Attention Deficit Hyperacativity Disorder (ADHD)

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Overview

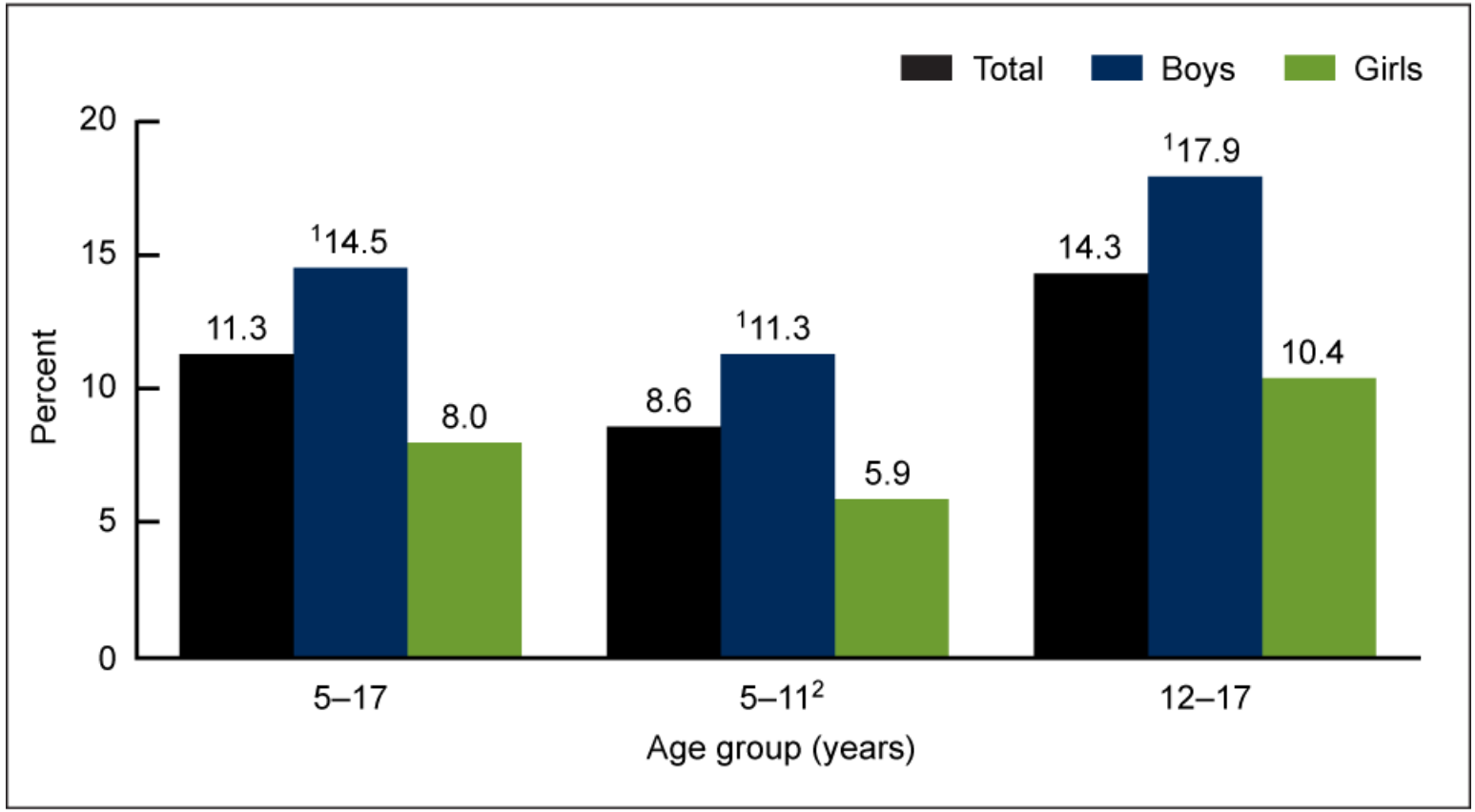
- Background
- Pathophysiology
- Diagnosis
- Adult ADHD
- Medical Treatment Algorithm
  - Non-pharmacological Treatments
  - Stimulants
    - Amphetamines
    - Methylphenidate
    - Other Stimulants
    - Stimulant Adverse Effects
      - Substance Abuse
  - Non-Stimulants
- Effects of Estrogen on ADHD

Background

Background

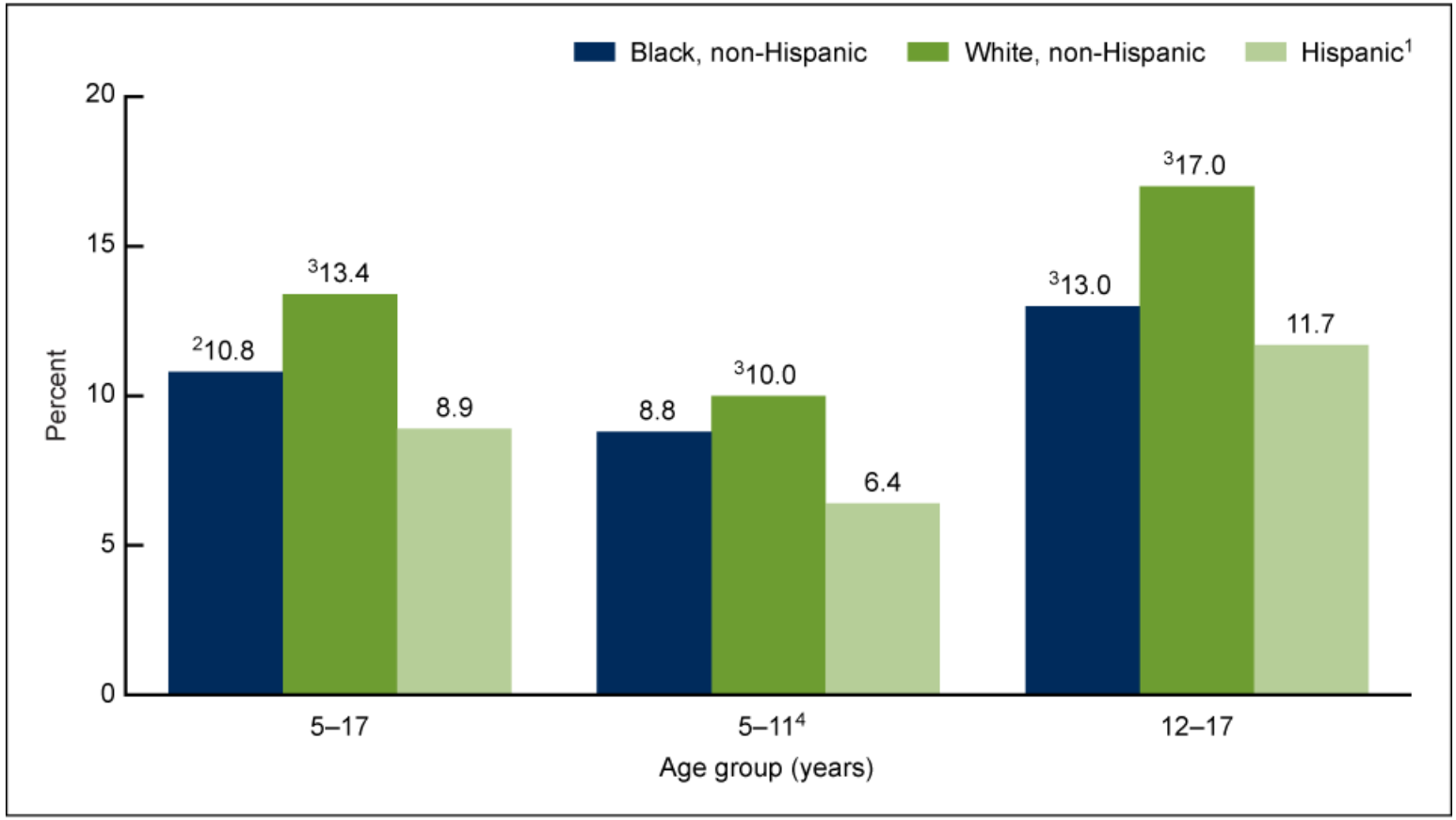
- Most common behavioral disorder in childhood
- Approximately 8-15% of school-aged children
- Characterized by inattention, impulsivity and hyperactivity
- Lack of gender predominance (1:1)
- Symptoms may persist into adolescence (68%) and adulthood (20-50%)
  - ADHD is a lifelong condition

ADHD Aged 5-17 Years in the U.S. (2020 - 2022) [14.5% Boys vs. 8.0% Girls]



[1]Significantly different from girls ($p < 0.05$).
[2]Significantly different from children ages 12–17 years ($p < 0.05$).
NOTES: Attention-deficit/hyperactivity disorder is based on a response to the question, "Has a doctor or other health professional ever told you that [sample child] had Attention-Deficit/Hyperactivity Disorder or ADHD or Attention-Deficit Disorder or ADD?" Estimates are based on household interviews of a sample of the civilian noninstitutionalized population.

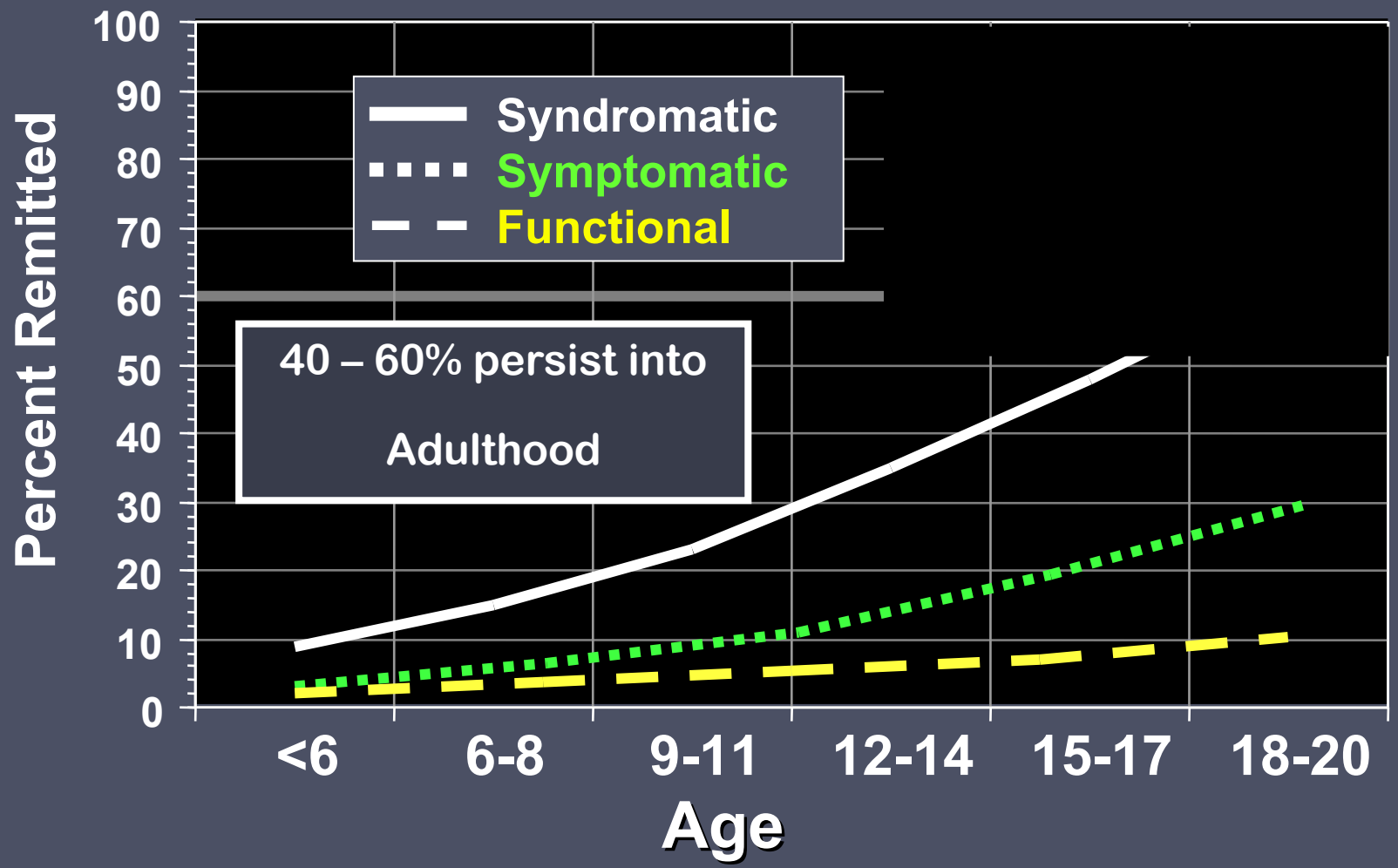
ADHD Aged 5-17 Years in the U.S. (2020 - 2022)



[1]Children of Hispanic origin may be of any race.
[2]Significantly different from non-Hispanic White children ($p < 0.05$).
[3]Significantly different from Hispanic children ($p < 0.05$).
[4]Significantly different from children ages 12–17 years ($p < 0.05$).
NOTES: Attention-deficit/hyperactivity disorder is based on a response to the question, "Has a doctor or other health professional ever told you that [sample child] had Attention-Deficit/Hyperactivity Disorder or ADHD or Attention-Deficit Disorder or ADD?" Estimates are based on household interviews of a sample of the civilian noninstitutionalized population.
SOURCE: National Center for Health Statistics, National Health Interview Survey, 2020–2022.

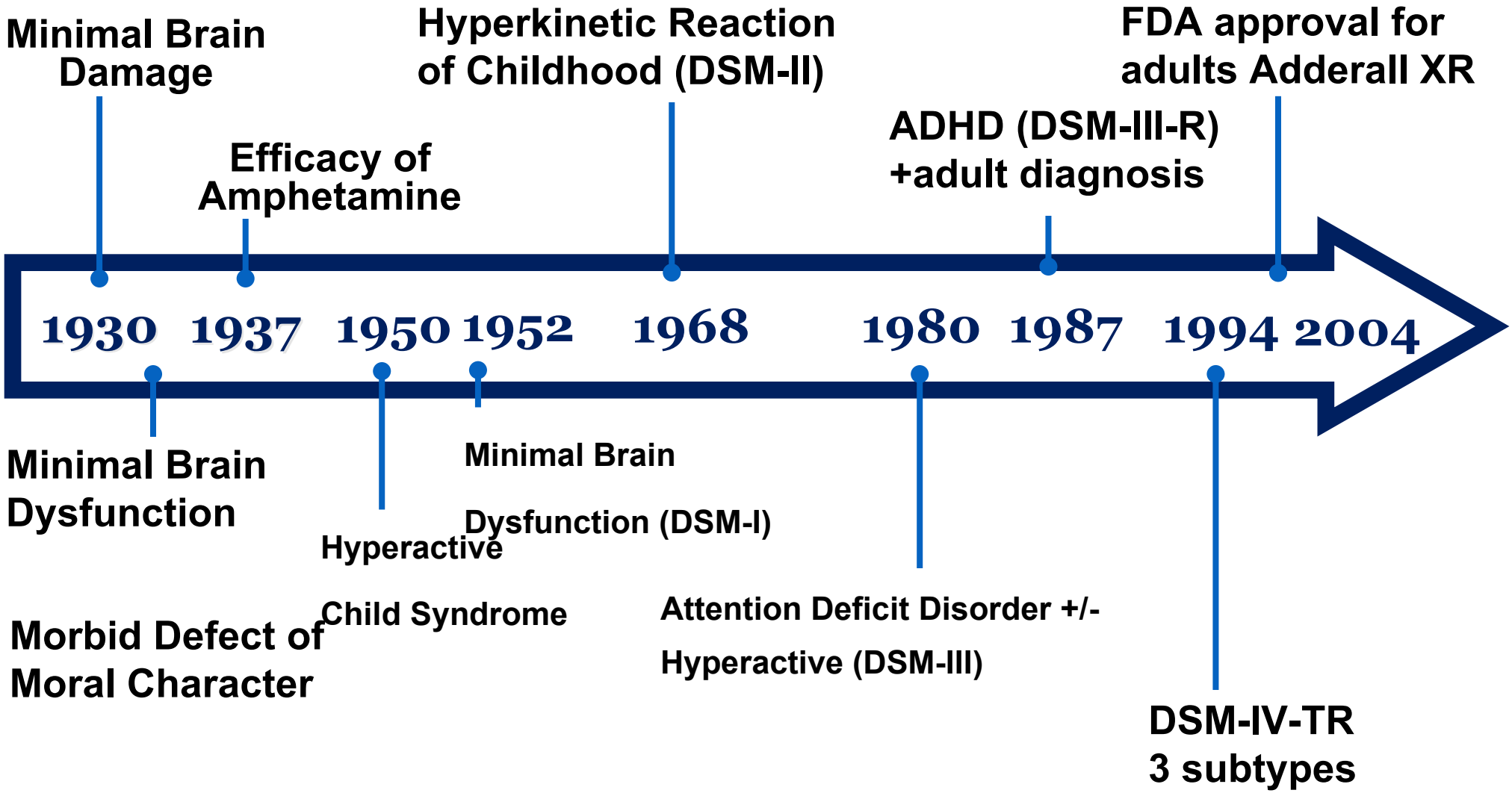
Age Specific Prevalence of ADHD

Remission DSM-5 Criteria in Adults with ADHD



Biederman J et al. Am J Psych. 2000 (May);157(5):816-818; Klein RG et al. Arch Gen Psych. 2012;69:1295-303.

ADHD Historical Timeline



Background

ADHD: Etiology

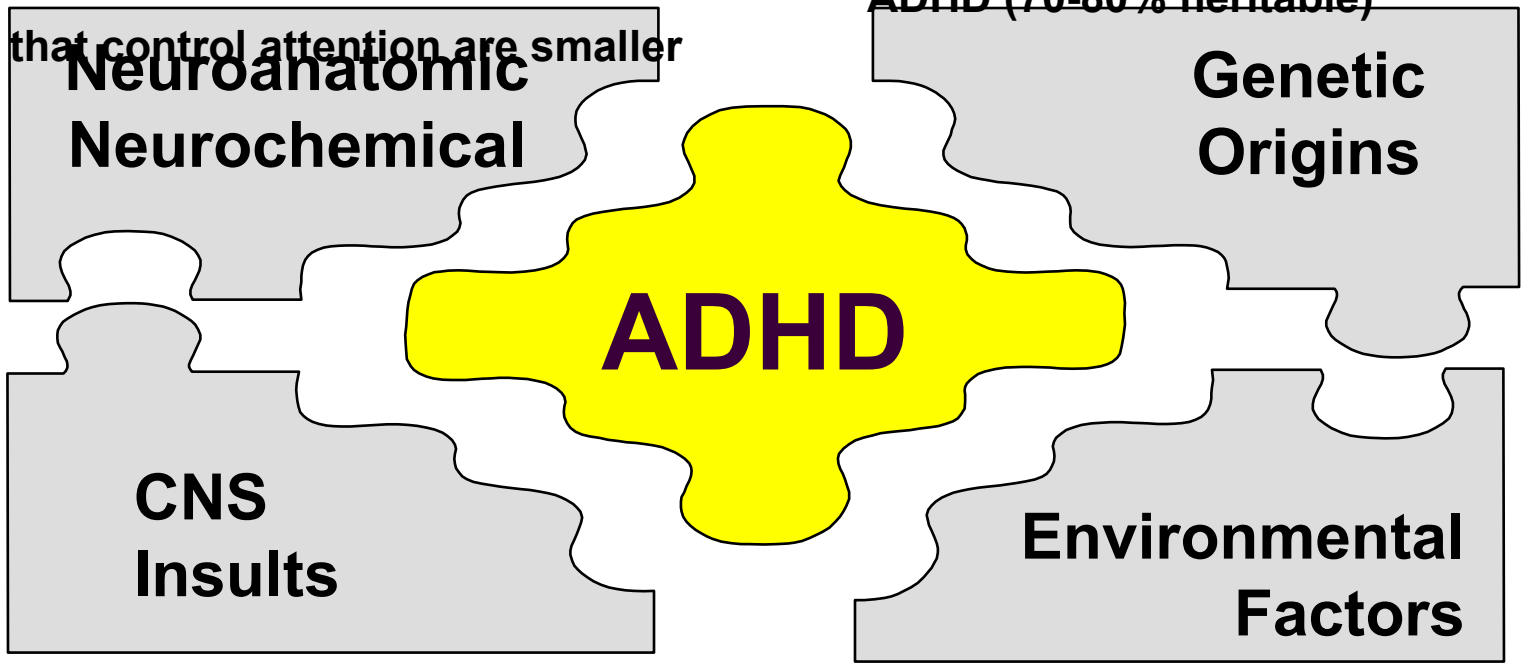
Smaller cerebellar, temporal gray,

and total cerebral volume

Circuits that control attention are smaller

Up to 8-fold increased risk with parental

ADHD (70-80% heritable)



