ADHD rollercoaster.com by Gina Pera.

The Problem With FDA Stage 3 Trials

- Stage 3 trials are the last hurdle to getting a medication to market. How are they designed?
- Must demonstrate only two things:
    1. Safety with the worst clinician imaginable
    2. For the indications they say they treat.
- They are design to find potential problems NOT to show clinicians how to best use the medication.
- Association is treated as Causation

Is there a "Typical Daily Maximum"?

- "Typical Daily Maximums" have no basis in either research or clinical experience. (SWAG's) 60 -100% higher "off-label" dosing allowed by AACAP guidelines.[1]
- Wide range of doses. >6% of people optimize at doses lower than the lowest doses manufactured. 40% optimize at doses higher than FDA approved.
- The PDR was never intended to be used in clinical practice. It does not contemplate b.i.d. or 24-hr usage.
- Therefore, document:

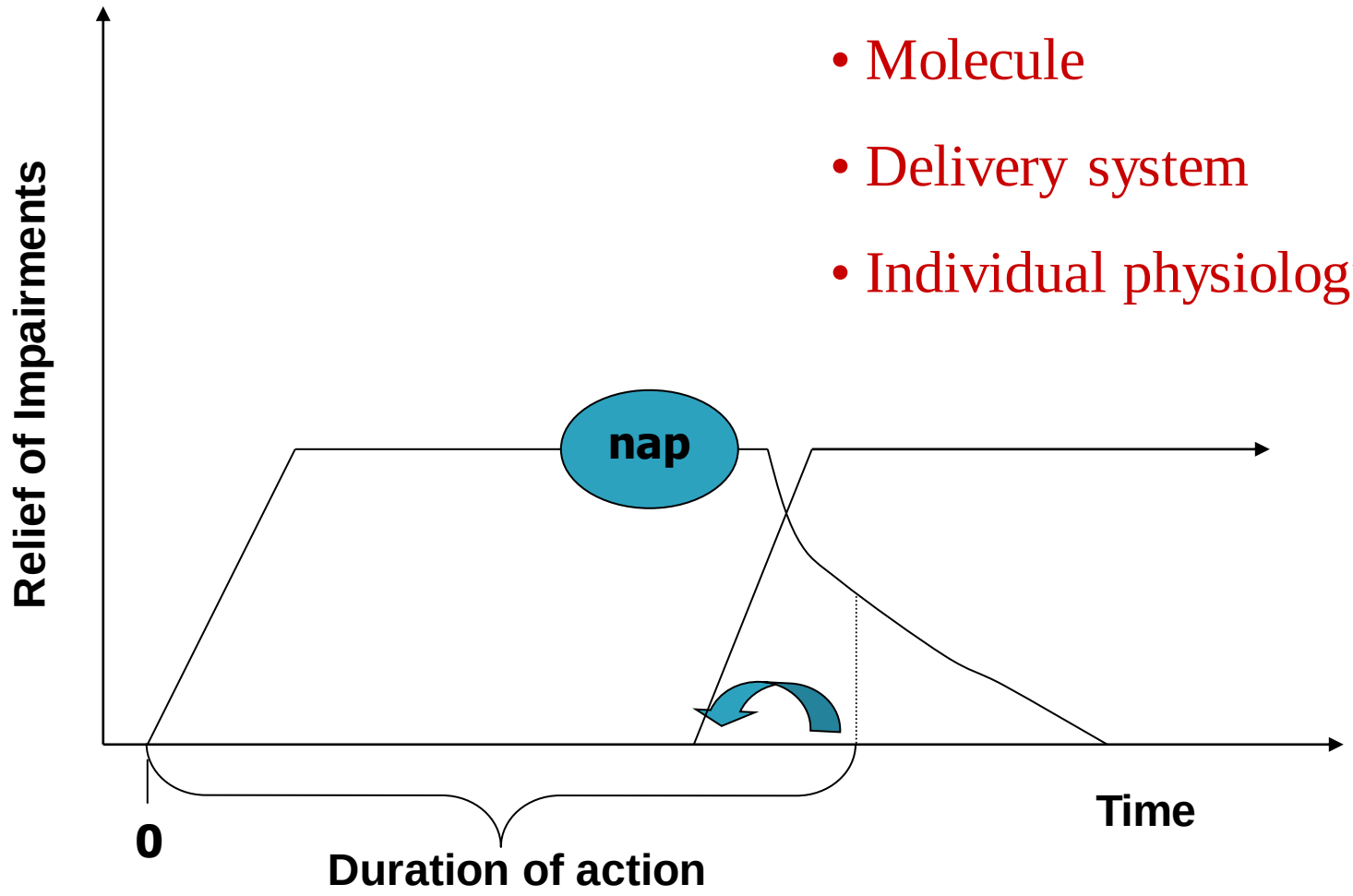
1. Continued alleviation of symptoms without significant side effects.
2. Baseline and medicated BP and pulse are the quickest and most objective proof of no autonomic nervous system hyperarousal.

[1]AACAP Practice Parameter. *JAACAP* (2007);46(7):894-921.

Then Adjust the Timing of Doses.

Determined by:

- Molecule
- Delivery system
- Individual physiology



Concurrent Stimulant Medications

Produce side effects that are blamed on ADHD medication:

- Decongestants (pseudoephedrine)
- Caffeine (coffee, tea, Red Bull)
- Nicotine
- OTC or Rx weight loss products
- Systemic steroids (inhaled OK)
- Systemic asthma medications containing albuterol (inhaled usually OK)

Slide by William Dodson, M.D.

Clinical Pearl: Acidifying Agents Impair GI Absorption

- **Acidifying agents, especially citric acid and vitamin C, ionize BOTH methylphenidate and amphetamine, preventing absorption from the GI tract**

- **Foods to avoid for one hour before & after dose**
  - All fruit juices
  - Soft drinks, Kool-Aid, Gatorade,
  - High vitamin cereals,
  - Pop-Tarts, granola bars, Power Bars,
  - Dietary supplements
- **Medications to avoid**
  - Oral suspensions / antibiotics,
  - Vitamin C

Physicians Desk Reference; 2006

MANAGEMENT OF TREATMENT EMERGENT SIDE EFFECTS

Sleep Disturbance in ADHD

- Sleep disorders are common in patients with ADHD of all ages — is it a symptom of ADHD or a side effect of treatment?
- Incidence of pre-treatment sleep problems in children is about 20%; increases to >85% by age 21.