Including in utero brain injuries, infections

Low birth weight (2-3x risk)

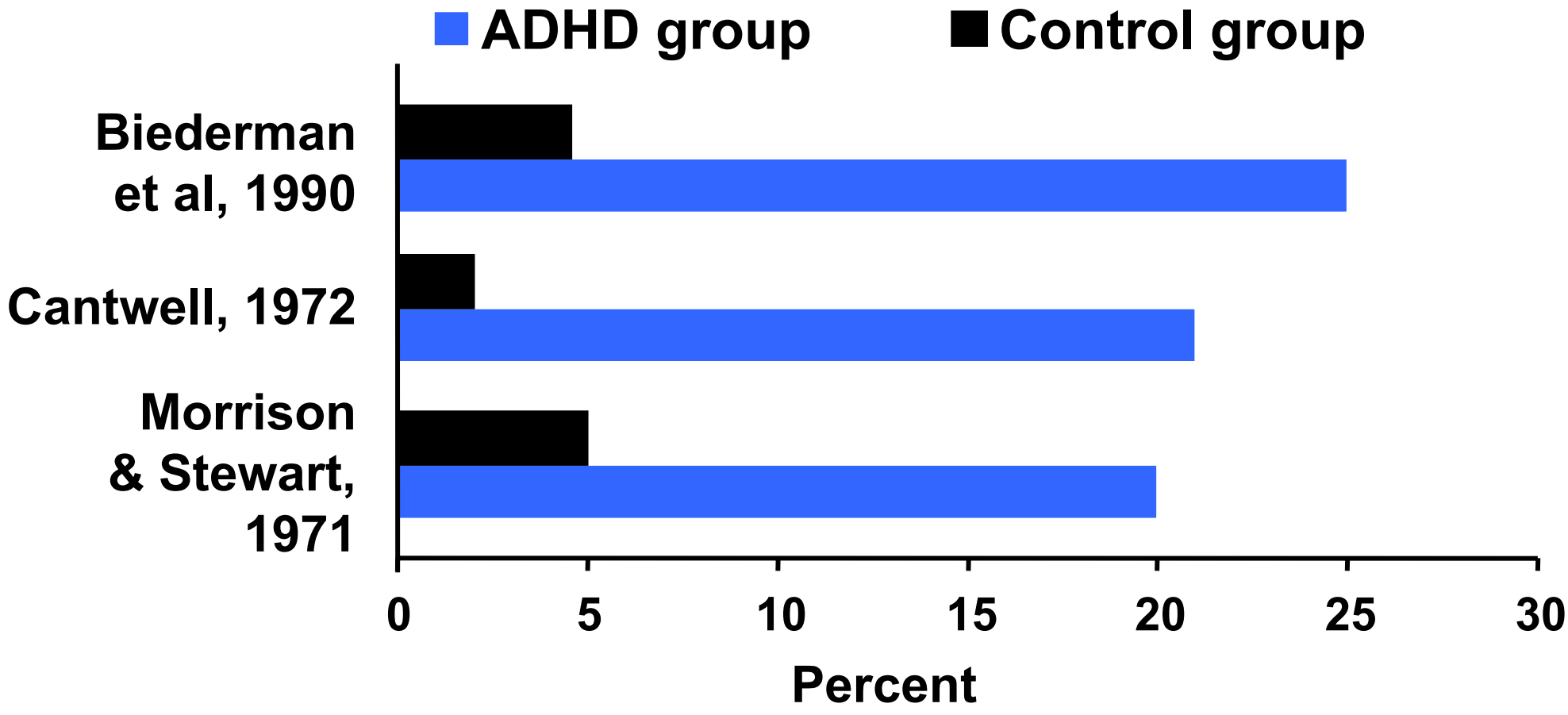
Exposure to cigarettes or ETOH in

utero (2-3x risk)

Also toxins such as lead

ADHD: Family Studies

ADHD in First-Degree Family Members of Children with ADHD



Biederman J, Faraone SV, Keenan K, et al. J Am Acad Child Adolesc Psychiatry. 1990(July);29(4):526-533.
Cantwell DP. Arch Gen Psychiatry. 1972(Sept);27(3):414-417; Morrison JR, Stewart MA. Biol Psychiatry. 1971;3(3):189-195

Summary: Genetics of ADHD

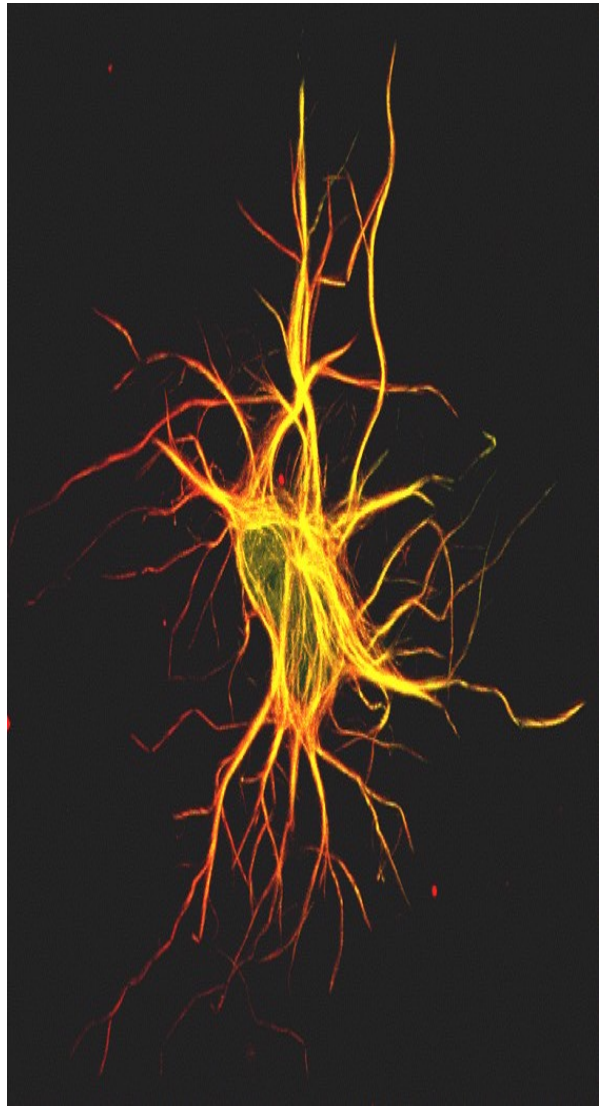
- Genes implicated by several studies
  - DRD_4, DAT, DRD_5, 5-HT_{1B}, 5-HTT, SNAP-25
- Genes have small effect
- No single gene causes ADHD
- These genes likely combine with each other and environmental risk factors to cause ADHD

Pathophysiology

Catecholaminergic Neurotransmission Relative to ADHD

Dopamine

- Striatal-prefrontal
- Enhances signal
- Improves attention
  - Focus
  - Vigilance
  - Acquisition
  - On-task behavior
  - On-task cognitive
  - Preception (?)



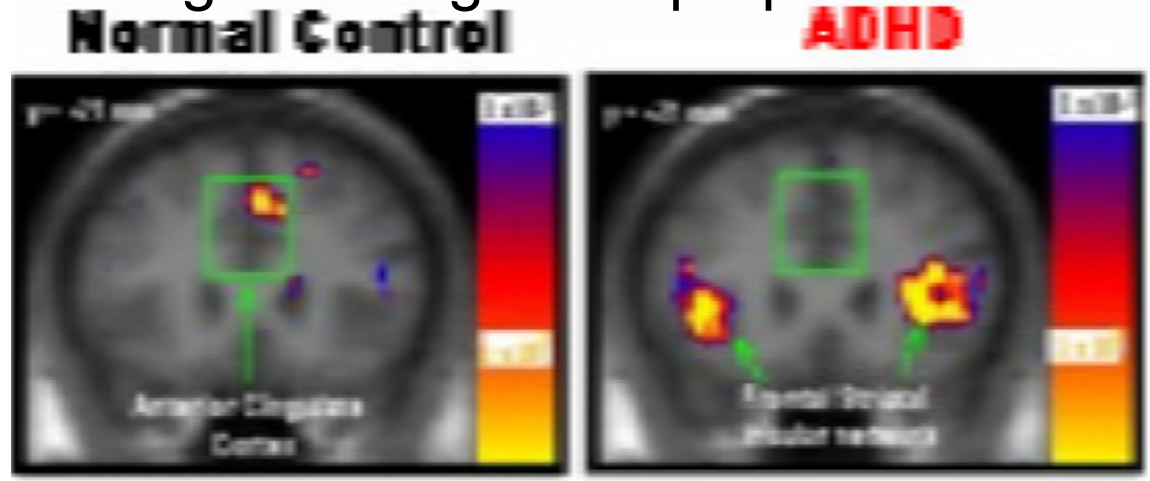
Norephinephrine

- Prefrontal
- Dampens noise
  - Distractibility
  - Shifting
- Executive operations
- Increases inhibition
  - Behavior
  - Cognitive
  - Motor

Neuro-Imaging Studies

Functional MRI

- Anterior cingulate gyrus showed activation in healthy subjects with memory tests but not in ADHD patients
- Higher connectivity b/w subcortical and cortical areas
- Not specific enough for diagnostic purposes



- Other Brain Imaging reveal smaller volumes in the cerebellum, frontal cortex & striatum

Bush G, et al. Biol Psychiatry. 1999 Jun 15; 4(12): 1542-52.

Hypothesized Neurochemical Pathophysiology of ADHD

- Current theory suggests problems with
  - Mesocorticolimbic dopamine pathway
  - Locus coeruleus-noradrenergic system
  - Perhaps other areas as well
    - Sertonergic, glutamatergic, cholinergic
- Psychostimulants increase neurotransmitter activity in these systems

ADHD Etiology and Impact

- Use of acetaminophen in pregnancy
  - 2019 study from Johns Hopkins appearing in *JAMA Psychiatry*
  - Collected cord blood from 996 births and measure acetaminophen and metabolites
  - Amounts classified into lowest, middle, and highest thirds
    - Compared to lowest third, middle third exposure associated with 2.26 times risk of ADHD
    - Highest third associated with 2.86 times the risk
  - ASD risk also higher
    - Middle third: 2.14
    - Highest third 3.62
  - Other studies also support these conclusions
  - Recommendation is to limit use
  - Risk of fever or pain that disrupts daily life is higher than risk of acetaminophen
  - Use less than 8 days did not increase risk

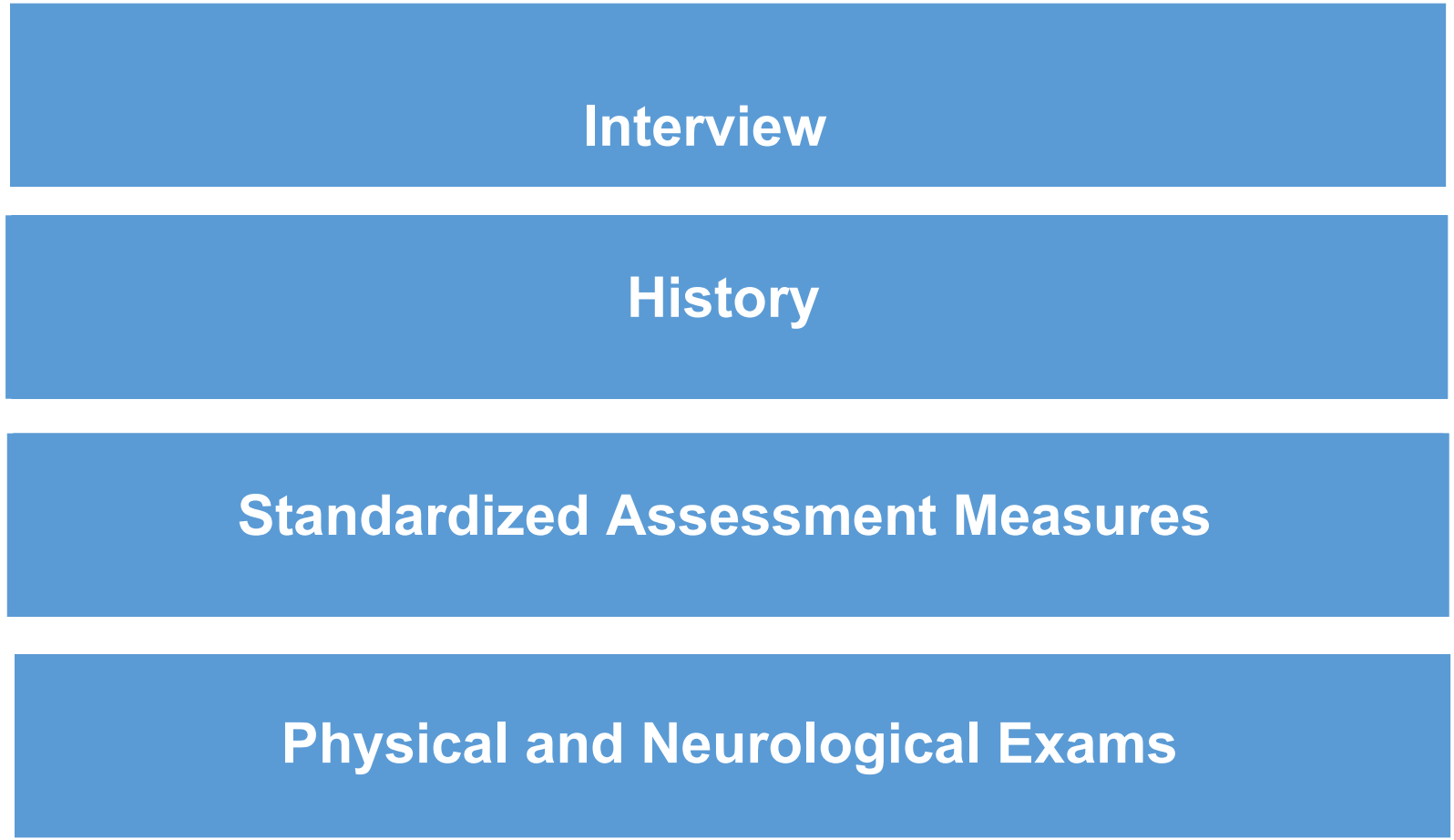
ADHD Etiology and Impact

Summary

- ADHD is a neurobehavioral disorder with
  - A complex etiology
  - A neurobiologic basis
  - A strong genetic component
- ADHD
  - Affects millions of people of both genders
  - Persists through adolescence and adulthood in a high percentage of cases
  - Can have negative impact on multiple areas of functioning

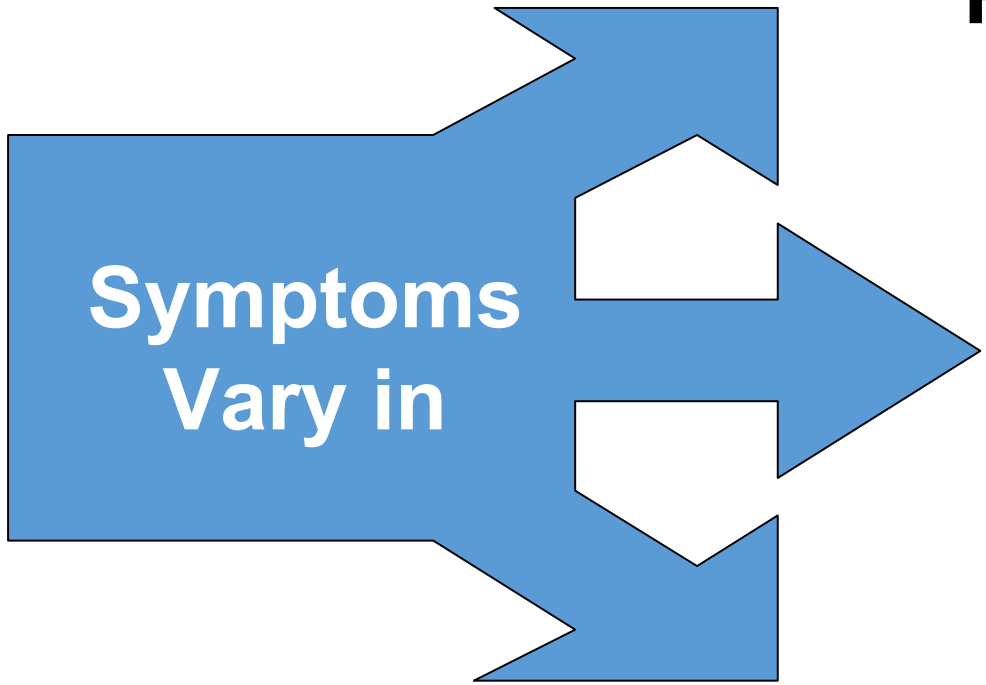
Diagnosis

Diagnostic Assessment Techniques



Conners, Jett. ADHD in Adults and Children. Compact Clinicals. 1999

ADHD: Variation in Symptoms



Pervasiveness

Frequency of Occurrence

Degree of Impairment

Formal Diagnosis – DSM-5

5 (17+), 6 (peds) or more of the following manifested **often:**

Inattention*

- Inattention to detail
- Difficulty to sustain attention
- Seems not to listen
- Fails to finish tasks
- Difficulty organizing
- Avoids tasks that require sustained attention
- Loses things
- Easily distracted
- Forgetful

*Must be met for at least 6 months in at least 2 settings (home, school, work, friends, etc)

*Several symptoms were present by age 12 years

Formal Diagnosis – DSM-5

5 (17+), 6 (peds) or more of the following manifested **often:**

Impulsivity/Hyperactivity*

- Impulsivity
  - Blurts out answer before finished
  - Difficulty awaiting turn
  - Interrupts or intrudes on others
- Hyperactivity
  - Fidgets
  - Unable to stay seated
  - Runs about or climbs in inappropriate situations
  - On the go
  - Unable to relax
  - Talks excessively

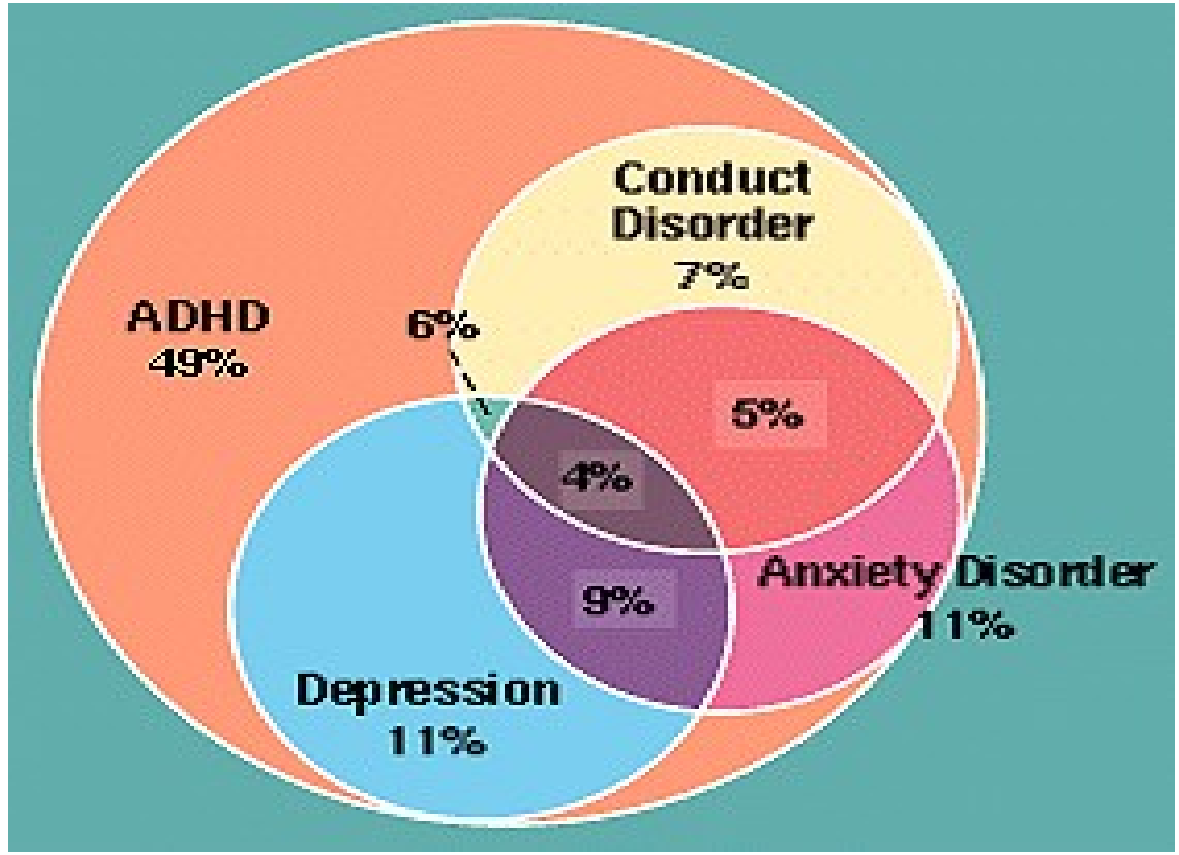
*Must be met for at least 6 months in at least 2 settings (home, school, work, friends, etc)
*Several symptoms were present by age 12 years

Diagnosis of ADHD in Adolescents

- Distractibility and lack of focus
- Disorganization and forgetfulness
- Self-focused behavior
- Hyperactivity and fidgeting
- Heightened emotionality and rejection
- Sensitive dysphoria
- Impulsivity and poor decision making
- Poor concentration and difficulty finishing tasks

Comorbidities and Differential

Prevalence of Comorbidity & ADHD in Children



Biederman J, Faraone S, Milberger S, et al. J Am Acad Child Adolesc Psychiatry. 1996(March);35(3):343-351; Biederman J, Faraone SV, Mick E, et al. J Am Acad Child Adolesc Psychiatry. 1999(Aug);38(8):966-975; Pliszka SR. J Clin Psychiatry. 1998;59(suppl 7):50-58; Spencer T, Biederman J, Wilens T. Pediatr Clin North Am. 1999(Oct);46(5):915-927, vii.

ADHD: Adulthood Common Comorbid Mental Health Diagnoses

	Referred Adults With ADHD (N=84)		Nonreferred Adult Relatives With ADHD (N=36)		Referred Children With ADHD (N=140)		Comparison Adults Without ADHD (N=207)	
Disorder	N	%	N	%	N	%	N	%
Oppositional disorder	24	29[a,b]	19	53[a]	92	66	5	2
Conduct disorder	17	20[a]	12	33[a,c]	30	21	8	4
Antisocial personality disorder	10	12[d]	6	18[a,e]	—	—	6	3
Major depressive disorder	26	31[a]	6	17[d]	40	29	11	5
Alcohol abuse	21	25[a,b]	6	17[b]	1	0.7	17	8
Alcohol dependence	23	27[b,d]	13	36[a,b]	2	1	27	13
Drug abuse	17	20[a,b]	7	19[b,d]	0	0	12	6
Drug dependence	15	18[a,b]	6	17[b]	1	0.7	12	6
Multiple anxiety disorders	42	50[a,c]	15	42[a]	39	28	28	14
Overanxious disorder	43	52[a,c,e]	14	40[a,e]	42	30	22	11
Separation anxiety disorder	6	7[c]	4	11	40	29	7	3
Generalized anxiety disorder	36	43[a]	7	20[a,e]	—	—	10	5
Agoraphobia	6	7[a]	1	3	13	9	1	0.5
Social phobia	27	32[a,c]	12	33[d]	18	13	27	13
Enuresis	23	28[a,e]	7	22[d,e]	45	32	15	8[e]
Speech/language disorder	10	12[d]	2	6	30	21	6	3
Stuttering	15	18[a,b]	1	3	5	4	4	2

Biederman J, Faraone SV, Spencer T, et al. Am J Psychiatry. 1993 (Dec);150(12):1792-1798

ADHD: Differential Diagnosis

- Mental Health
  - Mood disorders
  - Anxiety disorders
  - PTSD
  - Substance abuse
  - Sleep disorders
  - Personality disorder
  - ODD
  - ASD
  - Other learning disorders (ie reading, writing, math)
- Medical
  - Hearing and vision impairment
  - Hyperthyroid
  - Seizure disorder
  - Lead toxicity
  - Medication adverse effects
  - Many others

ADHD: Bipolar Disorder

- Often co-morbid
  - Up to 85% of children with BD have ADHD
  - Up to 22% of children with ADHD have BD
- Many overlapping symptoms
  - Talkativeness
  - Distractibility
  - Psychomotor agitation
  - Impulsivity
  - Poor concentration
  - Mood instability
  - Impairments in social and familial relationships and school performance
- Key differences
  - Episodic nature of BD vs chronic nature of ADHD
  - Elevated mood and decreased need for sleep with BD

ADHD: Bipolar Disorder

- Can be difficult to differentiate
  - Some may have both disorders
  - Some may have only one with symptoms of the other
  - Theory exists that they are a singular disorder on a continuum
- Treatment
  - Recommendation to first treat BD with mood stabilizer then add stimulant
  - Mixed evidence for risk of induction of mania/psychosis with stimulant alone
  - Case series of 2 patients with both BD and ADHD successfully treated with stimulant without a mood stabilizer

ADHD: Medical Comorbidities

- Mild cognitive impairment and dementia
- Obesity
- CVD
- DMII
- These metabolic disorders are also associated with MCI and dementia
- Important to treat ADHD with not only medication but also lifestyle factors

Adult ADHD

ADHD in Adults

- 93% of psychiatry residencies do not mention adult ADHD
- 50% of pediatric residencies do not mention ADHD
- There has never been a board question on adult ADHD
- As many as 20% of adults seeking MH care have ADHD
  - As little as 25% are identified; fewer receive treatment
- IQ of those with ADHD may be higher than average
  - Leads to ability to overcome symptoms masking ADHD
- It is a neurodevelopmental disorder so does not have acute onset in adulthood
  - May have gone undetected in childhood
    - Executive control demands increase with age -> symptoms become more obvious
  - One exception may be in the case of TBI

Diagnosis of ADHD in Adults

- Symptoms are more heterogeneous & subtle
  - Reduced symptoms of hyperactivity
  - Impulsivity moves inward
    - Motor disinhibition
      - Leg shaking, pacing, fidgeting
    - Verbal disinhibition
    - Impatience
    - Difficulty lingering and enjoying the moment
    - “Get on with it”
  - Persisting attention deficit
- Adults are more likely to self-refer to treatment due to problems that impact their well-being
  - Not good self-observers
  - 5/9 symptoms in adults
    - 6/9 symptoms required for diagnosis in childhood (DSM-5)
  - Impairment in ≥ 2 settings

JAMA 2004 292:5;619-623

Diagnosis of ADHD in Adults

- Abundance of attention (not deficit)
  - When interested patients have “super” attention on that thing
  - When (book, meeting, conversation, etc) is boring, mind goes to whatever is enchanting without regard for danger or authority
    - Productivity decreases
- Seeking high stimulation, risk, conflict
  - Work: stock trader, trial attorney, neurosurgeon, entrepreneur, **military**
    - Avoidance of details, paperwork, etc
  - Having many projects going simultaneously
  - Low frustration tolerance
  - Difficulty with follow through
  - Substance use, spending, sex, gambling
- Women more likely to have “quiet underachieving”

Diagnosis of ADHD in Adults

- Cognitive impulsivity
  - Impulsive decision making
  - Poor contemplation
- Motivational impulsivity
  - Discounting future rewards
    - Procrastination
    - Inability to generate forced effort
    - Lack of motivation
  - Need for immediate reward (environmental dependence)
    - Dysregulated sleep, nutrition, exercise, health
    - Risk taking; inability to tolerate low stimulation
- Emotional impulsivity
  - Reactivity
  - Mood lability
  - Temper outbursts
  - Poor frustration tolerance
  - Inept social skills or lack of social judgment

Diagnosis of ADHD in Adults

- Executive functioning impaired (“Adulting is hard”)
  - Stopping an action when change is needed; flexibility
  - Organizing things and thoughts
    - Managing multiple schedules for yourself, school, work, family
    - Often over-committing
  - Time blindness: knowing how long it takes to do things
    - Deadlines (bills, work, child activities)
    - 2 times: Now and not now
      - If not now then it is easily forgotten
      - Panic and adrenaline at the last moment can help with focus
  - Sustained attention
    - Less likely to resist distractions
    - Trouble reengaging after distractions
  - Task initiation
  - Goal-directed persistence
  - Awareness of your own thought processes

Clinical Presentation: Across the Lifespan

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	Criminal involvement
Impulsivity and carelessness	Becomes	Unwanted pregnancy, STDs, etc.
Repetitive failure	Becomes	Hopelessness, frustration, giving up

Good Questions to Ask for History

- Were you a very active child?
- Did parents and/or teachers complain you were difficult?
- Are you accident prone?
- How did you do academically?
- Did you ever fail a grade?
- Were you ever suspended or expelled?
- Was your performance at school variable or unpredictable?
- How many jobs have you had? How many times have you been fired?
- What kinds of things give you problems at work?
- Do you have trouble living with others?
- How much do you smoke? Drink? Use marijuana?
- How many car accidents have you had? How many traffic tickets or speeding tickets?
- What do you enjoy doing with your spare time?
- Do you have trouble with money? Housework? Being on time?
- Do you feel addicted to anything? Gambling? Computers? Games?

Overdiagnosed? Underdiagnosed?

- Many go undiagnosed or are misdiagnosed with mood disorders, anxiety, bipolar disorder
- Many seek the diagnosis
  - Desire stimulants
  - Seeking socially acceptable answer to their problems
- How to guard against overdiagonsis
  - Tell patient you cannot diagnose or start treatment in one visit
    - This will prevent many from returning
    - However, if they are not seeking the diagnosis, but it seems like a reasonable explanation to their problem, I will diagnose and treat on the first visit
    - Gives time to get collateral information directly and indirectly
    - Gives time to get the diagnosis right

Positives of ADHD in Adults

- Control the power that you have
  - Nobel prize winners
  - Self-made millionaires and billionaires
  - Pulitzer prize winners
- Distractibility
  - Curiosity
- Impulsivity
  - Creativity
  - Imagination
  - Spontaneity
- Restlessness
  - Energy

Negatives of ADHD in Adults

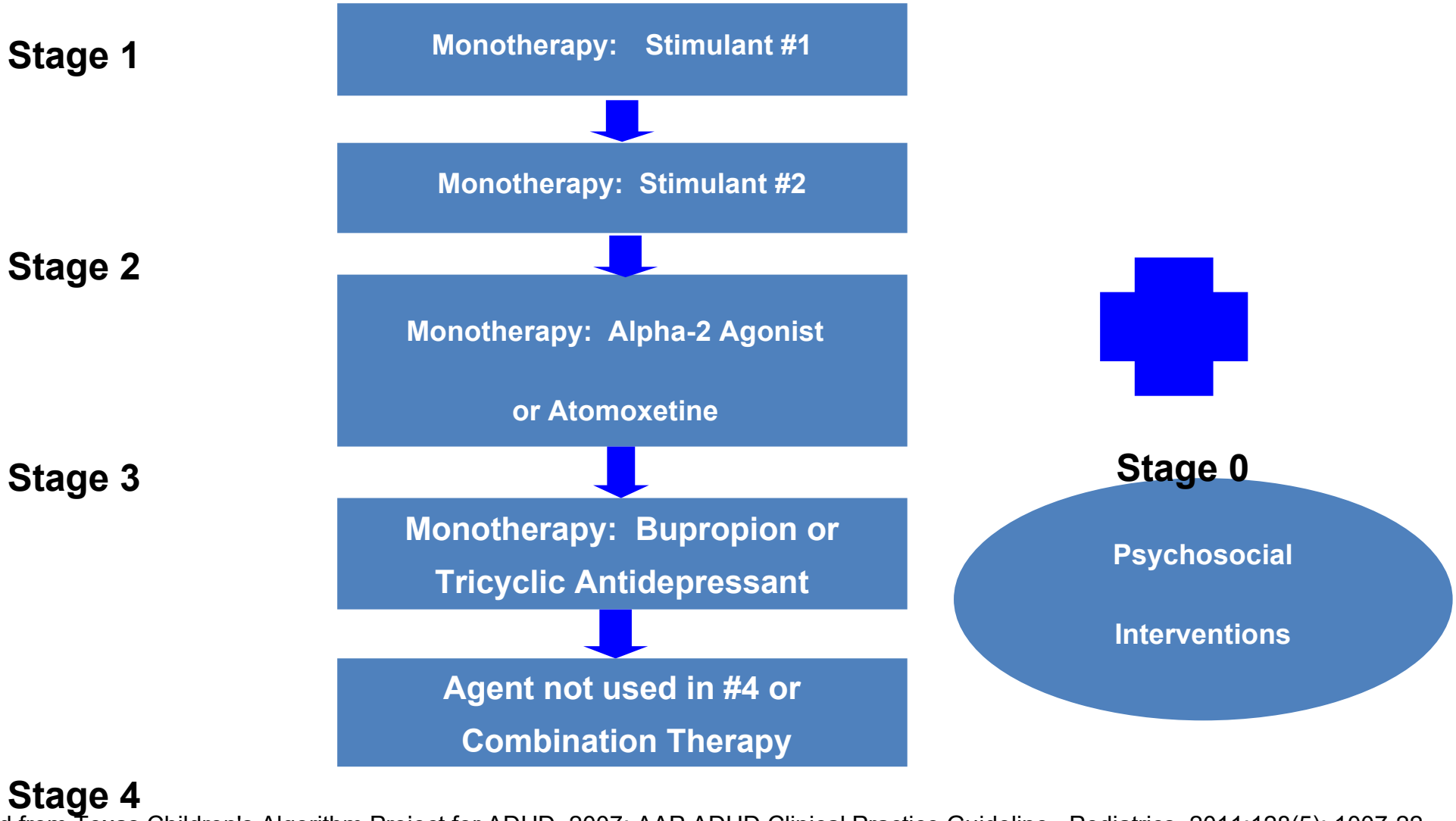
- Prison population
- Addiction
- Multiple failed relationships
- Unemployment
- Accident prone

Treatment Algorithm

ADHD Treatment Goals

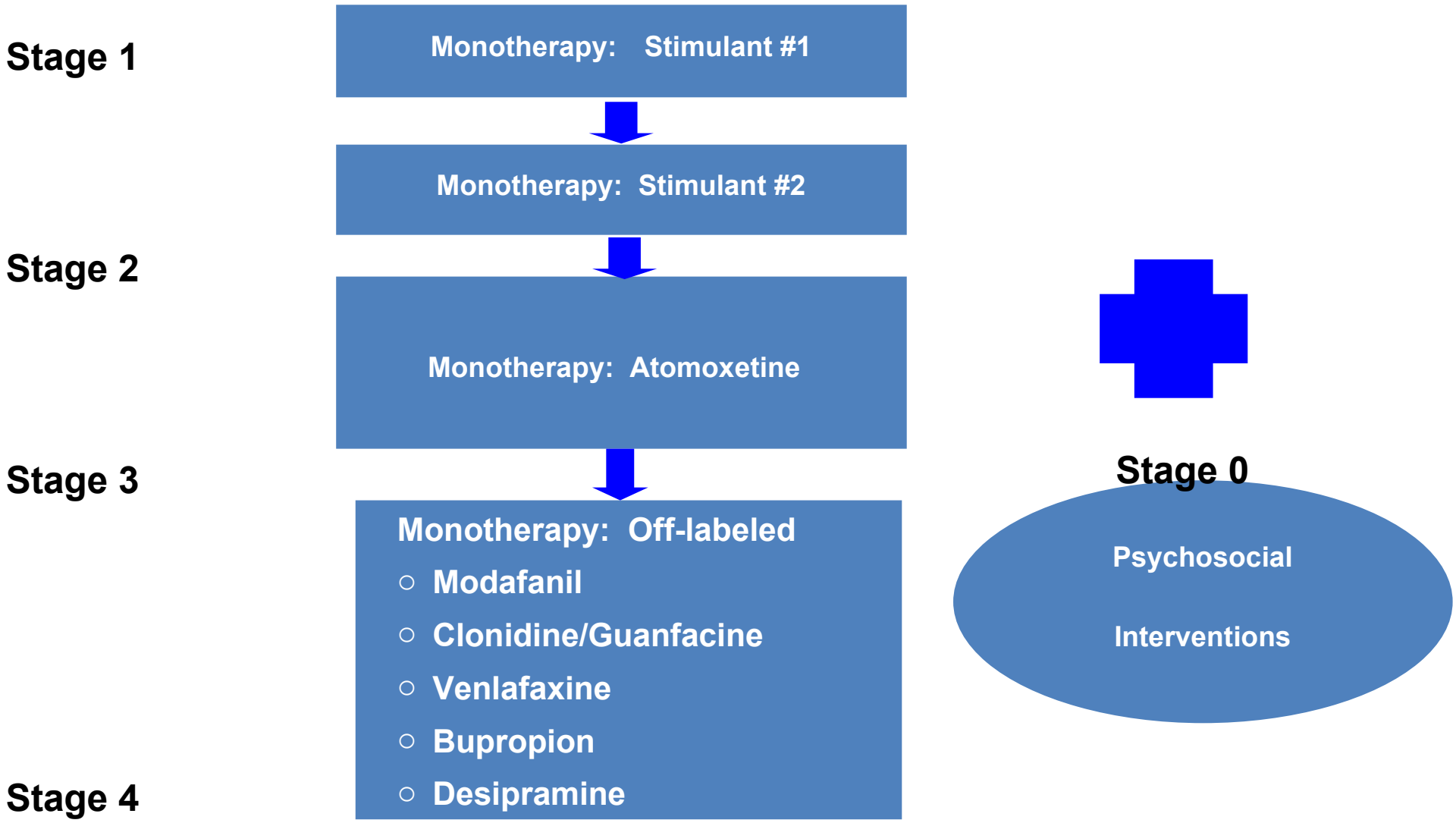
- Reduce pervasiveness of the disease, frequency of symptoms & degree of impairment
- Improve quality of life (QOL)
- Reduce disability short & long-term

ADHD Treatment Algorithm in Children



1999 Adapted from Texas Children's Algorithm Project for ADHD, 2007; AAP ADHD Clinical Practice Guideline. Pediatrics 2011;128(5): 1007-22.

ADHD Treatment Algorithm in Adults



www.cdc.gov/ncbddd/adhd/treatment.html

Non-Pharmacological Treatments

Non-pharmacological Treatments for ADHD

- Psychotherapy
- Educational Interventions
- Parent Training
- EEG Biofeedback
- Diet
- Trigeminal Nerve Stimulation
- Digital Treatment

Non-pharmacological Strategies

- Lifestyle modifications
  - Exercise
  - Nutrition
  - Avoiding substances
  - Caffeine
  - Sleep hygiene
- Social Interventions
  - Get the right job
  - Be with the right person
  - Educational Interventions
  - Parental Training
- Psychotherapy
  - Meditation
  - Coaching
- EEG Biofeedback
- Trigeminal Nerve Stimulation
- Digital Therapies

Diet

- Avoid
  - Artificial colorings
  - Sodium benzoate
  - BPA
- Studies have shown benefit with
  - Omega-3 FA with 2:1 EPA:DHA ratio[1]
  - Zinc (though less so in the US as few are deficient)[2]
  - DASH (Dietary Approaches to Stop Hypertension) diet[3]
    - Fruits, vegetables, fish, whole grains, nuts, beans
    - Avoiding sugar, salt, saturated fats, cholesterol, refined grains
    - Compared to controls those on the DASH diet had significant improvements on multiple parent-, teacher-, and child-rated measures of ADHD after 3 months
    - Also more prosocial behaviors and few conduct problems

1: Bloch MH and Qawasmi A. Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: systematic review and meta-analysis. *J Am Acad Child Adolesc Psychiatry* 2011;50(10):991–1000.

2: Granero R et al. The Role of Iron and Zinc in the Treatment of ADHD among Children and Adolescents: A Systematic Review of Randomized Clinical Trials. *Nutrients* 2021;13(11):4059.