- Three types of sleep problems in ADHD:
  - initiation insomnia / "can't turn off"
  - multiple awakenings / restlessness
  - difficulty awakening in the morning

Chronic Delayed Sleep Phase Syndrome

Corkum et al. JAACAP.1999;38:1285; Regestein and Pavlova. *Gen Hosp Psychiatry.* 1995;17:335. Dodson WW. Gender Issues in ADHD. Advantage Press 2002; ch 13.

Treatment-Emergent Insomnia

- Fine tune the dose; evaluate other sources of stimulant medications that did not disrupt sleep prior to treatment of ADHD
- Take a “no-risk” trial nap in the afternoon.
- Switch molecule
- Move last dose earlier or use step down dose
- Melatonin 1 mg; When?
- Clonidine 0.1 mg or Guanfacine 1 mg at HS
- Mirtazapine; half of a 15 mg tablet at HS
- 2nd line or alternative agent

Appetite Suppression / Weight Loss

Is it clinically significant? Reported by 33%; clinically significant in 5%.

Most ADHD families cannot keep up complicated dosing schedules around meals.

1. Fine tune; appetite suppression is dose related.
2. Cyproheptadine 4 mg bid[1]
3. Mirtazapine (Remeron) 15 mg; ½ tab at HS
4. Switch molecules (the 40% Rule)

Daviss WB, Scott J (2004), A chart review of cyproheptadine for stimulant-induced weight loss. J Child Adol Psychopharmacology 14: 65-73.

Treatment Emergent Headaches

There are two types of headaches:

1. End of dose
   - Mild. Back of head. Relieved by next dose of stimulant or OTC pain medication.

2. Vascular – Migraine-like
   - Severe.
   - Constant (not throbbing)
   - From start of dose until the end.
   - Verapamil SR 120 mg each morning 1 hr prior to stimulant. Can usually stop after a month.

Dry Mouth

Xeroatoma

A common side effect of both the stimulants and the alpha agonists.

Saliva is necessary for the antibodies that control the bacteria that cause tooth decay. Just drinking more water rarely works.

- Pilocarpine (Salagen®) 5-10 mg; 30 minutes prior to meals.
- Cevimeline (Evoxac®) 30 mg; 30 minutes prior to meals.

Both are contraindicated in uncontrolled asthma.

Treatment Emergent Tics

- Just as many tics get better as get worse.
- If not impairing or embarrassing, do nothing. Tics naturally wax and wane. If impairing and persistent…
- Clonidine 0.1 mg up to 3 tabs per day.
- Atypical neuroleptics (ex. Risperidone 1-2 mg) can be just as effective as traditional neuroleptics (Orap, Haldol) but without long term dyskinesias.
- Off label: Metoclopramide (Reglan) 5 mg with meals

Medication Use in Pregnancy

(old FDA Ratings)

Amphetamine	C
Methylphenidate	C
Atomoxetine	C
Bupropion	B
Tricyclics	Unknown

B= no evidence of risk;

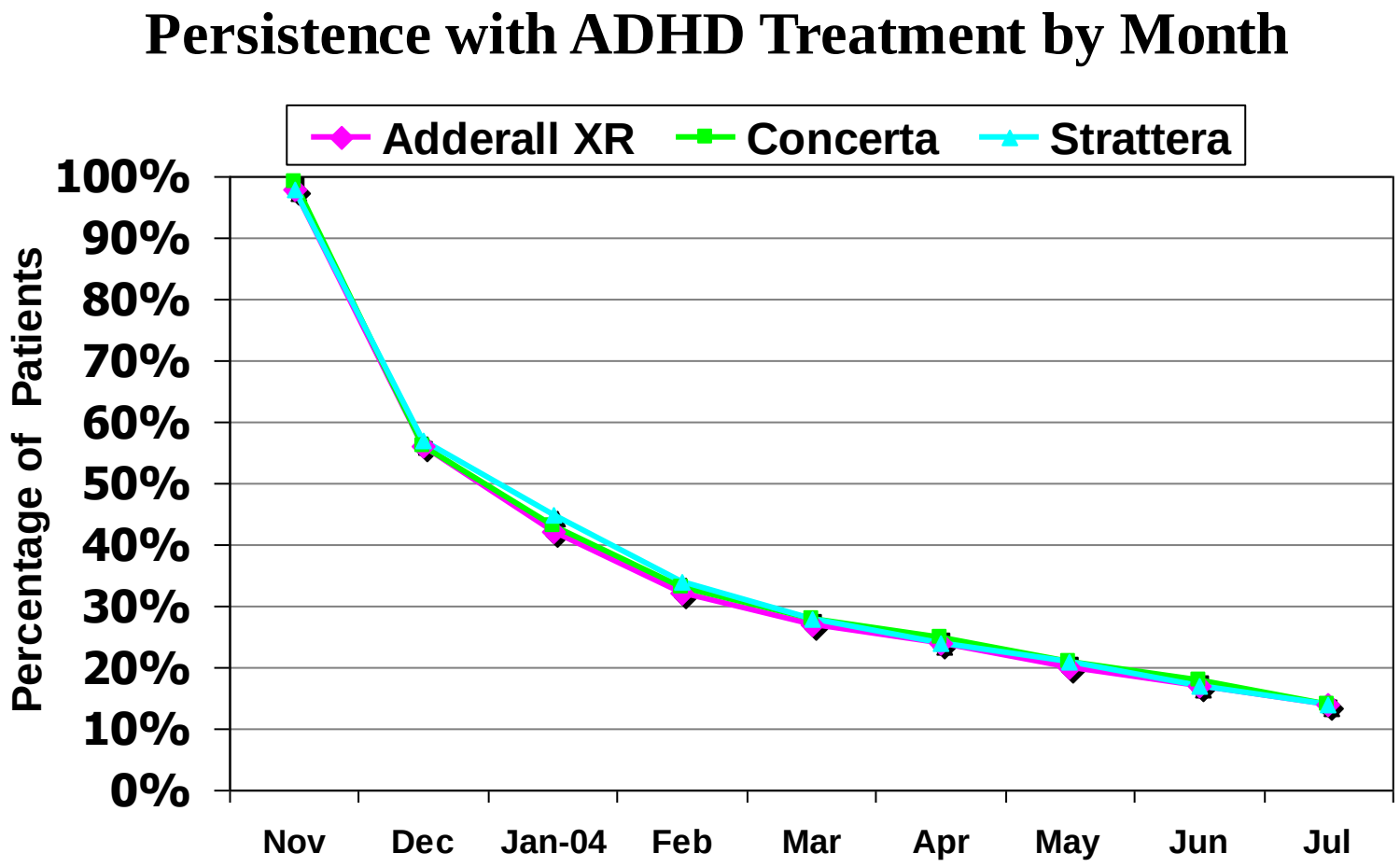
C= no known problem but unable to rule out risk.