Diet

- 2025 Danish registry study of 60000 mother-child pairs assessed at age 10
  - A western dietary pattern during pregnancy is associated with neurodevelopmental disorder in childhood and adolescence
    - Significant association with ADHD and autism diagnoses
      - Moderate shifts along this dietary spectrum associated with 66% increased risk of ADHD and 122% increased risk of autism
    - Diet high in fat, sugar, and refined products
    - Diet low in fish, vegetables, and fruit
    - Association strongest in early pregnancy

Coaching Strategies

- Set up times in your schedule to take care of specific tasks
- Make short-, intermediate-, and long-term plans
- Use a planner and stick to the plan
  - Create a system that allows you to use the planner
  - Paper book, wall calendar, App
- Have a place for everything and always keep those things there
- Use your words to benefit yourself and those around you
- Automatic bill pays
- Reminders and alarms on apps, clocks, smart watch, sticky notes
- Having things delivered to save time shopping
- Creating a system for managing electronics
  - Place to put your phone at night
  - Time to turn off electronics

external Trigeminal Nerve Stimulation (eTNS)

- Monarch eTNS® System (2019)
  - Delivers low level electrical pulses
  - Patch attached to forehead at bedtime
  - Trigeminal nerve near the eyebrows is a significant pathway to critical brain regions associated with attention, mood, and self-control

Digital Therapies

- EndeavorRx® (2019)
  - Video Game
  - FDA-authorized
  - Ages 8-12
- EndeavorOTC® (2024)
  - Authorized for adults
  - Available in app stores without prescription

Digital Therapies

- Skylar's Run® (2019)
  - Video Game
  - Not FDA cleared

Medication Algorithm

Algorithm

- Choosing a medication
- Dosing
- Duration of Action
- Formulation

Algorithm: Choosing a Med

- Amphetamine or Methylphenidate are first line
  - 88% will respond to one of these (70-75% to either individually)
  - Amphetamines have slightly better response (may be better for adults 1st line)
  - Children may tolerate methylphenidate a little better
- Stimulants have 1.0 effect size (0.4-0.8 in preschool children)
  - Up to 1.7 if fine-tuned appropriately!
- Most commonly will use Concerta® or Adderall® XR first and other second
  - Consider trying both and then picking the best
  - If adequate trial of 1st line (maxed out with no improvement) or intolerable side effects, move on to other class (AMP vs MPH)
- May switch to another drug within classes with different mechanism of action such as Vyvanse®, Dexedrine®, or Focalin®
- If patient's behavior worsens (more activated) consider anxiety or other alternative diagnosis and treat

Algorithm: Dosing

- No parameter predicts optimal stimulant dose
  - Not weight
  - Not age
  - Not gender
  - Not scale scores
  - Each person MUST have the dose titrated to their individual needs and duration of dose!
- Teachers are typically a better judge of child's symptoms and response than parents
- Child's treatment failure is often due to failure to treat ***parent's*** ADHD

Algorithm: Dosing

- When prescribing initially have the patient increase the medication per dosing schedule so that patient can get to adequate dose more quickly before next visit
  - Often patients need one dose increase after a few months on a stable dose
    - If they go on a long drug holiday, they should not restart at the higher dose
- FDA approved dosing ranges only cover 50% of patients
  - 6-8% of patients may need doses lower than lowest dose
    - Can dose liquids lower more easily
    - Many formulations can be split or sprinkled
    - Some formulations can be dissolved in water including some long-acting like Vyvanse®
  - 40% of patients may need doses higher than highest dose
- Patients may need different doses at different stages of life or with different demands
  - With less responsibility may need less (ie summer break)
  - If having a late-night class or work may need extra IR dose
- If patient feels stimulated or “different” (Zombie-like), dose may be too high
- Right dose is the lowest dose that gives optimal performance and no adverse effects
  - Tolerance to adverse effects is much greater than tolerance to beneficial effects
  - Typically, dose will not need to be increased past the age of 16
    - Often advise drug holidays 2-3 days per week to maintain efficacy

Algorithm: Dosing

- Amphetamine excretion and acidity
  - Antacids may decrease excretion leading to increased levels
  - Acidification as with high dose vitamin C may increase excretion, decreasing levels
    - Can use in the evening if amphetamine is interfering with sleep (1000mg vitamin C); takes about 20 minutes
  - All stimulants may be affected to some degree
    - Most likely with short-acting amphetamines
    - Except Vyvanse® and Daytrana®
  - Foods most likely to cause this
    - Fruit juice
    - Coffee
    - Carbonated beverages
    - Energy drinks
    - Sports drinks
    - Vitamin C supplements (watch out for content in multivitamin)

Algorithm: Duration of Action

- Short-acting formulations are often used as the initial treatment in children <6 years who are more sensitive to dose-dependent adverse effects and should be started at low doses
- Short-acting formulations also may be used to determine the optimal daily dose before switching to a comparable long-acting agent
- In children >6 years, a longer-acting preparation may be used initially, starting at the lowest dose and titrating up
- A combination of a long-acting and late-afternoon short-acting medication may be necessary to provide adequate coverage in the evening hours for homework completion, work, driving, etc
- Higher doses typically do not last much longer but do increase adverse effects
  - Can dose XR twice daily

Algorithm: Formulation

- Duration of coverage
  - Homework, driving in the evening
- Ability to swallow pills
- Time of day when target symptoms occur
- Desire to avoid administration at school
- Coexisting tic disorder
  - Avoidance of stimulants or use of a2-agonists may be warranted
- Coexisting emotional or behavioral condition
  - a2-agonist (Intuniv®) may be useful for patients who are over-aroused, easily frustrated, highly active, or aggressive
- Potential adverse effects
  - Weight loss, hypertension
- Hx of substance abuse in patient or household member: avoid stimulants or use stimulants with less potential for abuse
  - Vyvanse®, Concerta®, Daytrana®
- Preference of the patient and his/her parent/guardian
- Expense/formulary

Stimulants

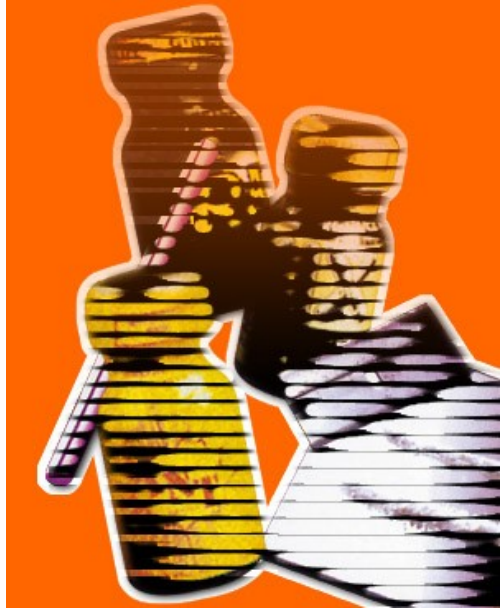
Pharmacological Management
Stimulants

- There are 7 types of FDA approved stimulants
  - Methylphenidates
    - Methylphenidate
    - Dexmethylphenidate
    - Serdexmethylphenidate
  - Amphetamines
    - Dextroamphetamine
    - Mixed amphetamine salts
    - Lisdexamfetamine
    - Amphetamine (base)
  - *Magnesium pemoline (Cylert®)*
    - *Withdrawn October 2005: life-threatening hepatotoxicity*

Stimulant Expectations

- Symptoms that respond well
  - Procrastination
  - Distractibility
  - Mind wandering
  - Daydreaming
  - Sticking with boring tasks
  - Impatience
  - Impulsivity/restlessness
- Symptoms that do not respond well
  - Disorganization
  - Argumentativeness
  - Oppositional behavior

Stimulants



- **Short–acting (4-6 hrs)**
  - Dexmethylphenidate (Focalin)
  - Methylphenidate (Ritalin, Methylin)
  - Dextroamphetamine (DextroStat+, Dexedrine, ProCentra+, Zenzedi)
  - Dextroamph + Amph (Evekeo)+
  - Amphetamine Mixed Salts (Adderall)+
- **Intermediate–acting (about 8 hrs)**
  - Methylphenidate (Ritalin SR, Metadate ER, Methylin ER)
- **Long–acting (10-12 hrs)**
  - Mixed Amphetamine Salts (Adderall XR)
  - Amphetamine XR-ODT (Adzenys XR-ODT)
  - Dextroamph + Amph (Dyanavel XR, Adzenys XR-ODT)
  - Dexmethylphenidate ER (Focalin XR)
  - Methylphenidate ER (Metadate CD, Ritalin LA, Concerta, Daytrana, Quillivant XR , Quillachew XR, Cotempla XR-ODT, Jornay PM)
  - Dextroamphetamine (Dexedrine Spansules)
  - Lisdexamfetamine (Vyvanse)
- **Longest-acting (16 hrs)**
  - Methylphenidate (Aptensio XR, Adhansia XR)
  - Ser-d-MPH + d-MPH IR (Azstarys)
  - Dextroamph + Amph (Mydayis)++

+ FDA Approved in Children 3 years and older ++ FDA Approved in Children 13 years and older

History of Stimulants

- Amphetamine-type stimulants originated from *Ephedra vulgaris*
  - Known as Mahuang in China
- Ephedrine was isolated from the plant in Japan in 1885
- The synthetic analogue amphetamine was synthesized in Germany in 1887
- Its stimulant properties were discovered in 1927
- Amphetamine sold as Benzedrine® began use in 1933 as a nasal decongestant
  - FDA banned as OTC in 1965 and limited to prescription only
- Later it would be used for narcolepsy, obesity, hypotension, libido, pain, and depression
- The beneficial effect on children for attention was discovered in 1937
  - Children at the Bradley Home in CT was run by Dr. Charles Bradley
  - Dr. Bradley performed LPs on all children with thought that it could elucidate their developmental disorders
  - Children developed headaches lasting 1-2 weeks from the procedure
  - Dr. Bradley hypothesized that Benzedrine might relieve the headaches
  - Students' academic motivation improved significantly while taking the medication

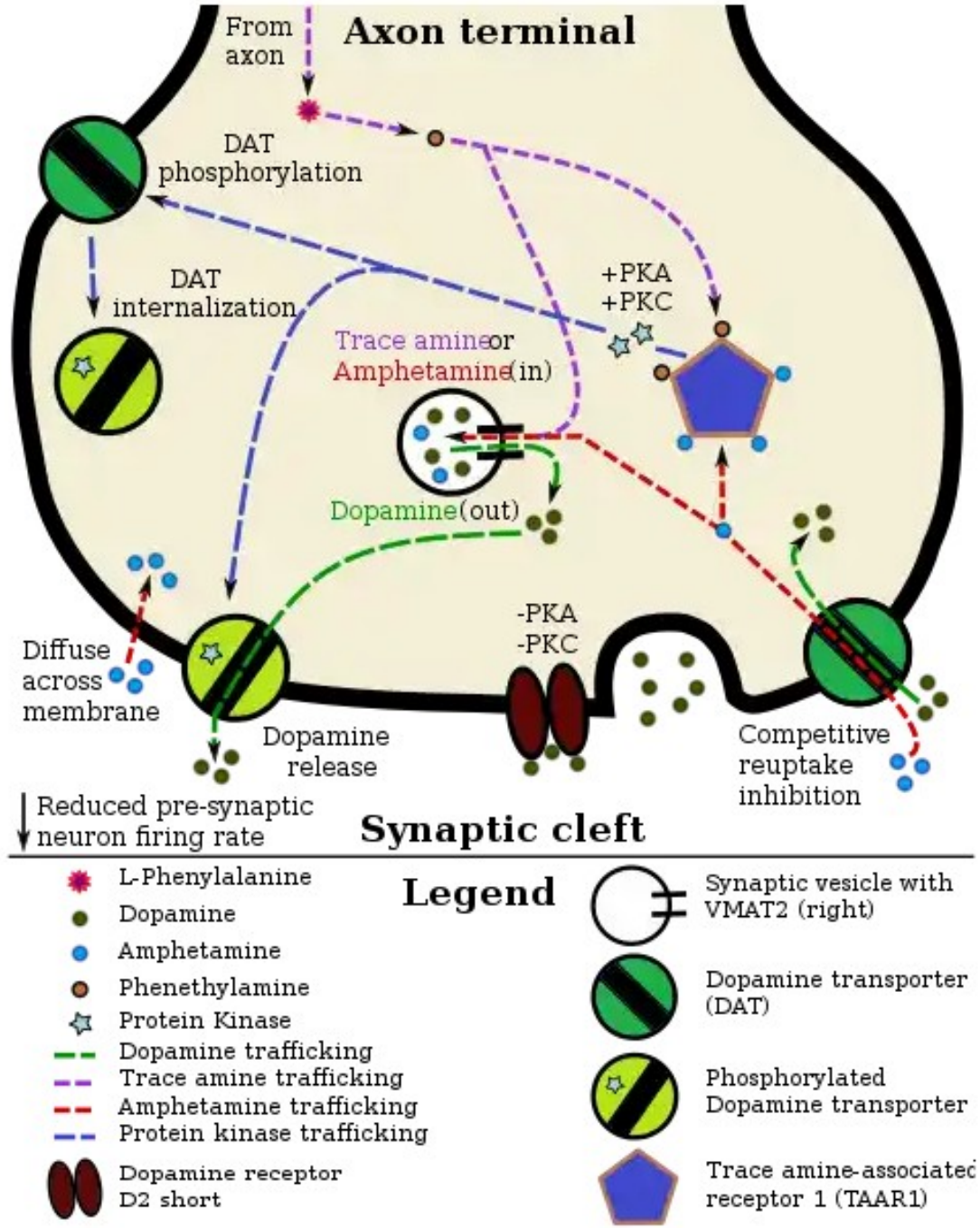
History of Stimulants

- Leandro Panizzon at Swiss company CIBA (Novartis) altered amphetamine molecule to produce methylphenidate in 1944
  - Dr. Panizzon experimented on his wife Margarite hoping the medication would help with her tennis game
  - It worked and he named the medication after her, Ritalin® (“Rita”)
- Amphetamine and methamphetamine were extensively used on both sides during WWII
- A mixture of methamphetamine and amphetamine was sold as Obetrol® for weight loss in the 1950s and 1960s
  - FDA withdrew approval in 1973
  - Reformulation without methamphetamine was later rebranded as Adderall®
    - Approved for ADHD in 1996

Amphetamines

Amphetamine Mechanism of Action

- Trace amine-associated receptor 1 (TAAR1) full agonist
  - Through protein kinase A/C (PKA/C) phosphorylation can result in DAT/NET internalization, decreasing DA and NE reuptake
  - Through PKC-mediated phosphorylation can induce DAT/NET reverse transporter function causing DA and NE efflux
- Vesicular monoamine transporters (VMAT1/2) inhibition
  - Blocks packaging of DA and NE in storage vesicles
- VMAT2 uptake
  - Amphetamine passes through VMAT2, induces collapse of vesicular pH gradient, resulting in DA and NE release
- Effective NDRI
  - Amphetamine can enter the cell through DAT/NET which competes with DA and NE effectively blocking their reuptake; NET also transports dopamine
- Similar but much less pronounced effects for serotonin
- MAOI activity at high levels
  - Decreased metabolism for monoamines


From axon
Axon terminal
DAT phosphorylation
DAT internalization
+PKA
+PKC
Trace amine or Amphetamine (in)
Dopamine (out)
-PKA
-PKC
Diffuse across membrane
Dopamine release
Competitive reuptake inhibition
Reduced pre-synaptic neuron firing rate
Synaptic cleft
Legend
L-Phenylalanine
Dopamine
Amphetamine
Phenethylamine
Protein Kinase
Dopamine trafficking
Trace amine trafficking
Amphetamine trafficking
Protein kinase trafficking
Dopamine receptor D2 short
Synaptic vesicle with VMAT2 (right)
Dopamine transporter (DAT)
Phosphorylated Dopamine transporter
Trace amine-associated receptor 1 (TAAR1)

Methamphetamine

- Discovered in 1893
- Marketed as Pervitin® in Germany to promote wakefulness
- Currently Schedule II and available for ADHD as Desoxyn® but rarely prescribed
  - Effect size ~1.8
- Levo- enantiomer is much less potent and is available as an OTC for nasal decongestion
- **Methamphetamine is more potent and crosses the blood brain barrier more easily compared to amphetamine**

Methamphetamine (Desoxyn®) (1943)

- Dosing: 5mg qAM – 10mg BID
  - When abused dose starts at ~2g per dose
- Dose equivalent of 5mg is ~20mg of methylphenidate
- Formulation: Tablet
- Onset of Action: 20-60 minutes
- Time to Peak: 3 h
- Duration: 4-6 h
- Can split? Yes
- Age: 6+
- Immediate release

Dextroamphetamine

- FDA approved
  - Adults
    - ADHD (patch only)
    - Narcolepsy
  - Children
    - ADHD
    - Narcolepsy
    - Obesity secondary to hypothalamic-pituitary dysfunction
- Black Box Warning
  - Abuse potential
  - CV events

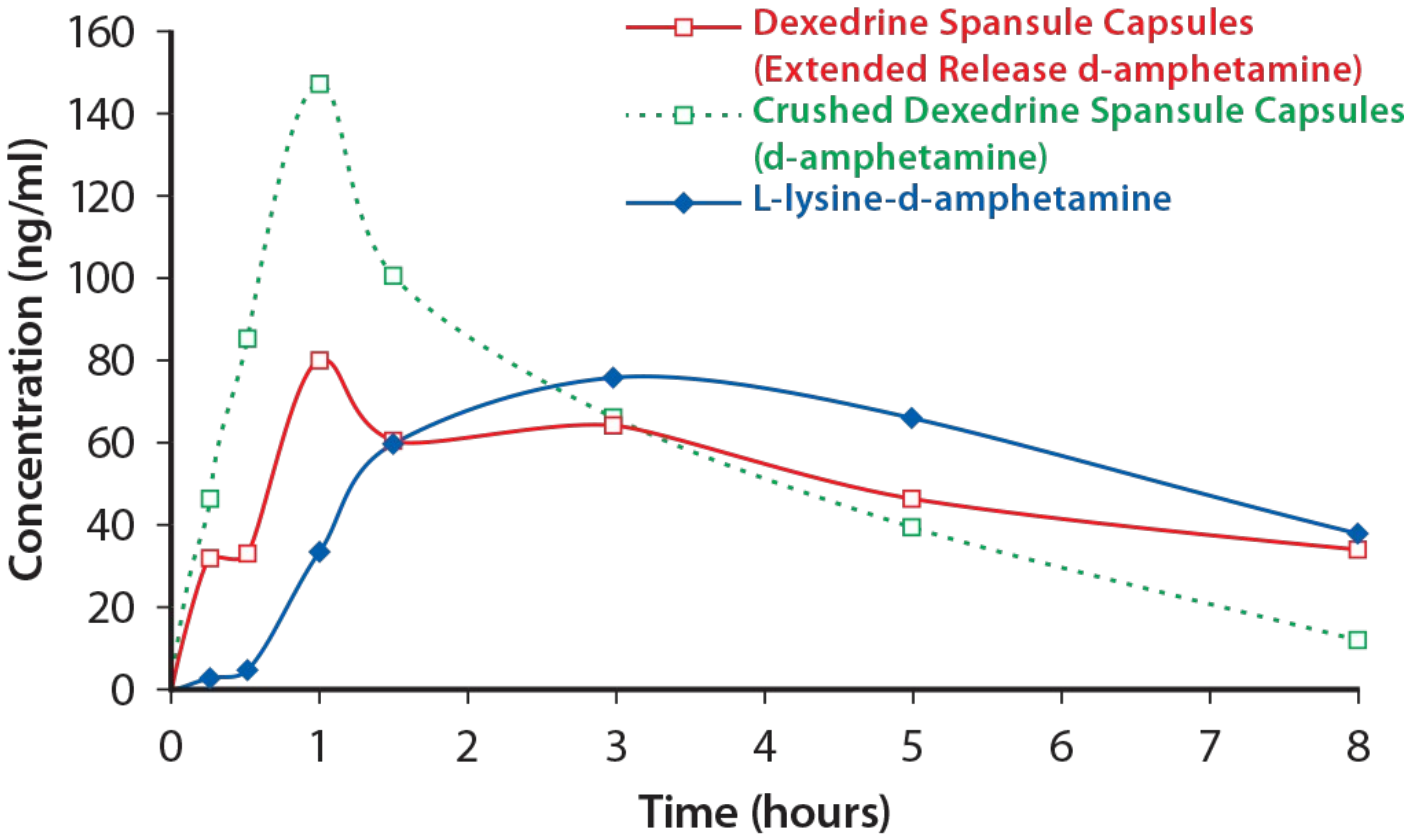
Dextroamphetamine (DextroStat® / Dexedrine®) (1975)

- Dosing
  - 3-5 yo: 2.5 qAM - 20 BID
  - 5-16 yo: 5 qAM – 20 BID
- Dose equivalent of 7.5mg is ~20mg of methylphenidate
- Formulation: Tablet
- Onset of Action: 20-60 minutes
- Time to Peak: 3 h
- Duration: 4-6 h
- Can split? Yes
- Age: **3-16**
- Immediate release
- **Has been discontinued**

Dextroamphetamine (Dexedrine Spansule®) (1976)

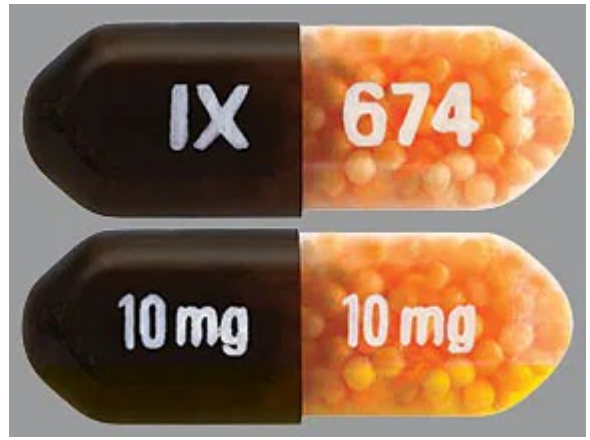
- Dosing: 5 qAM – 20 BID (off-label 30 BID)
- Dose equivalent of 7.5mg is ~20mg of methylphenidate
- Formulation: Capsule
- Onset of Action: 20-60 minutes
- Time to Peak: 8 h
- Duration: **4-8 h**
- Can split? Can be sprinkled, do not crush or chew
- Age: 6+
- Capsule of immediate and delayed release beads

Dextroamphetamine (Dexedrine Spansule®)



Plasma concentrations of d-amphetamine levels following oral administration of Dexedrine Spansule® capsules, crushed Dexedrine Spansule® capsules, or L-lysine-d-amphetamine dimesylate (at dose 3 mg/kg d-amphetamine base) to rats (ELISA analysis).

Figure 20 from the Shire patent application for Vyvance®, recreated by aeon.



Dextroamphetamine (ProCentra®) (2009)

- Dosing
  - 3-5 yo: 2.5 qAM - 20 BID
  - 5-16 yo: 5 qAM – 20 BID
- Dose equivalent of 7.5mg is ~20mg of methylphenidate
- Formulation: **Liquid** (5mg/5mL)
- Onset of Action: 20-60 minutes
- Time to Peak: 3 h
- Duration: 4-6 h
- Can split? Liquid
- Age: **3-16**

Dextroamphetamine (Zenzedi®) (2013)

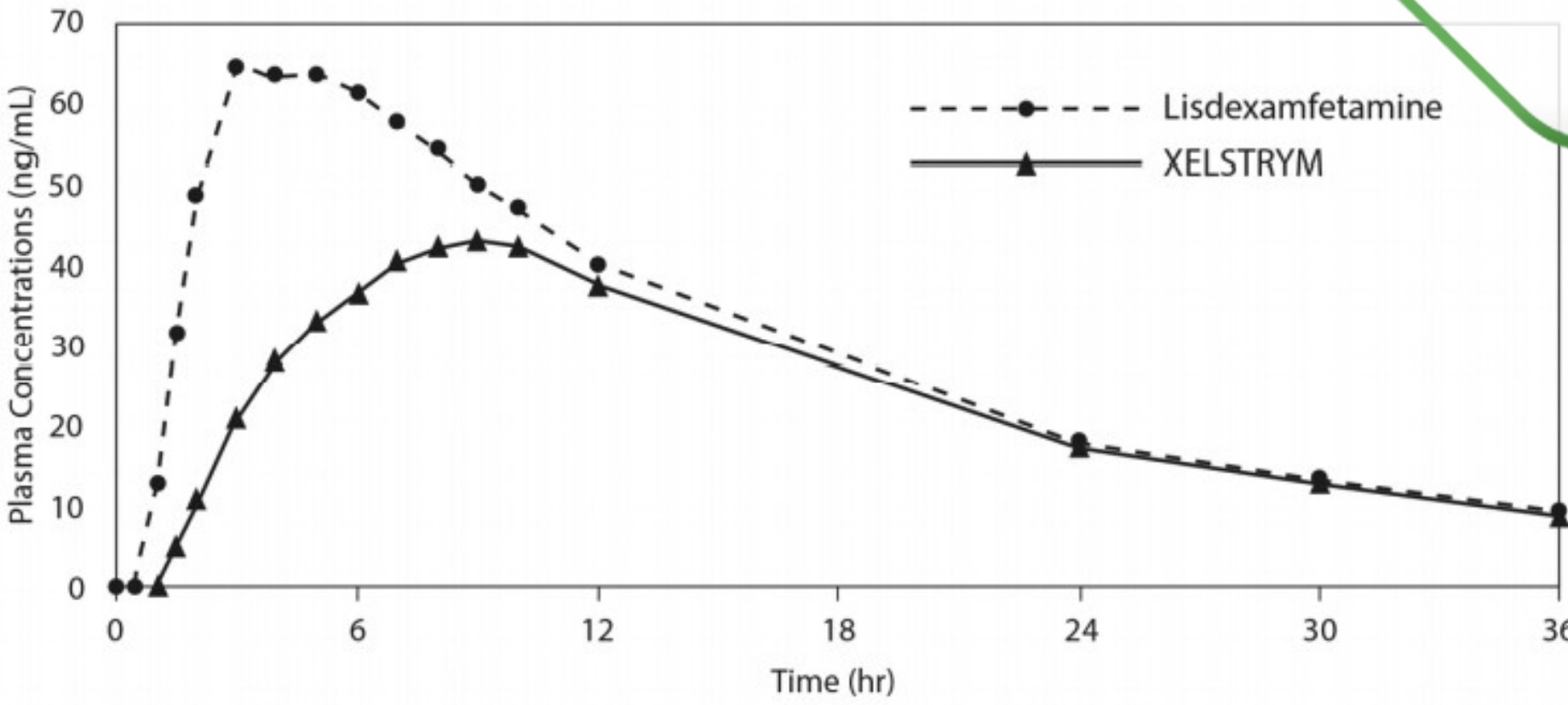
- Dosing
  - 3-5 yo: 2.5 qAM - 20 BID
  - 5-16 yo: 5 qAM – 20 BID
- Dose equivalent of 7.5mg is ~20mg of methylphenidate
- Formulation: **Tablet**
- Onset of Action: 20-60 minutes
- Time to Peak: 3 h
- Duration: 4-6 h
- Can split? Yes
- Age: **3-16**
- Same as DextroStat / Dexedrine, which has been discontinued

Dextroamphetamine (Xelstrym®) (2022)

- Dosing
  - 6-18 yo: 4.5 qAM – 18 qAM
  - 18+ yo: 9 qAM – 18 qAM
- Dose equivalent is ?
  - 18mg has same duration of action as 70mg lisdexamphetamine but shorter peak
- Apply patch for 9 hrs (2 hrs delay in onset)
  - Upper chest, deltoid, upper back, flank, hip
- Formulation: **Patch XR**
- Onset of Action: **120 minutes**
- Time to Peak: 6-9 h
- Duration: 9 h
- Can split? No
- Age: **6+**

Dextroamphetamine (Xelstrym®)

Xelstrym™
(dextroamphetamine) Ⓒ
transdermal system
4.5mg/9 hours 9mg/9 hours 13.5mg/9 hours 18mg/9 hours



Mixed Amphetamine Salts

- FDA approved
  - Adults and children
    - ADHD
    - Narcolepsy
- Black Box Warning
  - Abuse potential
  - CV events (Adderall®)

Mixed Amphetamine Salts (Adderall®) (1996)

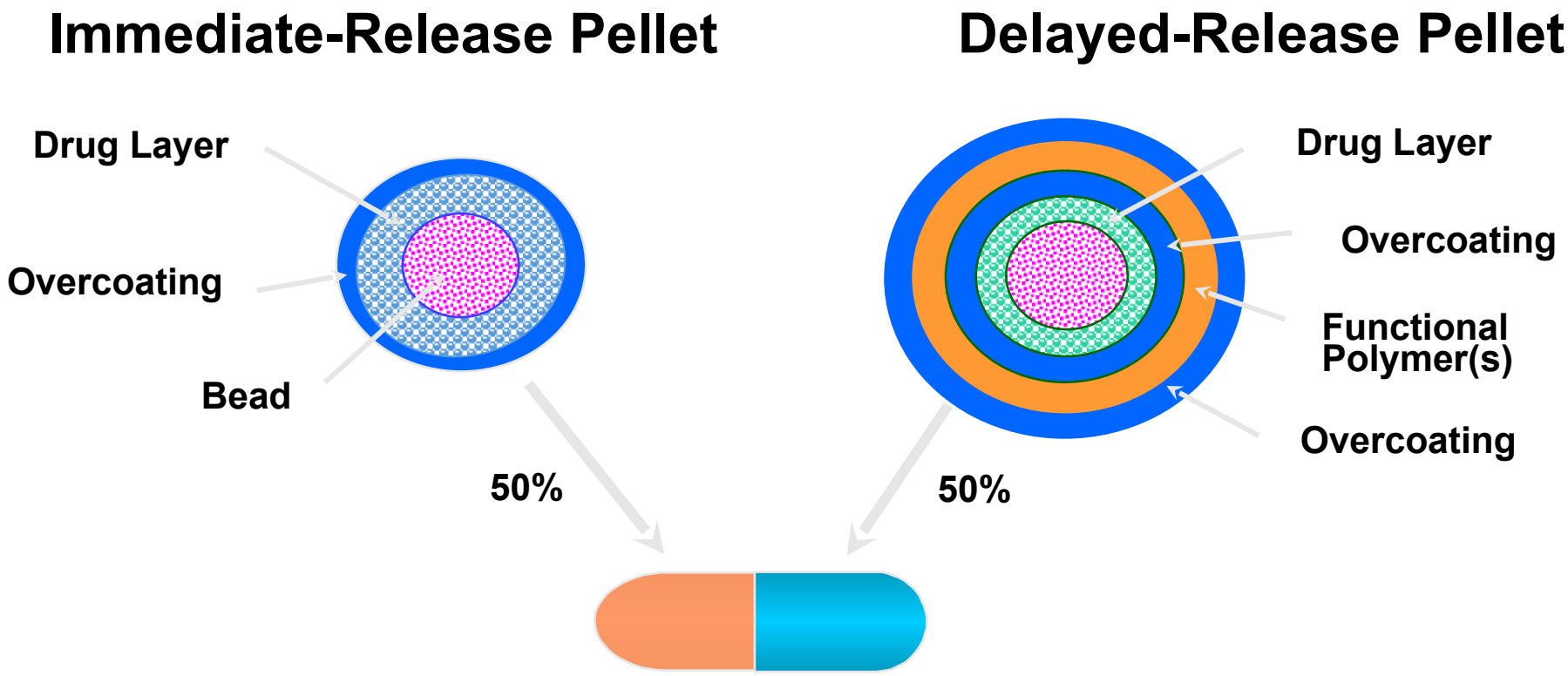
- Dosing
  - 3-5 yo: 2.5 qAM - 20 BID
  - 6+: 5 qAM - 30 BID
- Dose equivalent of 10mg is ~20mg of methylphenidate
- Formulation: Capsule
- Onset of Action: 20-60 minutes
- Time to Peak: 3 h
- Duration: 4-8 h
- Can split? Yes, can be crushed
- Age: **3+**
- **3:1 racemic mixture of d:l-amphetamine**
  - Mixed salt of d-AMP sulfate, d-AMP saccharate, d/l-AMP sulfate, d/l-AMP aspartate monohydrate

Mixed Amphetamine Salts (Adderall XR®) (2001)

- Dosing: 10-60 qAM
- Dose equivalent of 10mg is ~20mg of methylphenidate
- Formulation: Capsule
- Onset of Action: 20-60 minutes
- Time to Peak: 7 h
- Duration: **8-12 h**
- Can split? Can be sprinkled, do not crush or chew
- Age: 6+
- Same MAS 3:1 racemic mixture of d:l-amphetamine
  - Capsule of 50% IR beads & 50% delayed release beads

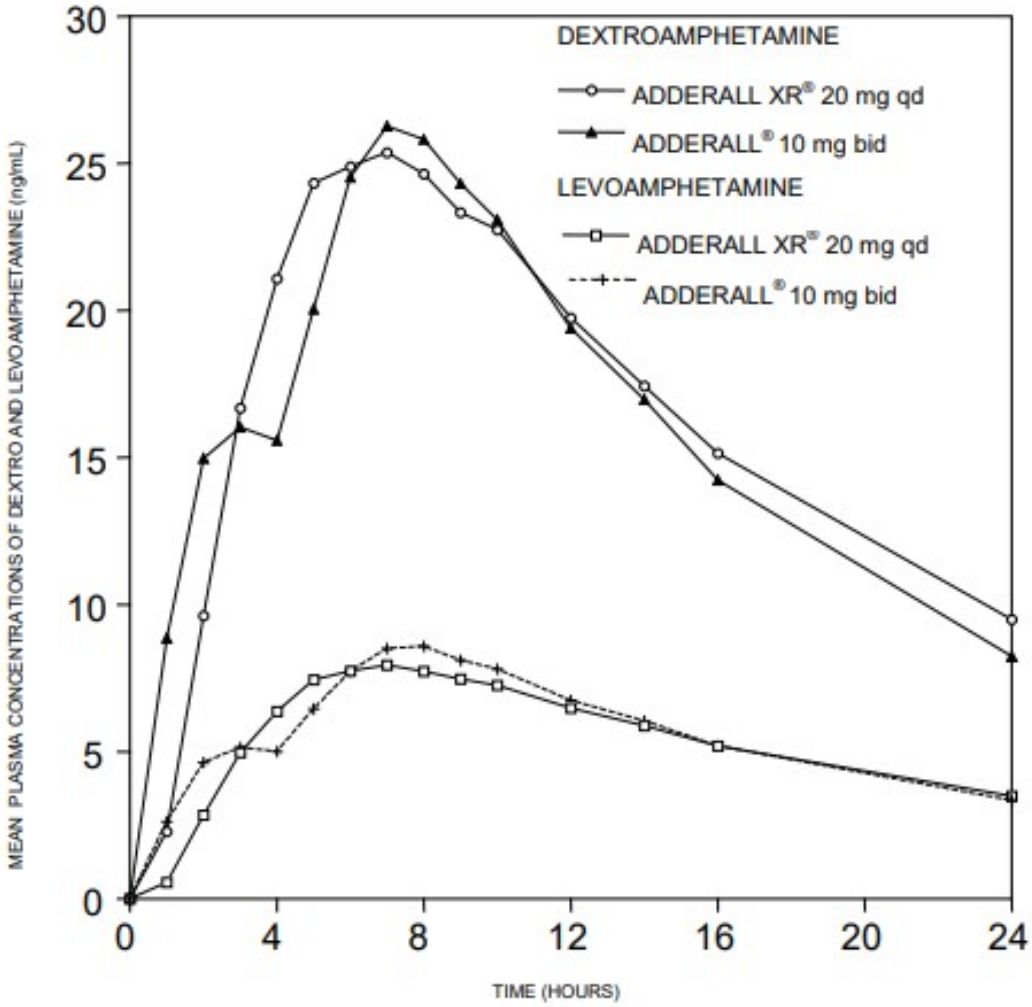
Stimulants

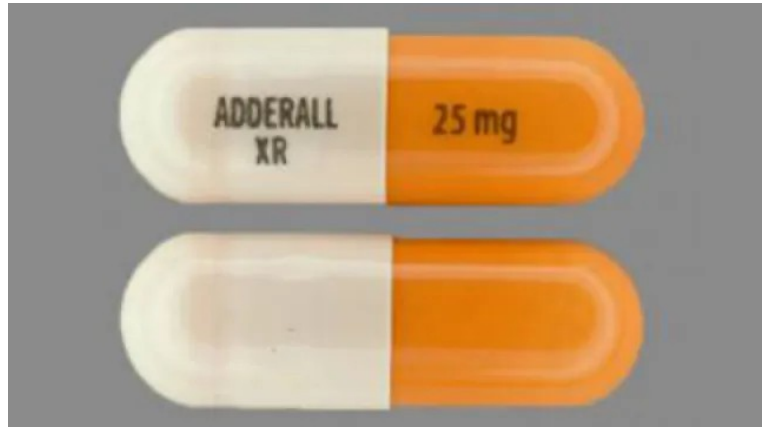
Mixed Amphetamines (Adderall XR®) Pulsed-Delivery System



FDA indicated for Children 6 years & Older

Mixed Amphetamine Salts (Adderall®)

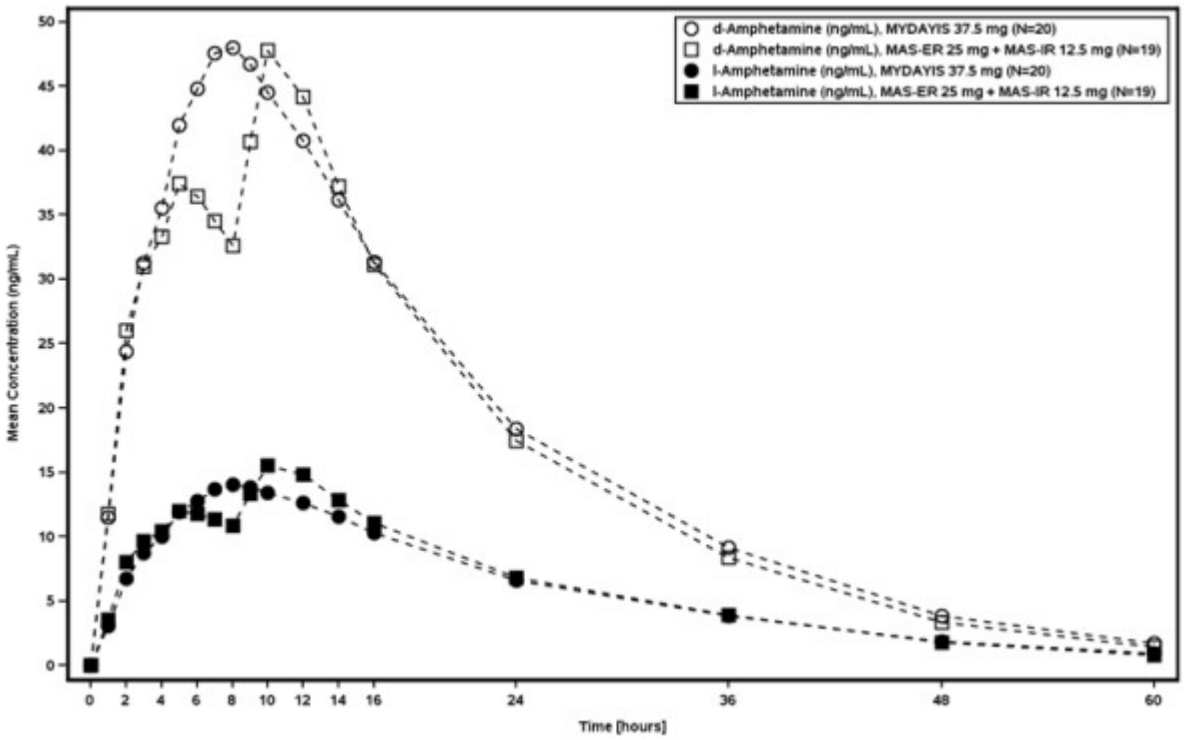




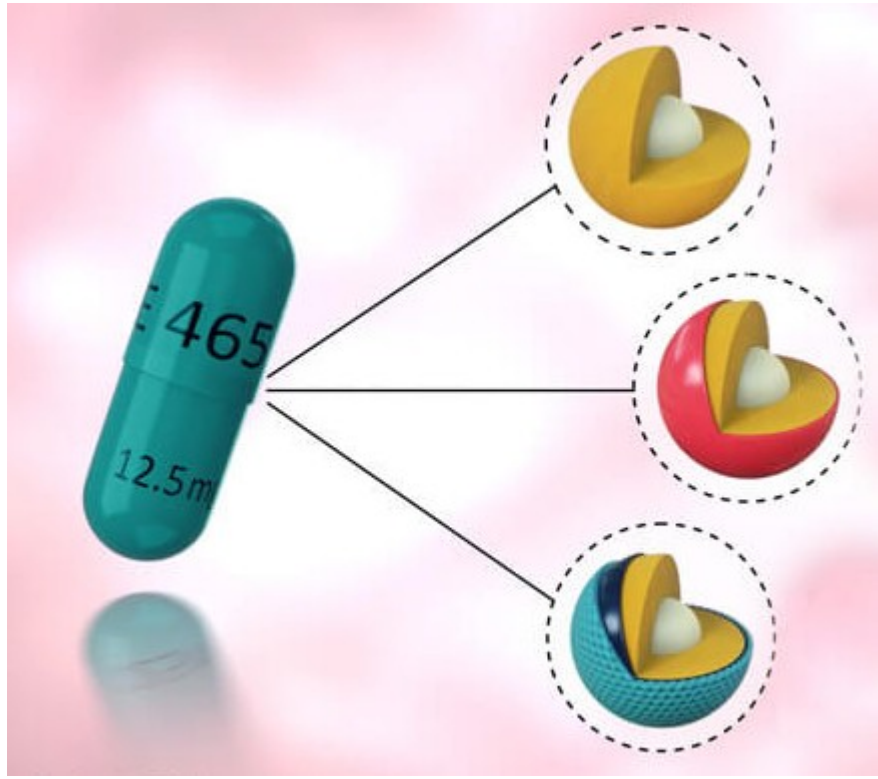
Mixed Amphetamine Salts (Mydayis®) (2017)