Breastfeeding is contraindicated by AAP due to lack of data, not due to known problems.

Briggs GG, Freeman RK, Yaffe SJ. Drugs In Pregnancy and Lactation. 2003

MEDICATION ADHERENCE AND COMPLIANCE!!

Persistence with ADHD Therapy is Poor Across Brands



Hodgkins P, Boken M, Capone NM, DeLeon A. 19th U.S. Psychiatric Congress; Nov. 15-19, 2006; New Orleans, LA. Abstracts 123 and 124.

Causes of Treatment Dropout

- The medications for ADHD work dramatically well.
- However, only 13% of patients are still taking medication 9 months later. Why?

1. Meds don't adequately control symptoms (dose too low or wrong molecule).
2. Meds produce intolerable side effects (dose too high or wrong molecule) or when mixed with other stimulant medications.
3. Patient is in the 15% for whom stimulant medications don't work.

Causes of Treatment Dropout – cont.

1. Both patient and clinician believe that a Rx will magically cure everything. “Antibiotic fantasy”
2. Patient did not understand why they were taking the medication and the role of meds in prevention of future impairment.
3. Clinician was perceived as being unsupportive of consistent medication through the entire day for life.
4. Patient or parent was not organized enough to take the medications as directed or get new refill each month. Treat the entire family.
5. Cost was next to last (listed by only 11%).

Successful Clinicians…

- Choose the best molecule and delivery.
- Determine the optimal dose.
- Never assume the patient is compliant…

1. Psycho-education about ADHD and lifelong impairment.
2. Write down everything.
3. Vigilance effect (ask; count pills; PDMP, call backs)
4. Pillbox timers, ticklers on PDA's
5. Assess the entire family

WHAT IF THE 1ST LINE MEDICATIONS ARE NOT EFFECTIVE OR NOT TOLERATED?

Medication Non-Response

- A 70% robust response without side effects to either AMPH or MPH. 30% will not benefit or tolerate the 1st stimulant they try.
- About 85% robust response rate if both AMPH and MPH are ***sequentially*** tried and the full range of dosages is used.
- But that means that 15% of people do not benefit from or tolerate AMPH or MPH.
- There is nothing in the research literature or Practice Parameters to guide clinicians about what to try next.
- Therefore, what follows is based on clinical experience and may be off-label.

Responses to Medication Treatment Failure

- Make sure the diagnosis is correct.
- Make sure the patient is not Oppositional Defiant or Conduct Disordered.
- Make sure the patient actually did the medication trial correctly. Count the pills still in the bottle. Check the paperwork. Check the PDMP.
- What are the medications that are FDA-approved for ADHD and have an Effect Size of 0.7 or greater?
    1. Alpha agonists (guanfacine, clonidine) (ES=1.3)
    2. Atomoxetine (Strattera) (ES=0.7)
    3. Viloxazine (Qelbree) (ES=0.7)
    4. Methamphetamine (in the US) (ES unknown)

Atomoxetine (Strattera)

- FDA approved for ADHD.
- Considered a 2nd or even 3rd line medication.
- Neurochemically similar to tricyclics without the sudden accumulation reported in children.
- Effect size of 0.6 to 0.7 in children and 0.4 in adults is better than no response to stimulants.
- ~ 50% response rate at all ages.
- Potent trigger of mania.

Henderson TA, Hartman K, (2004) Aggression, mania, and hypomania induction associated with atomoxetine. Pediatrics 114(3) 895-6

Atomoxetine

- **Atomoxetine** is a selective norepinephrine reuptake inhibitor (SNRI)
- Mechanism of action - Dopamine activation in the subcortical nucleus accumbens and striatum
- Short metabolic half-life of just 3.5 to 5 hours by P450 2D6. Therefore, there is a high variability of optimal doses. 40 to 80 mg
- Much better results and tolerability if the dose is divided into 2 or 3 doses.
- Unfortunately, this doubles or triples the cost of taking atomoxetine.

Side Effects of Atomoxetine

- Relatively heavy side effect burden
- Sedation
- Dry mouth and eyes
- Decreased appetite
- Dizziness
- Nausea
- Constipation
- Erectile dysfunction and impotence
- Urinary problems

Viloxazine (Qelbree)

- Was an SSRI antidepressant for > 20 years in Europe before it left the market because it wasn't a good antidepressant and wasn't profitable.
- FDA-Approved in the US for ADHD in 2021.
- Once a day due to Microtrol delivery system.
- Not everyone benefits from viloxazine but those who do improve quickly and at moderate doses.
- Starting dose is 200 mg usually increased in a week to 400 mg. Very little further improvement at higher dose of 600 mg in most people.

Viloxazine – cont.

Side effects in trials:

- Drowsiness 16%
- Decreased appetite 7%
- Tiredness 6%
- Nausea 5%

Only 3% discontinued due to side effects.

Alpha 2a Adrenergic Receptor Agonists

- FDA approved for ADHD in children and adolescents.
- FDA approved for hypertension in adults.
- In responders the Effect Size is 1.1.to 1.3 for ADHD.
- Guanfacine and clonidine appear to work equally well. Clonidine is slightly more sedating.
- Disappointingly low robust response rate of 30% to each of the alpha agonists.

Alpha Agonists Have Many Uses

- Clonidine can be very effective for tics and Tourette's.
- Clonidine is a non habit-forming sleep aid because it treats the cause of the insomnia (ADHD hyper-arousal) and does not merely suppress the symptom.
- Clonidine can block the experience of opiate withdrawal at the brain stem.
- Anesthetic for eye surgery.