- Dosing: 12.5-50 qAM (Max is 25 for <18 yo)
- Dose equivalent of 10mg is ~20mg of methylphenidate
- Formulation: Capsule
- Onset of Action: 20-60 minutes
- Time to Peak: 7-10 h
- Duration: **<=16 h**
- Can split? Yes
- Age: **13+**
- Same MAS 3:1 racemic mixture of d:l-amphetamine
  - **1/3 beads IR, 1/3 releases core at pH 5.5 in proximal intestine, 1/3 releases porous core continuously and other core at pH 7.0 in distal small intestine**

Mixed Amphetamine Salts (Mydayis®)



Mydayis 37.5mg compared to MAS ER 25mg + IR 12.5mg



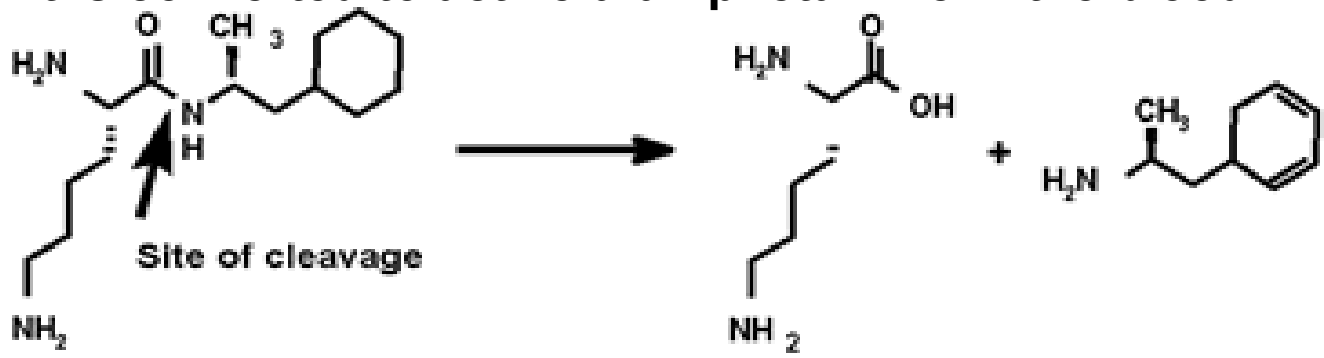
Lisdexamfetamine

- FDA approved
  - Adults and children
    - ADHD
  - Adults
    - Binge eating disorder
- Black Box Warning
  - Abuse and dependence
  - CV events

Lisdexamfetamine (Vyvanse®)

Prodrug that is therapeutically inactive until

it is converted to active *d*-amphetamine in the blood



- **LDX dimesylate**
  - Amphetamine prodrug
  - L-lysine covalently linked to d-amphetamine
- **Releases d-amphetamine after metabolic hydrolysis**

LDX = lisdexamfetamine.

Jasinski D, et al. Presented at: College on problems of Drug Dependence Meeting; June 2006; Scottsdale, Arizona; Boyle L, et al. Presented at: New Clinical Drug Evaluation Unit Meeting; June 2006; Boca Raton, Florida.

FDA indicated for Children 6 years & Older

Lisdexamfetamine (Vyvanse®) (2007)

- Dosing: 30-70 qAM
  - Max dose of 70mg roughly equivalent to 28mg MAS
  - Despite this dose being relatively lower, lisdexamfetamine lacks the peaks of MAS where some of the dose is “wasted”
- Dose equivalent of 25mg is ~20mg of MPH, ~10mg MAS
- Formulation: Capsule, chewable
- Onset of Action: **60 minutes**
- Time to Peak: 3-4 h
- Duration: **8-14 h**
- Can split? No, can dissolve in water
- Age: 6+
- **Prodrug, converted steadily to d-AMP by hydrolytic activity of RBCs**
- **Only FDA approved treatment for binge eating disorder (adults)**

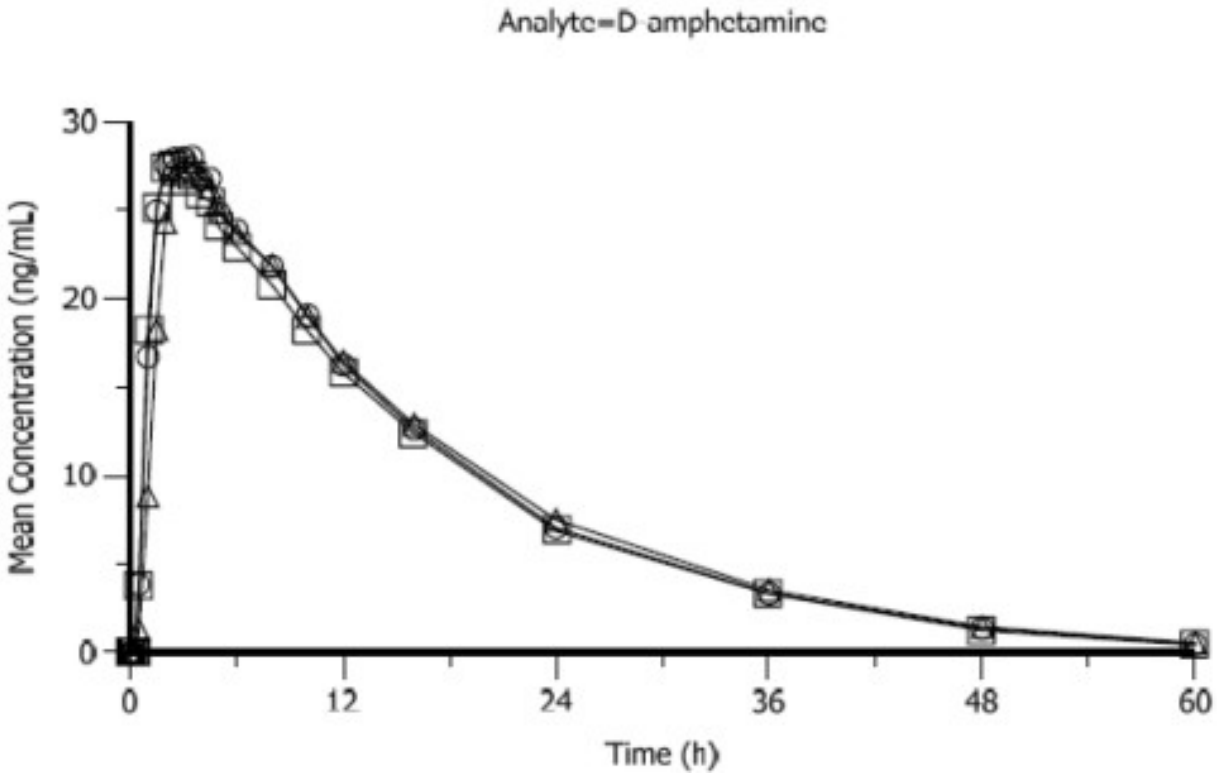
Amphetamine (base)

- FDA approved
  - Adults
    - ADHD (patch only)
    - Narcolepsy
  - Children
    - ADHD
    - Narcolepsy
    - Exogenous obesity (Evekeo®)
- Black Box Warning
  - Abuse potential
  - CV events (Evekeo®)

Amphetamine Sulfate (Evekeo® 2012) (Evekeo ODT® 2019)

- Dosing
  - 3-5 yo: 2.5 qAM - ? (only tablet, not ODT)
  - 6+: 5 qAM - 20 BID
- Dose equivalent of 15mg is ~20mg of methylphenidate
- Formulation: Tablet, ODT
- Onset of Action: 20-60 minutes
- Time to Peak: 4 h
- Duration: **4-6 h**
- Can split? Yes
- Age: **3+**
- **Tablet of 1:1 d-AMP sulfate to l-AMP sulfate**

Amphetamine Sulfate (Evekeo®)



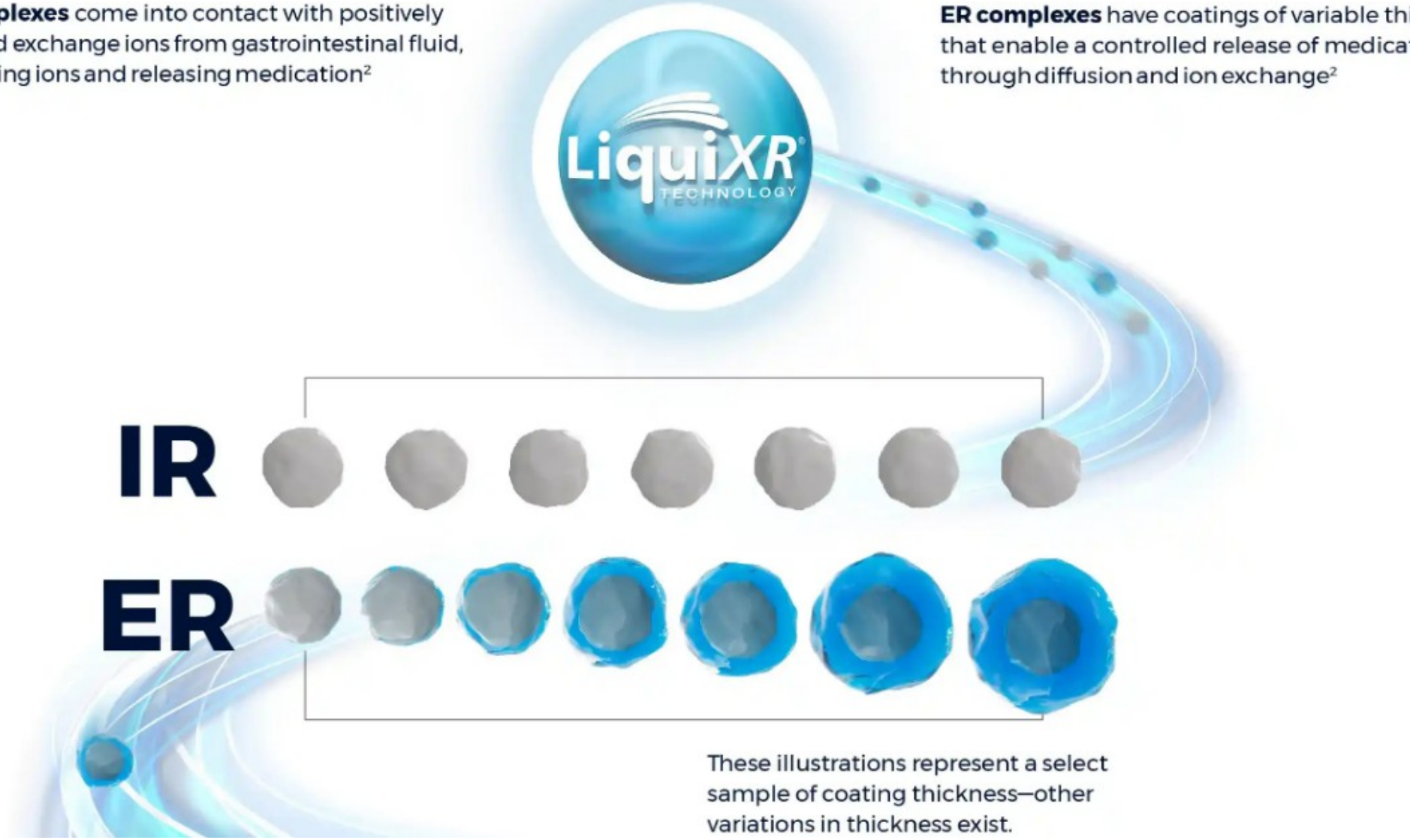
Amphetamine (base) (Dyanavel XR®) (2015)

- Dosing: 2.5-20 qAM (2.5mg/mL)
- Dose equivalent of 6.25mg is ~20mg of methylphenidate
- Formulation: **Liquid XR, capsule**
- Onset of Action: 20-60 minutes
- Time to Peak: 4-7 h
- Duration: **8-12 h**
- Can split? Liquid can titrate
- Age: 6+
- **Liqui*XR*® Technology**
  - ?% uncoated microparticles & ?% film coated ER microparticles
  - **3.2:1 d-AMP to l-AMP (base)**

Liqui*XR* technology precisely combines millions of IR and ER drug resin complexes in all Tris ADHD products[2]

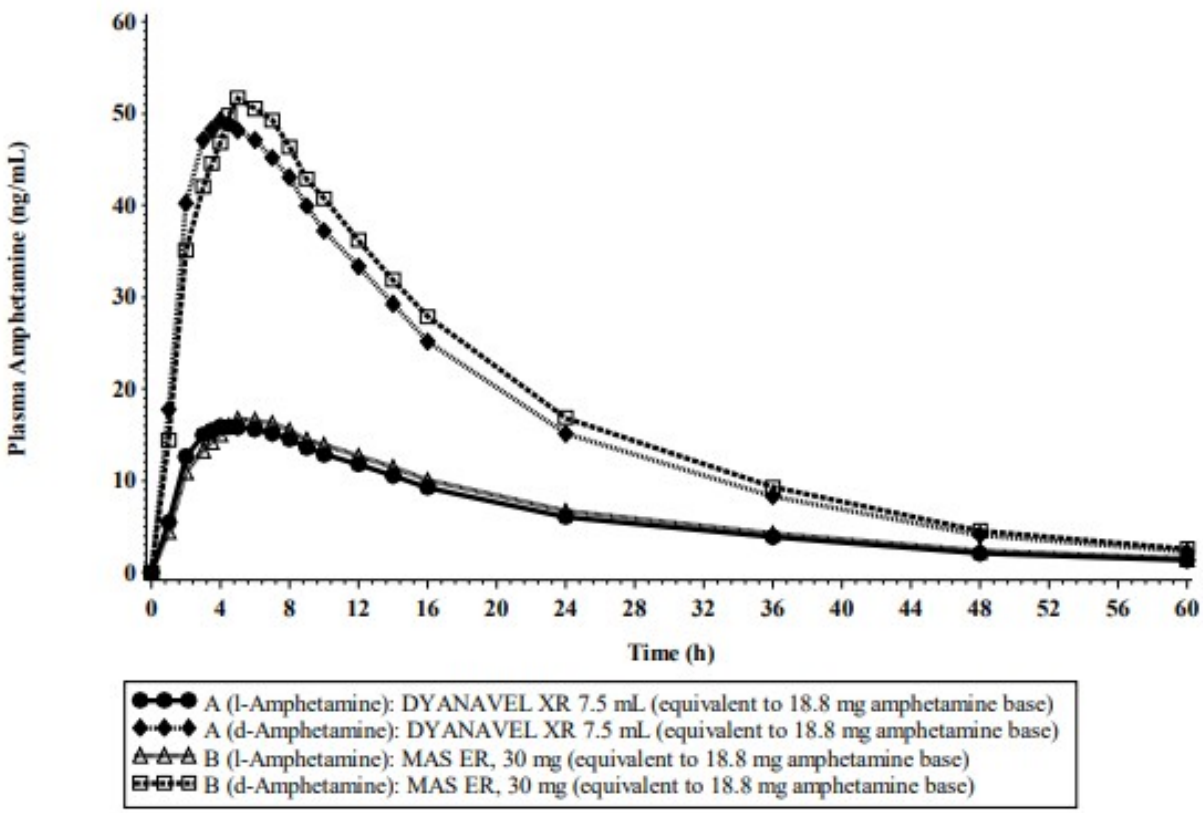
IR complexes come into contact with positively charged exchange ions from gastrointestinal fluid, displacing ions and releasing medication[2]

ER complexes have coatings of variable thickness that enable a controlled release of medication through diffusion and ion exchange[2]



These illustrations represent a select sample of coating thickness—other variations in thickness exist.

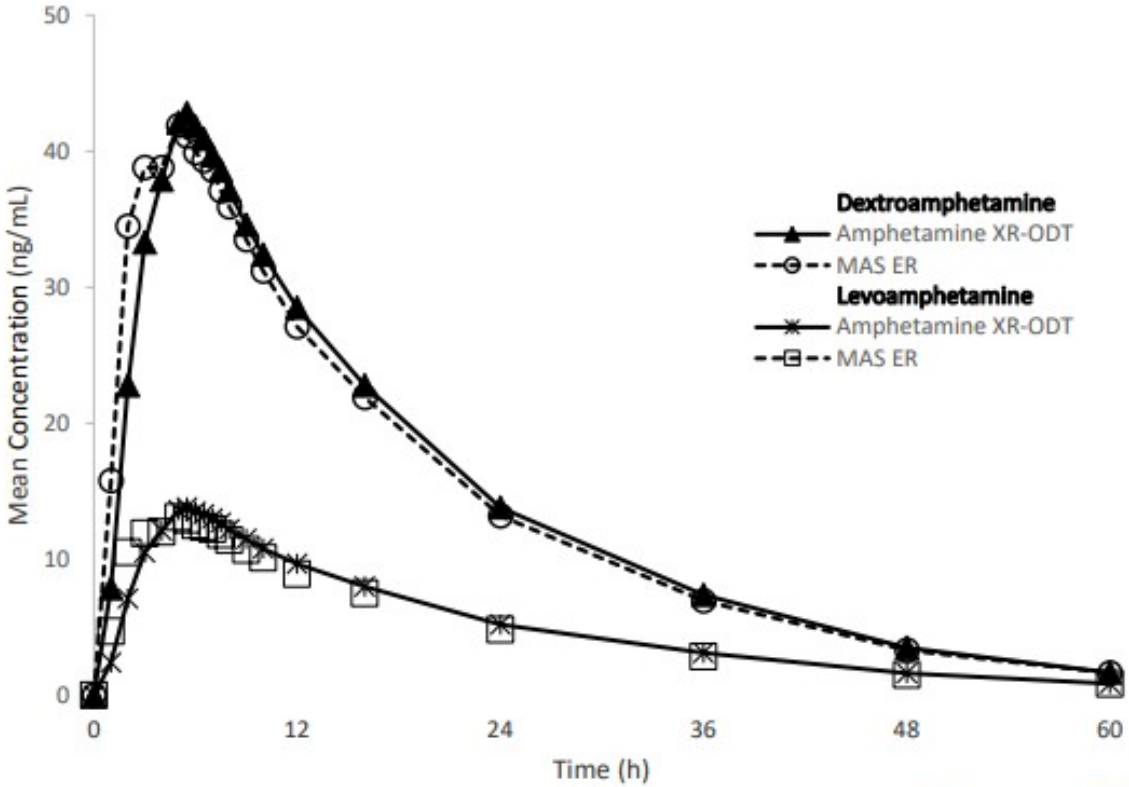
Amphetamine (base) (Dyanavel XR®)

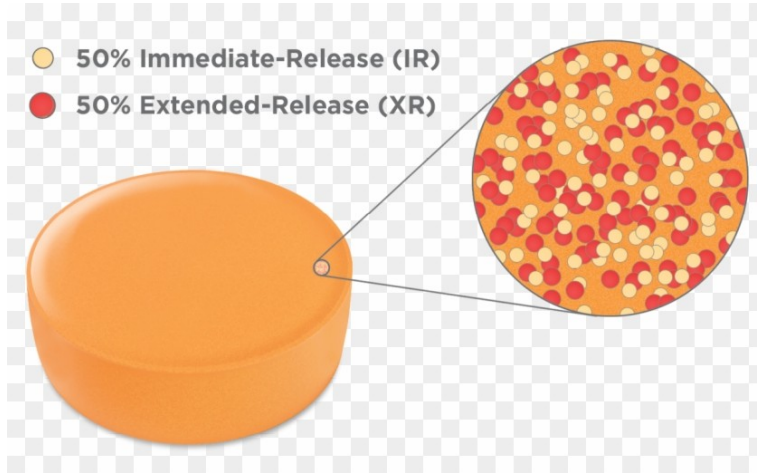


Amphetamine (base) (Adzenys XR-ODT® 2016) (Adzenys ER® 2017)

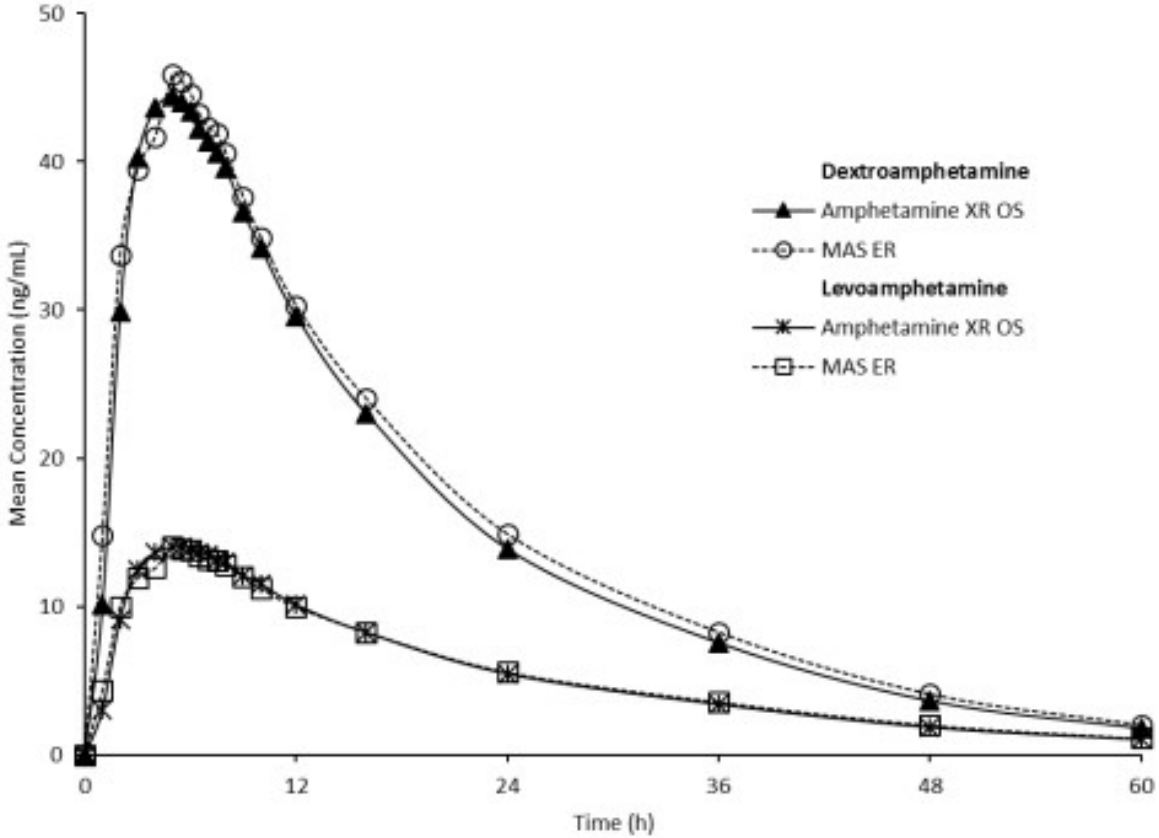
- Dosing
  - 6-12 yo: 6.3-18.8 qAM
  - 13-17: 6.3-12.5 qAM
  - 18+: 12.5-18.8 qAM
- Dose equivalent of 6.3mg is ~20mg of methylphenidate
- Formulation: **liquid, oral disintigrating tablet**
- Onset of Action: 20-60 minutes
- Time to Peak: 5 h
- Duration: **8-12 h**
- Can split? liquid can titrate, ODT can split
- Age: 6+
- **3:1 d-AMP to l-AMP (base)**
  - **50% IR microparticles, 50% delayed release microparticles**

Amphetamine (base) (Adzenys XR-ODT®)





Amphetamine (base) (Adzenys ER®)



Methylphenidate

Methylphenidate

- FDA approved
  - Adults and children
    - ADHD (methylphenidate and (ser)dexmethylphenidate)
    - Narcolepsy (only methylphenidate)
- Off-label for adults (methylphenidate)
  - Fatigue, severe, cancer related or in palliative care setting
  - MDD (unipolar) in medically ill, palliative care, terminal illness, or elderly patients
- Black Box Warning
  - Abuse and dependence

Methylphenidate Mechanism of Action

- NDRI
  - dl-MPH
    - DAT: K_i 121
    - NET: K_i 788
  - d-MPH (Focalin®)
    - DAT: K_i 206
    - NET: K_i 161
  - May work as an inverse agonist on DAT versus only antagonism with bupropion
  - Increased alertness, reduced fatigue, improved attention
- Initially used for barbiturate-induced coma, narcolepsy, and depression
- Later used to treat memory deficits in the elderly
- Beginning in the 1960s began use for ADHD in children

Methylphenidate (Ritalin®) (1955)

- Norepinephrine-dopamine reuptake inhibitor (NDRI)
- Dosing: 5 BID – 20 TID (off-label 100mg total daily)
- Formulations: Tablet, liquid, chewable
- Onset of Action: 20-60 minutes
- Time to Peak: 1-4 hours
- Duration: 3-4 hours
- Can split? Yes
- Age: 6+, off-label <6
- Immediate release

Methylphenidate (Methylin Oral Solution®) (2002)

- Dosing: 5-30 BID
- Formulation: **Liquid**
  - Liquids can be adjusted in smaller gradients by the mL
- Onset of Action: 20-60 minutes
- Time to Peak: 1-2 h
- Duration: 3-4 hours
- Can split? N/A
- Age: 6+
- Clear, grape-flavored liquid

Methylphenidate (Methylin CT®) (2003)

- Dosing: 5 BID - 20 TID
- Formulation: **Chewable**
- Onset of Action: 20-60 minutes
- Time to Peak: 1-2 h
- Duration: 3-4 hours
- Can split? Yes
- Age: 6+

Methylphenidate (Ritalin SR®) (1982)

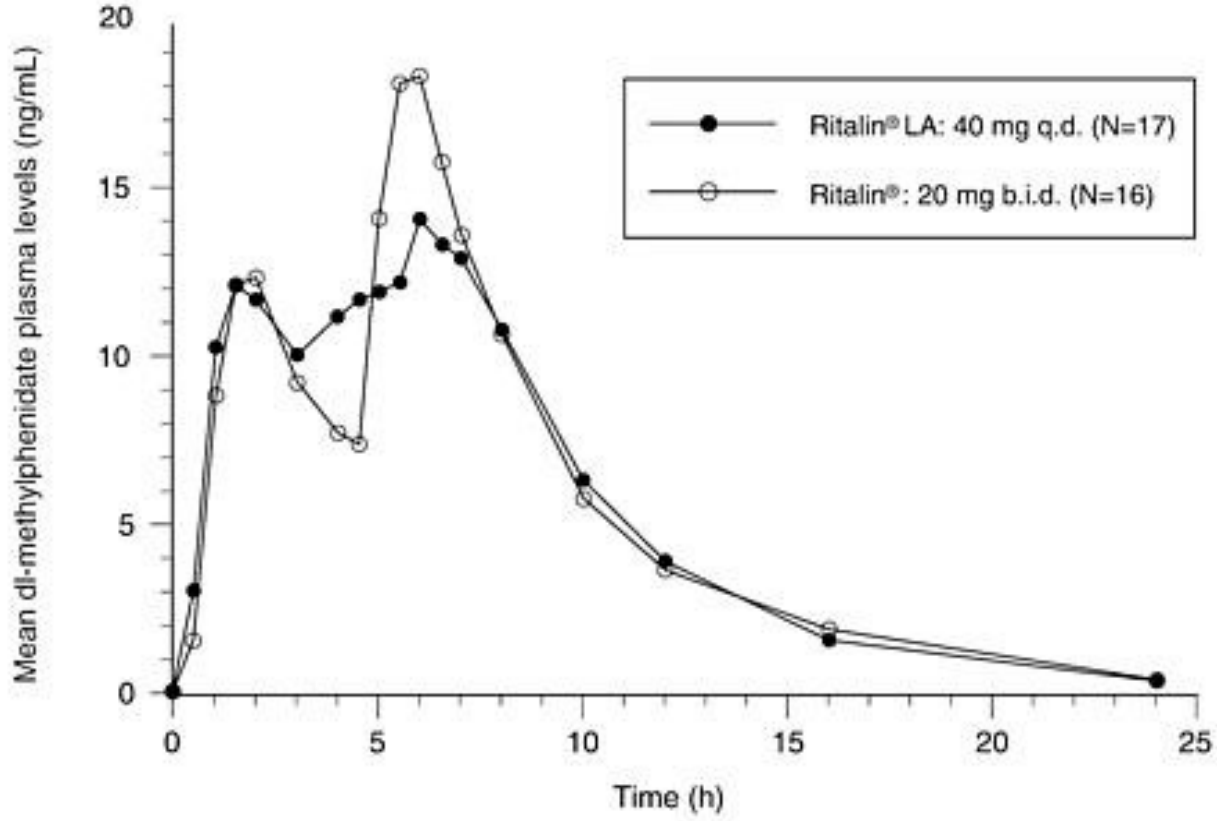
- Dosing: 10-60 qAM
- Formulation: Tablet
- Onset of Action: 20-60 minutes
- Time to Peak: 1.3-8.2 hours
- Duration: **4-8 h**
- Can split? **No**
- Age: 6+
- **Continuous release tablet**
  - Less predictable release due to wax matrix
- Branded generics
  - Metadate ER® (1988)
    - Dosed 10mg qAM – 30mg BID
    - Duration listed as 6-8 hours
  - Methylin ER® (2000)
    - Dosed 20-60 qAM
    - Uses hydrophilic polymer tablet which may be more continuous

Methylphenidate (Ritalin LA®) (2002)

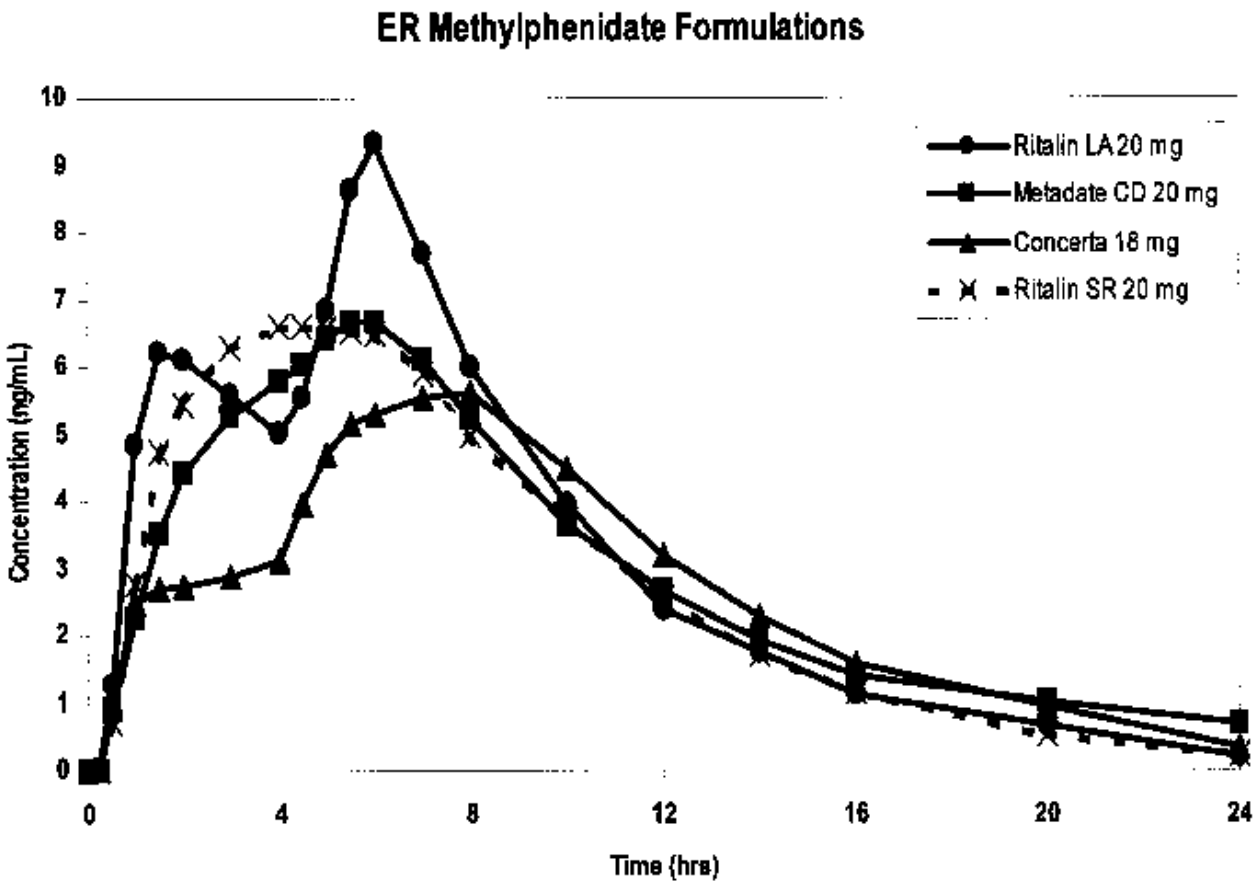
- Dosing: 20-60 qAM, (off-label 100)
- Formulation: Capsule
- Onset of Action: 20-60 minutes
- Time to Peak: 1-3 h, 5-11 h (adults 4.3-6.5 h)
- Duration: **8-12 h**
- Can split? Can sprinkle, do not crush or chew
- Age: 6+
- 50% IR beads & 50% delayed release beads
- Branded generic
  - Metadate CD® (2001)
    - 30% IR beads & 70% delayed release beads

Methylphenidate (Ritalin LA®)

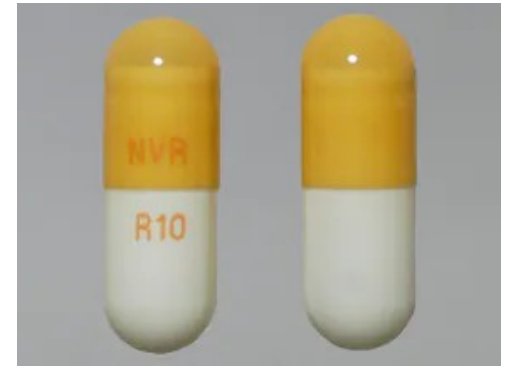
Figure 1. Mean plasma concentration time-profile of methylphenidate after a single dose of Ritalin® LA 40 mg q.d. and Ritalin® 20 mg given in two doses four hours apart

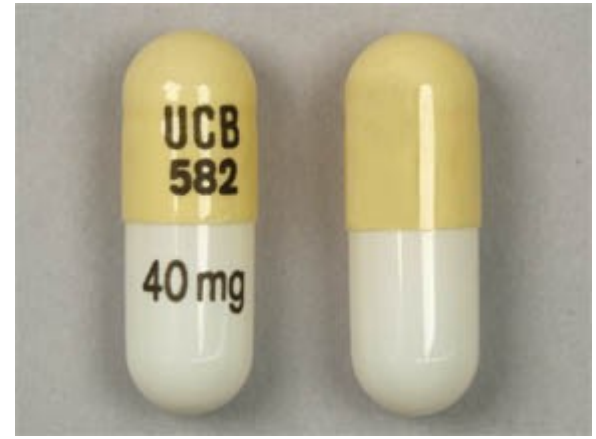


Methylphenidate ER Formulations



*Data presented are intended for illustrative purposes only and are not derived from a single cross-over study. These pharmacokinetic profiles represent the superimposition of data generated in three previously published bioavailability studies of MPH dosage formulations at similar strengths administered to healthy adult volunteers.[102,105,107]

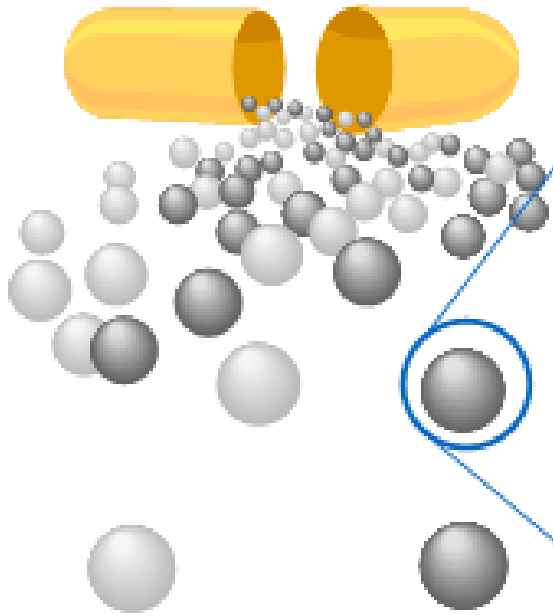




Stimulants

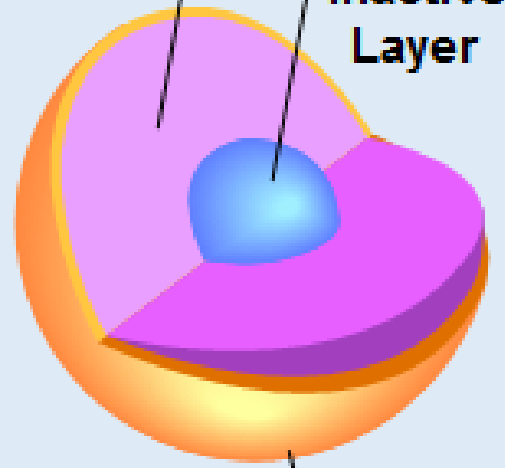
Methylphenidate LA (Ritalin® LA): Bimodal Release for Once-Daily Dosing

Each Ritalin® LA capsule contains 50% immediate-release beads and 50% extended-release beads



Immediate-Release Beads

Extended-Release Polymer-Coated Beads



How the extended-release beads work:

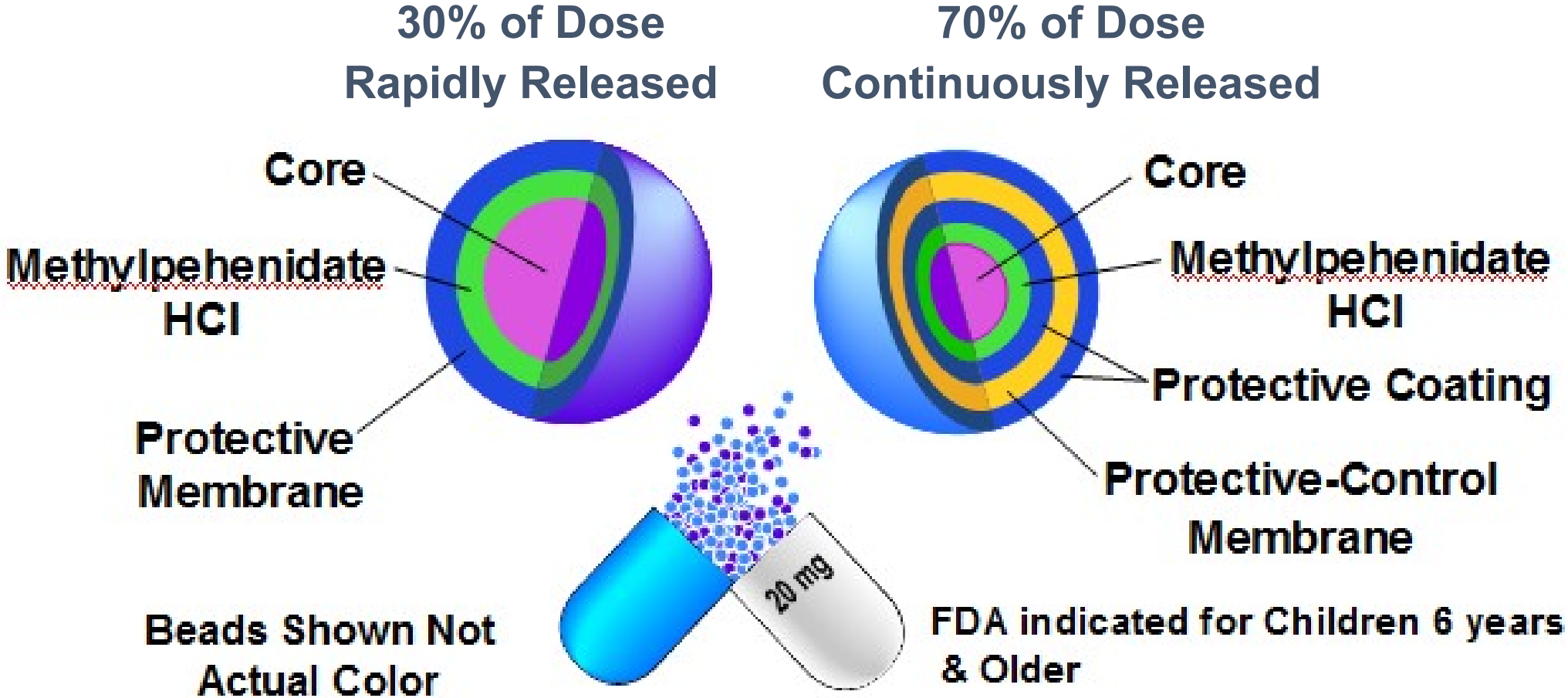
1. Over 4 hours, fluid creates small pores through polymer coating
2. Fluid enters and dissolves the Ritalin® layer
3. This provides a second release of Ritalin® equivalent to the immediate release