Alpha Agonists have many uses in ADHD

- Stimulants are great for inattention but not so good for hyper-arousal/ impulsive features:
- Multiple simultaneous lines of thought.
- Initiation insomnia; Can't settle down to fall asleep. Treats the cause does not suppress the symptom.
- Never at peace.
- Decreases impulsive behaviors. Gives time to think and strengthen self-control.
- Rejection Sensitivity Dysphoria (RSD)

What About Taking With Other Blood Pressure Medications

- Alpha agonists lower blood pressure and can slow heart rate.
- Many adults are already prescribed anti-hypertensives that will be additive.
- 1st question is whether the ADHD patient is taking their BP medication consistently (half are not).
- Taper off original BP medication and then titrate alpha agonist as usual. Coordinate with PCP.
- Check to see if alpha agonist alone is adequate.

Clarifying Our Terms

Emotional Dysregulation

Vs.

Rejection Sensitivity

Vs.

Rejection Sensitivity Dysphoria

3 Types of Emotional Control Problems

- People who have an ADHD nervous system commonly have all three problems.
- Each of the following emotional control problems have different sources.
- Two respond to medication; one does not but does respond to CBT, DBT, and “somatic therapies” such as EMDR.

What is Emotional Dysregulation?

Difficulty controlling the expression of emotions was originally part of the diagnostic criteria until the DSM III (1980)

In 2019 the EU issued adult ADHD update that acknowledged ED as a 4th core diagnostic criteria for adults with ADHD in addition to:

- Distractibility/inattention
- Impulsivity and
- Hyperactivity/hyperarousal

CORE = It would not be ADHD without that feature.

Kooij J.J.S., Bijlenga D, Salerno L, et al. Updated European Consensus Statement on diagnosis and treatment of adult ADHD. (2019) European Psychiatry 56: 14–34. http://dx.doi.org/10.1016/j.eurpsy.2018.11.001

Emotional Dysregulation

Just added in the EU as a new core criterion for adult ADHD defined as:

- Mood lability
- Low frustration tolerance
- Emotional impulsivity
- Irritability
- Anger outbursts
- Premenstrual increase of symptoms

(Many people think this concept is too vague and non-specific)

Multiple Definitions of Emotional Dysregulation

Barkley[1]

- Inability to self-soothe
- Inability to redirect attention to less provocative events
- Emotional Impulsiveness
- Inability to substitute healthier responses
- Expression of Executive Function Deficit

Reimherr[2]

- Temper outbursts
- Mood lability
- Emotional Over-reactivity
- Largest contribution to ADHD Impairment
- Not due to comorbidities
- Responds to ADHD stimulant medications

[1] Barkley RA, Fischer M. (2010) JAACAP 49(5):503–513.
[2] Reimherr F, et al (2020) J. Clinical Psychiatry81(2) e1-e7

Loss of Emotional Control Can Be a Part of Many Conditions

- ADHD – Chronic, excessive positive (+) emotion
- Autism spectrum disorder- Chronic, excess + emotion
- Bipolar disorder, manic – Episodic, excess + emotion
- Borderline PD- Chronic, impulsive aggression, *empty*
- Oppositional defiant disorder – Chronic, argumentative
- Disruptive mood dysregulation disorder (DMDD) – Chronic, irritability, and anger/uncontrollable rage
- Intermittent explosive disorder – Episodic, anger
- Generalized anxiety disorder- Chronic, excessive fear
- Depressive mood disorder –Episodic, excessive sadness

How common is ED?

Forty to 50% of children with ADHD have significant impairments from:

- rages,
- irritability,
- outbursts of temper,
- susceptibility to anger and
- “low tolerance for distress.”

But that also means that half of children don’t have impairing emotional dysregulation.

ED is neither sufficient nor required for an ADHD diagnosis

Faraone SV, et al Journal of Child Psychology and Psychiatry 60:2 (2019), pp 133–150

Summary

- "Emotional symptoms are currently considered to be associated features of ADHD – much like learning problems or executive dysfunction."

- "They are not, however, diagnostic for the disorder." *i.e.* emotional dysregulation is found in so many other conditions.

Faraone SV, et al. Practitioner Review: Emotional Dysregulation in ADHD – Implications for clinical recognition and intervention. Journal of Child Psychology and Psychiatry 60:2 (2019), pp 133–150.

Medication Treatment of ED Part of ADHD?

- The few studies (11 by 2019) that specifically looked at the response of emotional dysregulation to medication found significant improvements:
- Methylphenidate: 2/3 had remission[1]
- Lis-dextroamfetamine (Vyvanse): 60% no longer had "emotional control impairments" [2]
- Atomoxetine: "Small but positive effects."
- Alpha agonists: No published studies but described as "promising."

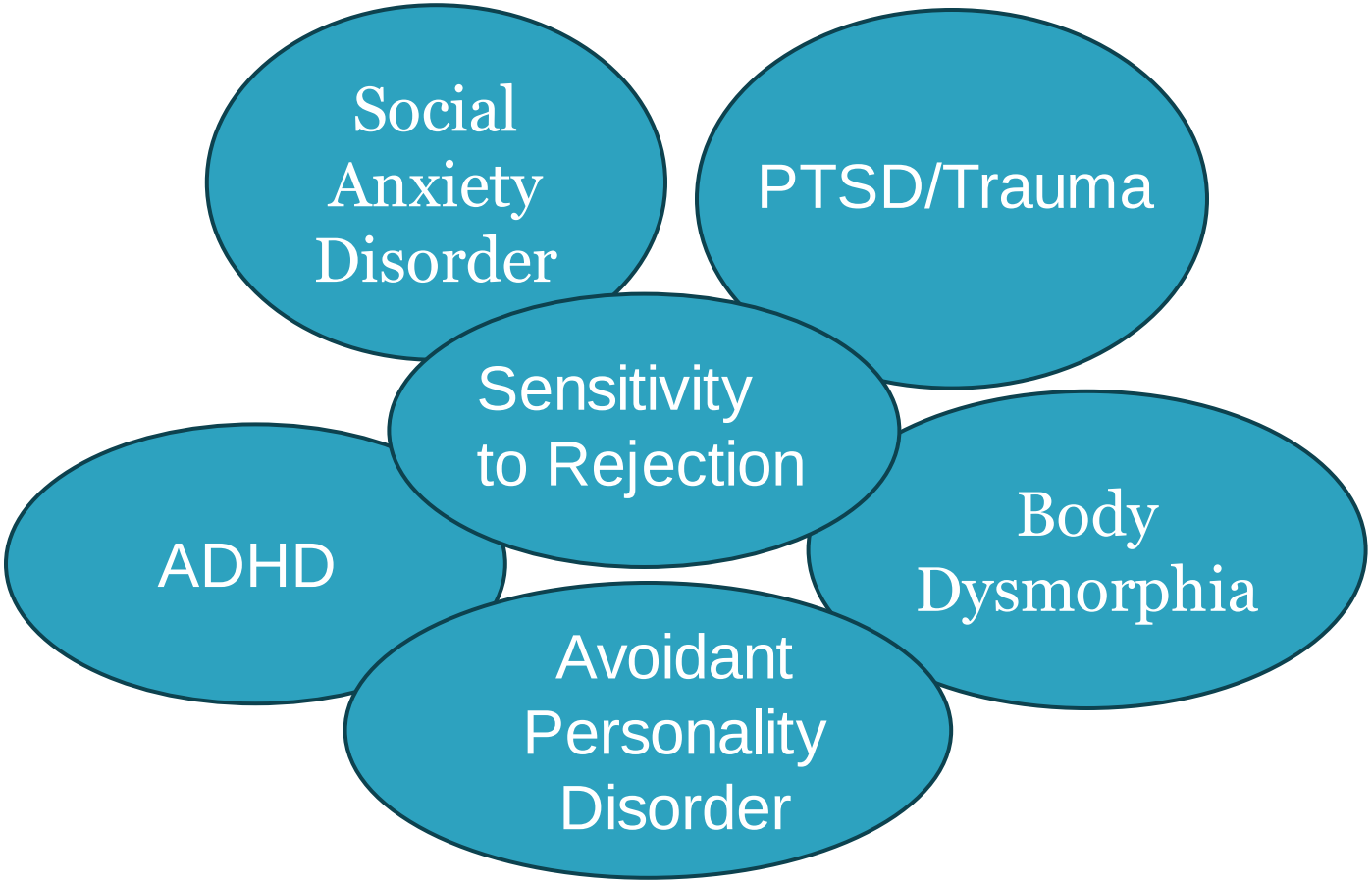
1 Katic et al. (2013) Journal of Child and Adolescent Psychopharmacology, 23, 386–393.
2 Blader et al. (2016) Journal of Child and Adolescent Psychopharmacology, 26, 164–173.

Sensitivity to Rejection

An Emotional Component of ADHD

NOT Specific to ADHD

Sensitivity to Rejection is Found in Multiple Conditions



SR is the Result of Years of Experiencing Rejection

- The average ADHD child hears 20,000 additional negative or corrective messages in school alone by the time they are 10 years old[1].
- 70% of ADHD 3rd graders do not have a friend. Rejections are very real to ADHD children
- The more we are rejected ("You are not what I wanted!"), the more we expect rejection and misinterpret neutral events as rejecting.

1 Jellinek M. (2010) Clinical Psychiatry News. Page 12

SR Comes From Traumatizing Experiences

- Sensitivity to Rejection can happen to anyone based on their adverse life experiences. It is only a specific feature of the trauma diagnoses.
- There is nothing in this world that cannot be made worse by a toxic, hostile childhood.
- SR has a profound effect on self esteem, self-confidence, and self-worth.
- Because SR comes for experiences that happen to us, SR has very little response to medications.

Rejection Sensitivity Dysphoria

(The Emotional Component Possibly Specific to ADHD)

Rejection Sensitivity Dysphoria

- "For your entire life have you always been much more sensitive than other people you know to…
- 1.Rejection
- 2.Teasing
- 3.Criticism, or
- 4.Your own perception that you have failed or fallen short?"

- In my practice 98% answered a strong "YES!" and 33% said that it was the most impairing aspect of their adult ADHD.

Rejection Sensitive Dysphoria

- Reported by 98% of people with ADHD.
- 30-40% report that RSD is the most impairing aspect of their ADHD.
- They have found compensations for academic and work performance but not for the sudden, catastrophic emotional “wounds” of ADHD that can throw them off for days.

The 12 Features of RSD

(The criteria for RSD are as precise as ED and RS are vague)

1. There is always a trigger even if only seen by the person.
2. There are only a limited number of triggers: rejection, teasing, criticism, perception of failure.
3. The mood matches the person's perception of the trigger (*i.e.* mood congruent).
4. Change from one mood to the new dysphoric mood is instantaneous.
5. If internalized the mood looks like MDD;
   If externalized, it looks like a rage at the person or situation that "wounded" them so severely.
6. The pain is often physical as well as emotional.

The Associated Features of RSD

7. Age of onset is usually in early childhood but may not appear until adolescence.
8. The emotional pain is not describable in words, just the intensity…"It's horrible, terrible, catastrophic."
9. People commonly report feeling cut off from the rest of he world. "In another dimension."
10. Once the episodes starts, it commonly has to run its course. Most people have little control over RSD episodes.

Associated Features of RSD – cont.

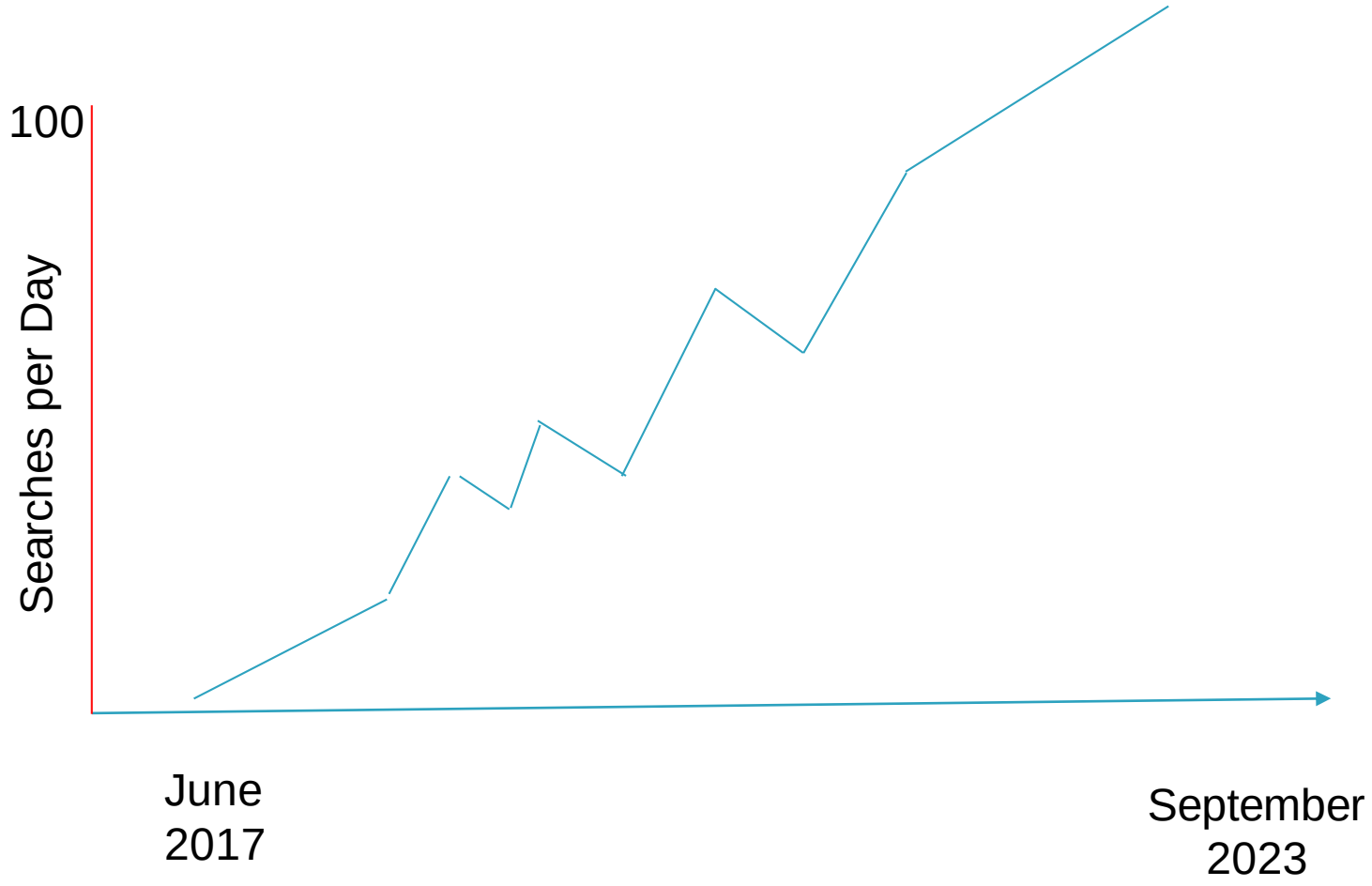
11. After the episode is over the person is commonly overwhelmed by Shame and humiliation. A "head case", a weakling, or defective because they cannot control themselves.

12. If the person is one of the about 60 % of people who get benefits from medications they "Put on emotional armor." *i.e.* They still see the triggers but "they bounce off without wounding me."

RSD is still in the early phases of inquiry.

- RSD is not an official condition and there is virtually nothing written on RSD as an integral part of ADHD in the scientific literature.
- All of the literature refers to RSD as a hallmark symptom of Atypical or Non-typical depression. The unanswered question is whether the depression is not typical because it is actually ADHD and not a formal mood disorder.

Google Trends for USA
Searches for the term “RSD ADHD”



Take Home Messages on ADHD Emotionality

Emotional Dysregulation	Sensitivity to Rejection	Rejection Sensitivity Dysphoria
Found in practically every DSM diagnosis.	Universal life experiences that come from life's rejections.	Probably unique to ADHD.
Periodic loss of control of one's emotions.	Severe vulnerability to rejection from experiences since childhood.	Catastrophic emotional responses to anticipated withdrawal of love, approval and respect.
Deep and profound sense of shame over loss of self-control.	Deep and profound sense of shame over loss of self-control.	Deep and profound sense of shame over loss of self-control.
~ 66% respond very well to stimulant medication.	Doesn't respond to medication. Responds to somatic therapies.	~ 60% respond well to Alpha$_{2a}$ Agonists.

⇨ People with ADHD have to manage all three of these types of emotional impairments.

The 1st Research to validate Rejection Sensitive Dysphoria

If you are 18 or older, have 20 minutes free and willing to be either….

- a subject with clinician-diagnosed ADHD or
- a control who does not have ADHD…

send your name and email address to

BillDodson19@gmail.com

When to Use Alpha$_{2a}$ Agonists

- “Have you ever been mentally and physically at Peace?”
- “How many simultaneous thoughts do you still have even when on an optimal stimulant dose of a stimulant?”
- “Inability to settle down to sleep even on a fine-tuned stimulant.”
- “Are you extremely sensitive to rejection, teasing, criticism or failure. (RSD)

Alpha $_{2a}$ Specific Adrenergic Agonists (guanfacine or clonidine)

- Commonly used as FDA-approved adjuncts to stimulants for hyperactivity but have an effect size of up to 1.3 as a monotherapy.
- Take up to 5 days to see effects after each dosage change.
- Only 1/3 of people get a robust response to either.
- Optimal dose varies from 0.5 mg to as high as 7 mg of guanfacine or 0.1 mg to 0.6 mg of clonidine.
- Side effects: Dizzy if stand up quickly, dry mouth, sedation, headache.

Methamphetamine (Desoxyn)

- If the patient is a "pillar of the community" the highest response rate is with meth-amphetamine (Desoxyn).
- Probably the most effective medication ever found for ADHD. Half of non-responders will get robust response.
- FDA approved.
- Typical dose = 10-20 mg (1/200th of the abused dose) Typical duration of action = 4 to 6 hours
- Downsides: Very expensive; only med with true abuse potential; Just the name gives people the willies.

ADHD Use in Co-Existing Conditions

Anxiety Disorders

- Anxiety is “a baseless apprehensive fear.”
- Often mistaken for the hyperarousal of ADHD due to difficulty with self-appraisal and dyslexithymia.
- Jitteriness is often due to taking a dose that is too high.
- 6-8% of people optimize at stimulant doses lower than the lowest doses manufactured

Coughlin CG, *et al*. (2015) Meta-analysis: Reduce Risk of Anxiety with Psychostimulant Treatment in Children with ADHD. J. of Child and Adol. Psychopharmacology. 25 (X) 1-7

Anxiety Disorders Usually Get Better

- Meta-analysis of 23 studies of children with pre-existing anxiety disorders. (N=2959)
- "The risk of anxiety associated with psychostimulant treatment was significantly lower than that experienced with placebo."
- As always, "This finding does not rule out the possibility that some children may experience increased anxiety."

Coughlin CG, *et al*. (2015) Meta-analysis: Reduce Risk of Anxiety with Psychostimulant Treatment in Children with ADHD. J. of Child and Adol. Psychopharmacology. 25 (X) 1-7

Stimulants with Bipolar Disorder

- A very common problem since 25-40% of people with Bipolar will also have ADHD.
- If Bipolar is not recognized or not medicated, the addition of a stimulant increases the risk of inducing mania by 600%!
- If, however, the patient is taking any mood stabilizer (lithium, lamotrigine, etc.) the risk of a treatment emergent mania decreases 60%.
- The person can still have manias just not as frequently or severely

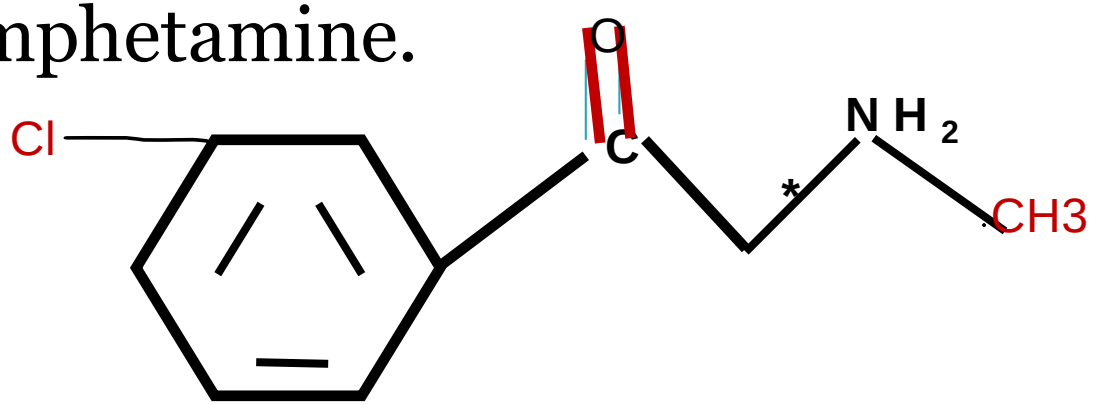
Viktorin A, et al. (2017) The risk of treatment-emergent mania with methylphenidate in Bipolar. American Journal of Psychiatry 174:4. 341-348.

DISCUSSION AND QUESTIONS

OFF-LABEL MEDICATIONS

Bupropion (Wellbutrin)

- An early antidepressant that is structurally similar to amphetamine.



- Only two studies show statistically significant efficacy.
- Stahl does not mention bupropion in his chapter on the treatment of ADHD.

Stahl S. (2021) Stahl's Essential Psychopharmacology 5th Ed.

Tranylcypromine is a Drug of Choice For Atypical Depression

- Usually used in atypical or non-typical depression
- The mood shifts were always…
  - Triggered by events or perceptions.
  - Matched the perception of the trigger.
  - Instantaneous shifts.
  - Did not last >2 weeks.
- These were normal moods in every way except their intensity.

Tranylcypromine For Rejection Sensitivity

- 50 years ago RSD was a diagnostic feature of ADHD but since it was not always there and could not be measured, it was ignored by research.
- RSD became a marker for “atypical” depression. It was not typical because it had no features required of mood disorders.
- People recognize what they are taught to see…. Anxiety and depression rather than ADHD

Parnate (Tranylcypromine)

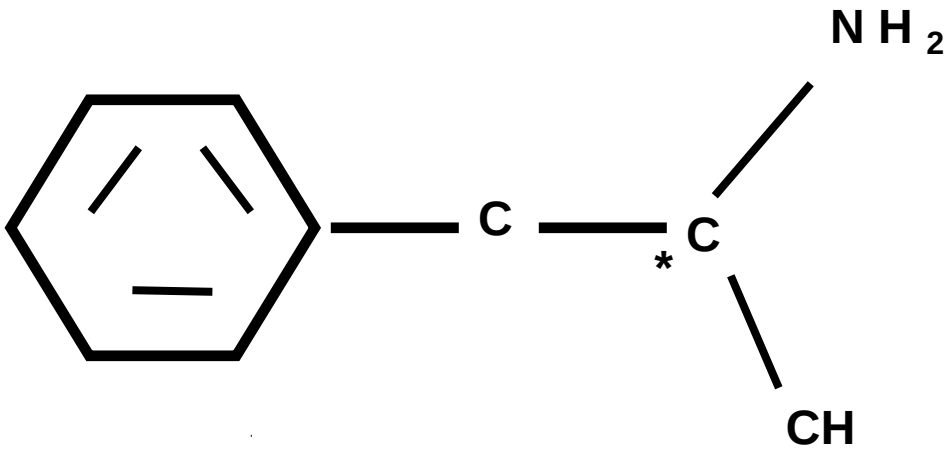
- Monoamine oxidase inhibitor (MAOI)
- Structurally very similar to amphetamine.
- Dr. Paul Wender thought that MAOI's were the treatment of choice for adults with ADHD[1] because…

1. One head to head study with MPH found them to be therapeutically equal.
2. True once a day dosing.
3. Not abusable,

Wender PH (1987) The Hyperactive Child, Adolescent, and Adult. Oxford University Press. New York

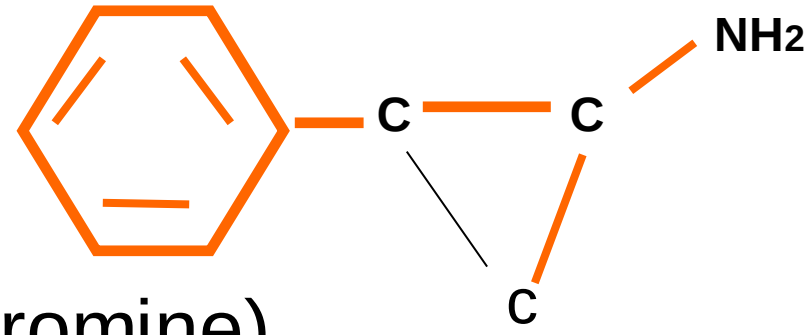
Similarity of Structure

Amphetamine



Parnate

(Tranylcypromine)



Parnate (cont.)

3. Not a controlled substance, so may be preferred for people with active or recent substance abuse, people in the criminal justice system or in prison, and people with a history of misuse of traditional ADHD stimulants.

4. MAOI's are probably the best medications ever discovered for Major Depression and Anxiety Disorders.

5. MAOI's are probably the best medications for ***Rejection Sensitive Dysphoria.***

Parnate – Downsides

- Tyramine is usually destroyed in the lining of the gut by monoamine oxidase.
- If MAO is inactivated, the tyramine is quickly metabolized into adrenaline in the synapse which causes a sudden increase in blood pressure leading to strokes.
- Modern MAOI diets are much less restrictive. People who eat healthy diets and amounts need almost no changes at all.

Modern MAOI Diet available at www. www.psychotropical.com

Parnate – Food Interactions

- "Cheese reaction": Foods that are aged rather than cooked contain an amino acid, tyramine, that the human body does not use.
- Expensive aged cheese ("super market" cheese, yogurt, uncured cheese are OK) Up to 6 oz is safe.
- Expensive aged meats (ex. Salami)
- Soy Sauce.
- Craft or "boutique" beers (Wine and commercial beers are safe.)

Parnate – Serotonin Syndrome

- SSRI's (ex. fluoxetine, citalopram, etc.)
- SNRI's (ex. duloxetine,venlafaxine)
- Imipramine and clomipramine (other TCA's are safe)
- Analgesics: Tramadol and Demerol.
- OTC cough suppressants containing decongestants or dextromethorphan.
- Must allow a minimum 2 week washout after stopping MAOI before using serotoninergic medications.

Modafinil

Modafanil (Provigil) – Not FDA approved for ADHD.

- Poor monotherapy for most children.
- 5 out of 6 FDA Stage 3 trials in children did not separate from placebo. 6th trial was statistically but not clinically effective.
- Possible use in hypo-active ADHD; usually female.
- Very expensive; may be associated with skin rashes.

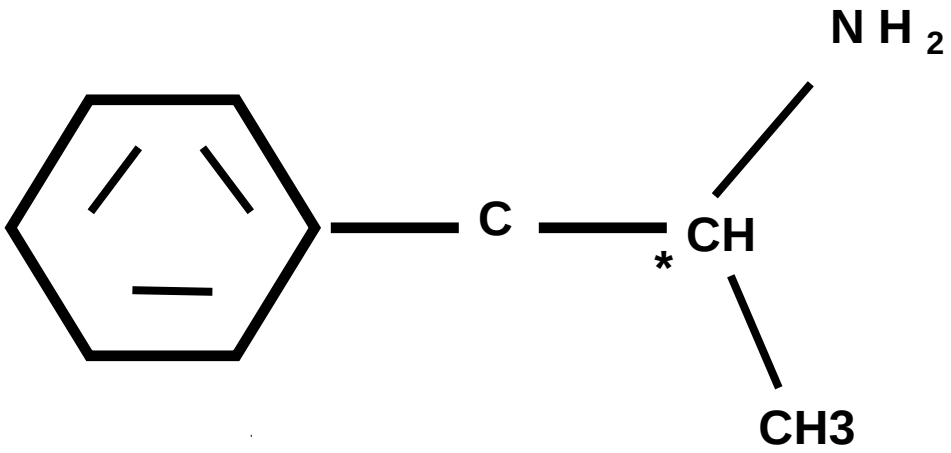
Phentermine

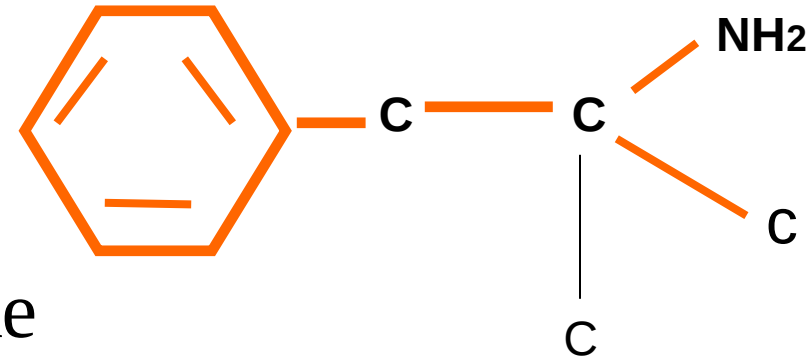
Phentermine (Adipex, et al.)

- FDA approved anorexiant (appetite suppressant);
- C-IV non-controlled.
- Typical dose = 37.5 mg qam (only one dosage size)
- Duration = 12 hours
- Tolerance develops to appetite suppression but not to ADHD benefits.
- Response rate of 10% of non-responders.

Similarity of Structure

Amphetamine





Phentermine

Amantadine

Amantadine (Symmetrel) / Memantine:

- No longer FDA recommended as antiviral.
- Inhibits NMDA receptor to block glutamate access to neurons thereby increasing DA activity. "Neuroprotective."
- Target symptoms are usually irritability, hyperactivity, and mood instability.
- Starting dose is 25 mg increasing by 25 mg/wk until behavioral goals achieved. Average dose = 150-200 mg.

Amantadine

- Only 1 RCT but that study found equal efficacy with methylphenidate[1].
- This has not been found clinically where it is less than half as effective as MPH with a response rate = <40%

[1]Hosenbocus S, Chahal R. (2013) Amantadine: A Review of Use in Child and Adolescent Psychiatry. J Canadian Acad. Child Adol. Psychiatry. 22:1; 55-60.

Amantadine (cont.)

- Well tolerated. Most common side effects (5-10%) are decreased appetite, nausea, dizziness, and insomnia.
- Approved by FDA for "long term use." but not for ADHD.
- Very rare, sudden onset of suicidal ideation with 3 deaths in children due to intentional OD with amantadine.

Take Home Messages

- Start treatment as early as possible before damage is done to Self-esteem.
- The goal is “normal functioning” not just academically but in the family, with peers, in the workplace, everywhere. “The Best Version of You”
- Optimize molecule, dose, and timing of dose.
- Use consistent extended release delivery systems if financially possible.
- Strongly urge all day, everyday medication.
- Pills don’t give skills. Refer for psychoeducation and counseling.

What Will Be Covered in 2nd Half

- Where do side effects come from?
- How do we quickly remove side effects?
- Treatment of ADHD-based sleep disorders.
- Emotional Dysregulations and Rejection Sensitivity.
- Medication Treatment of ADHD when the patient gets no benefit or does not tolerate 1st line stimulant medications.
- Non-stimulant medications