FDA indicated for Children 6 years & Older

Stimulants

Methylphenidate HCl, USP (Metadate® CD) Capsules Extended-Release

Biphasic Release: Difucaps Bead-Delivery System



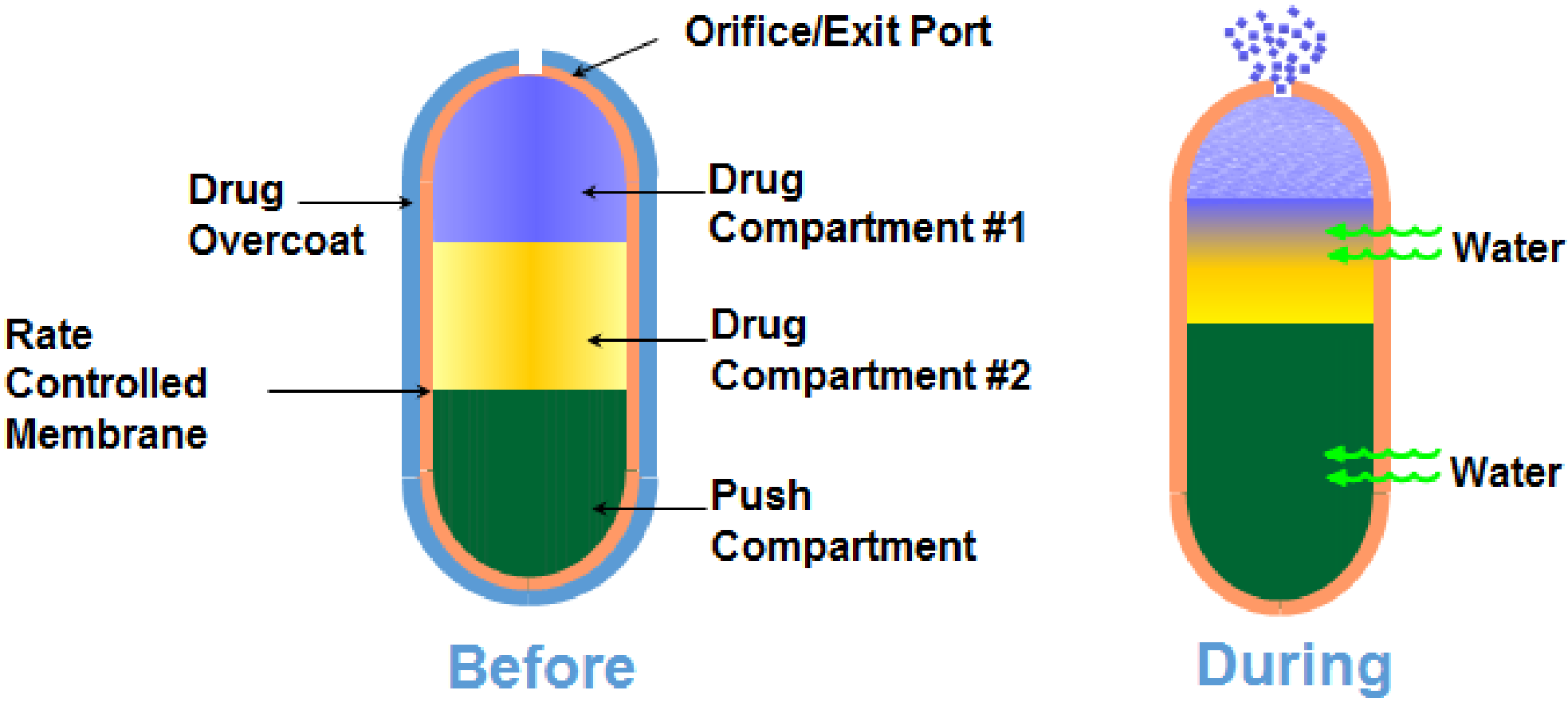
Methylphenidate (Concerta®) (2000)

- Dosing: 18-72 qAM (off-label 108mg), max dose is 54mg for ages 6-12
- Dose equivalent of 18mg is ~15mg of methylphenidate (5mg TID)
- Formulation: **OROS capsule**
- Generics: **Generic Concerta® is inferior**
- Off-brand Concerta®: Relexxii® (2024)
  - Only difference is that it is available in single pill 45mg and 63mg pills
- Onset of Action: 20-60 minutes
- Time to Peak: 1 h, 6-10 h
- Duration: **10-16 h**
- Can split? **No**
- Age: 6+
- Initial 22%, then continuous release tablet 78%

Stimulants

Attention-deficit/hyperactivity disorder (ADHD) – (Concerta®)

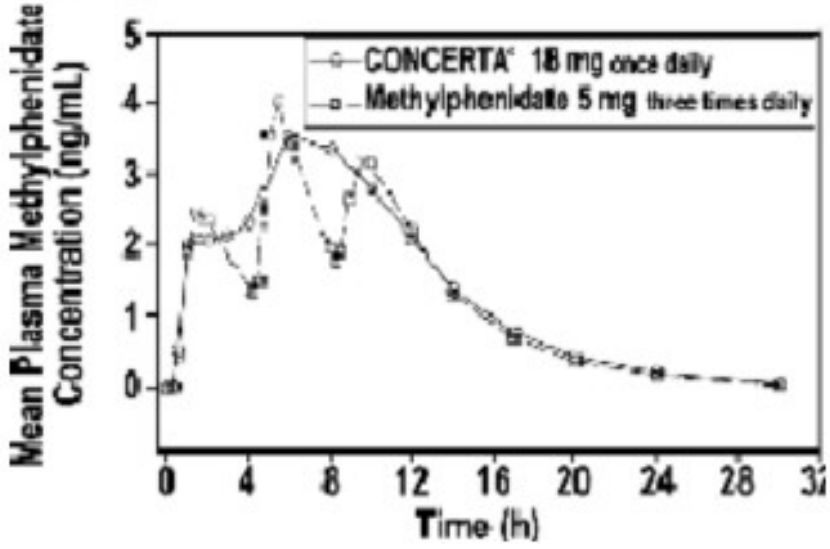
OROS™ System

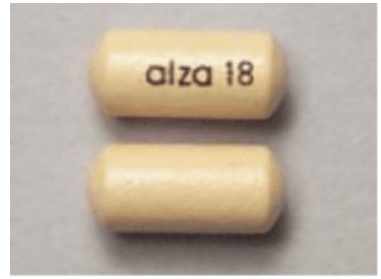


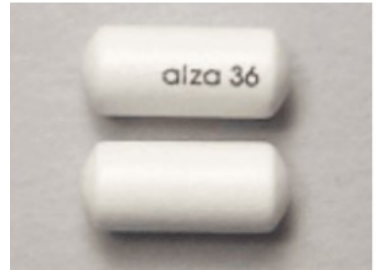
Trilayer tablet has 3 compartments (2 containing drug, 1 a "push" compartment) and an orifice at the head of the first drug compartment; water fills the push compartment and gradually pushes drug up and out of the tablet through the orifice. 22% of drug is located in coating and is released as IR form

Methylphenidate (Concerta®)

Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of CONCERTA® 18 mg once daily and immediate-release methylphenidate 5 mg three times daily administered every 4 hours.







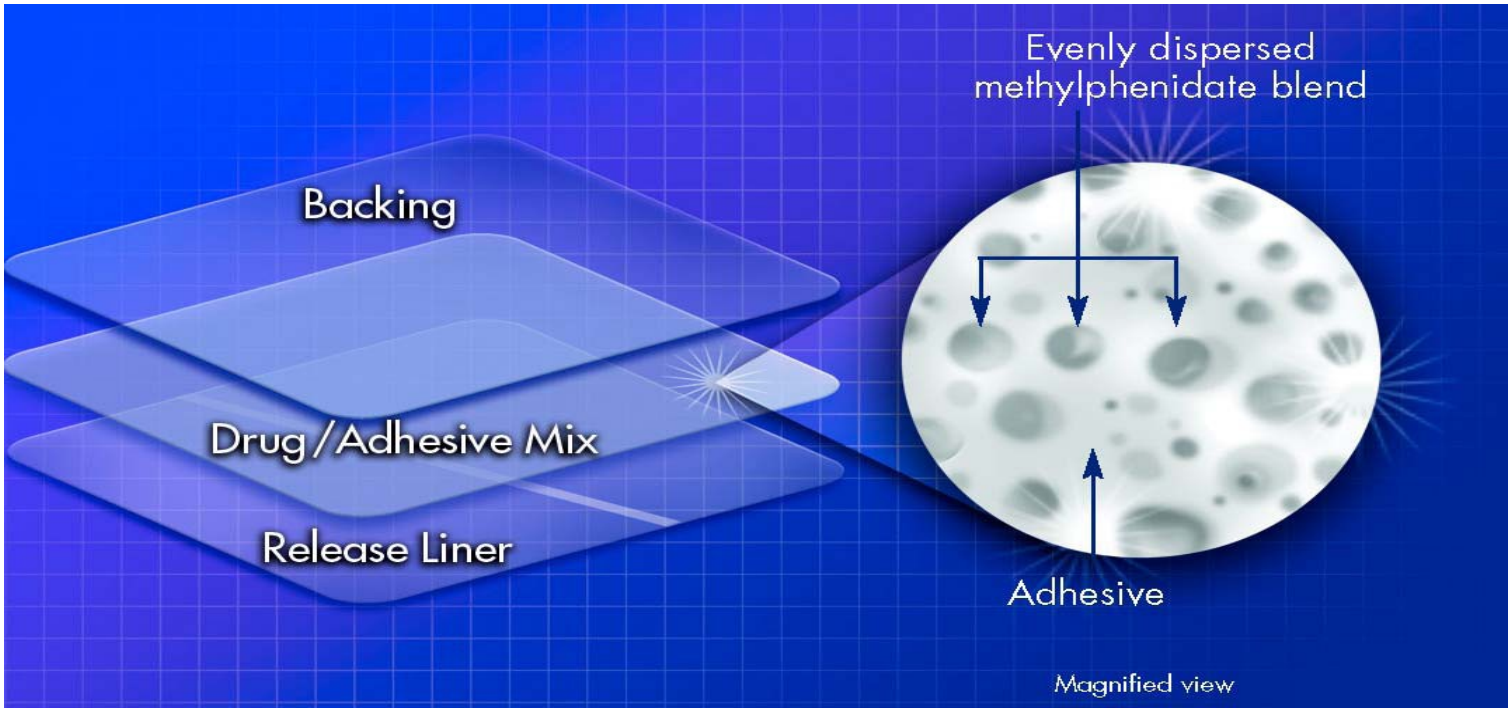
Methylphenidate Transdermal (Daytrana®) (2006)

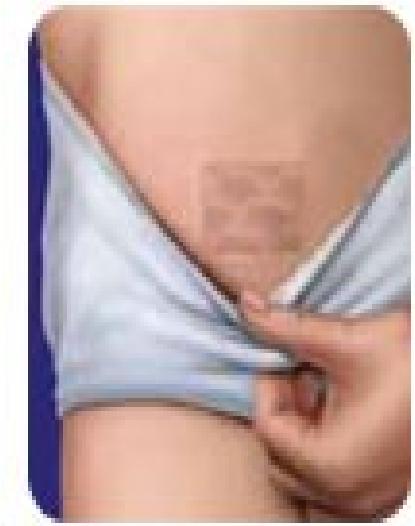
- Dosing: 10-**30** qAM
- Bioavailability is higher than oral formulations due to lower first-pass effect
  - **Roughly 1.5 times as potent as oral formulations but varies**
  - **Smoother absorption curve**
- Dose equivalent of 13.3mg is ~20mg of methylphenidate
- Formulation: **Patch XR**
- Onset of Action: **120 m** (shortened with external heat so do not use!)
- Time to Peak: **8-10 h**
- Duration: 8-12 h (lasts 2-3 hours after removal)
  - Can leave on less than or longer than 9 hours; patch contains more medication
- Can split? **Do not cut patch**
- Age: **6-12**

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

Methylphenidate Transdermal (Daytrana®)

- Methylphenidate is mixed with adhesive
- Apply patch to hip area for 9 hrs (2 hrs delay in onset)
- Milder SE (nausea, vomiting, insomnia) except rash



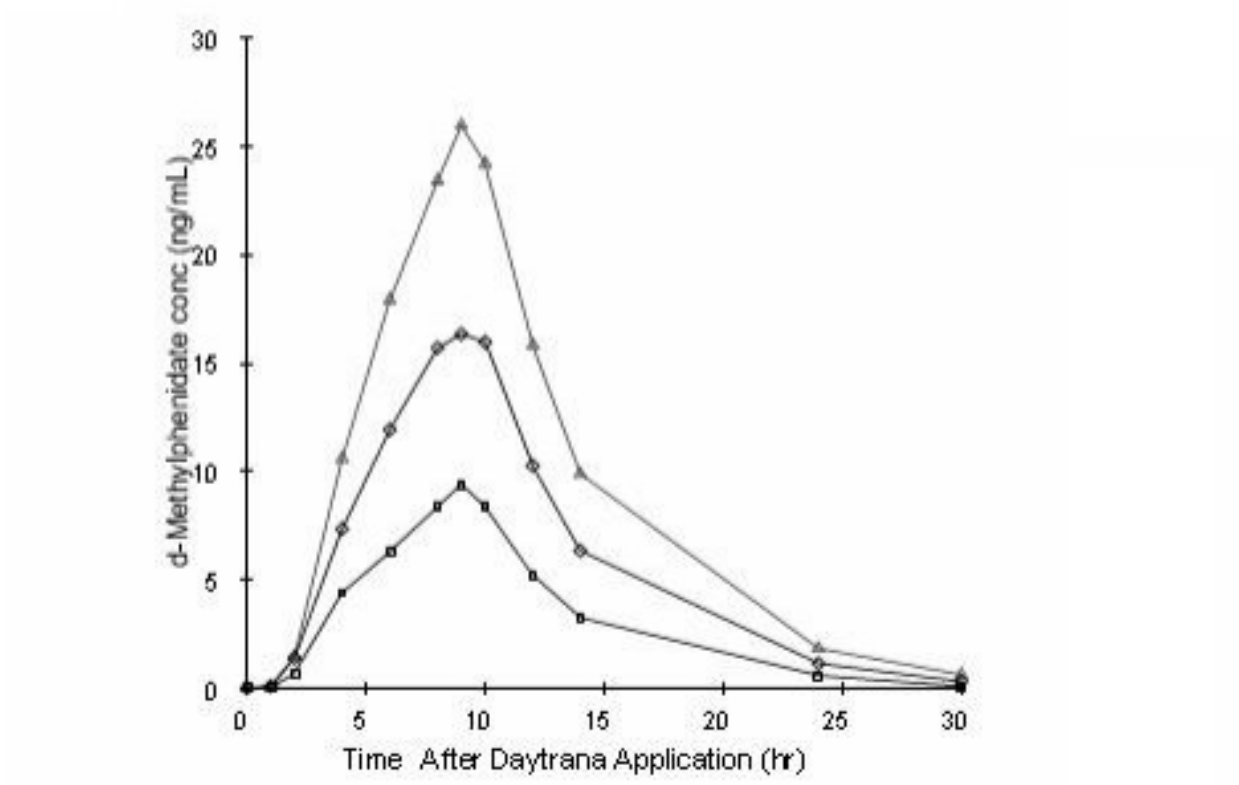


Arnold LE et al. Pediatrics. 2007;120(5):1100-06; Findling RL et al. J Clin Psychiatry. 2008;69(1):149-59

FDA indicated for Children 6 years & Older

Methylphenidate Transdermal (Daytrana®)

FIGURE 1 Mean Concentration-time Profiles for d-Methylphenidate in all Patients (N=34) Following Administration of Single Applications (9-Hour Wear Time) of d,l-Methylphenidate Using Daytrana 10 mg (□), 20 mg (◊) and 30 mg (Δ) per 9-Hour Patches



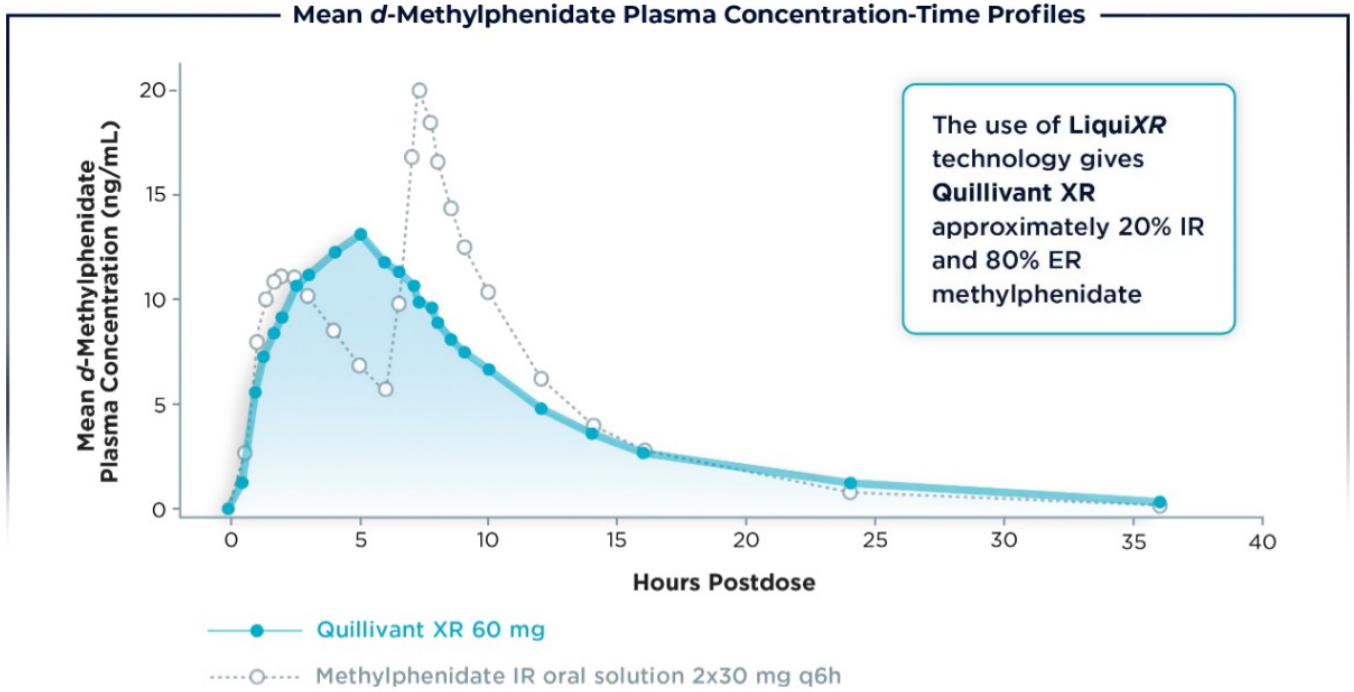
Methylphenidate (Quillivant XR®) (2012)

- Dosing: 20-60 qAM
- Formulation: **Liquid XR** (5mg/mL)
- Onset of Action: 20-60 minutes
- Time to Peak: 2-7 h
- Duration: 9-12 hours
- Can split? Dose by mL
- Age: 6+
- **Liqui*XR*® Technology**
  - Liquid containing 20% uncoated microparticles & 80% film coated ER microparticles

Methylphenidate Oral Suspension (Quillivant XR®)

- Comes as a powder that requires reconstitution prior to dispensing
- Shake vigorously for 10 seconds before use

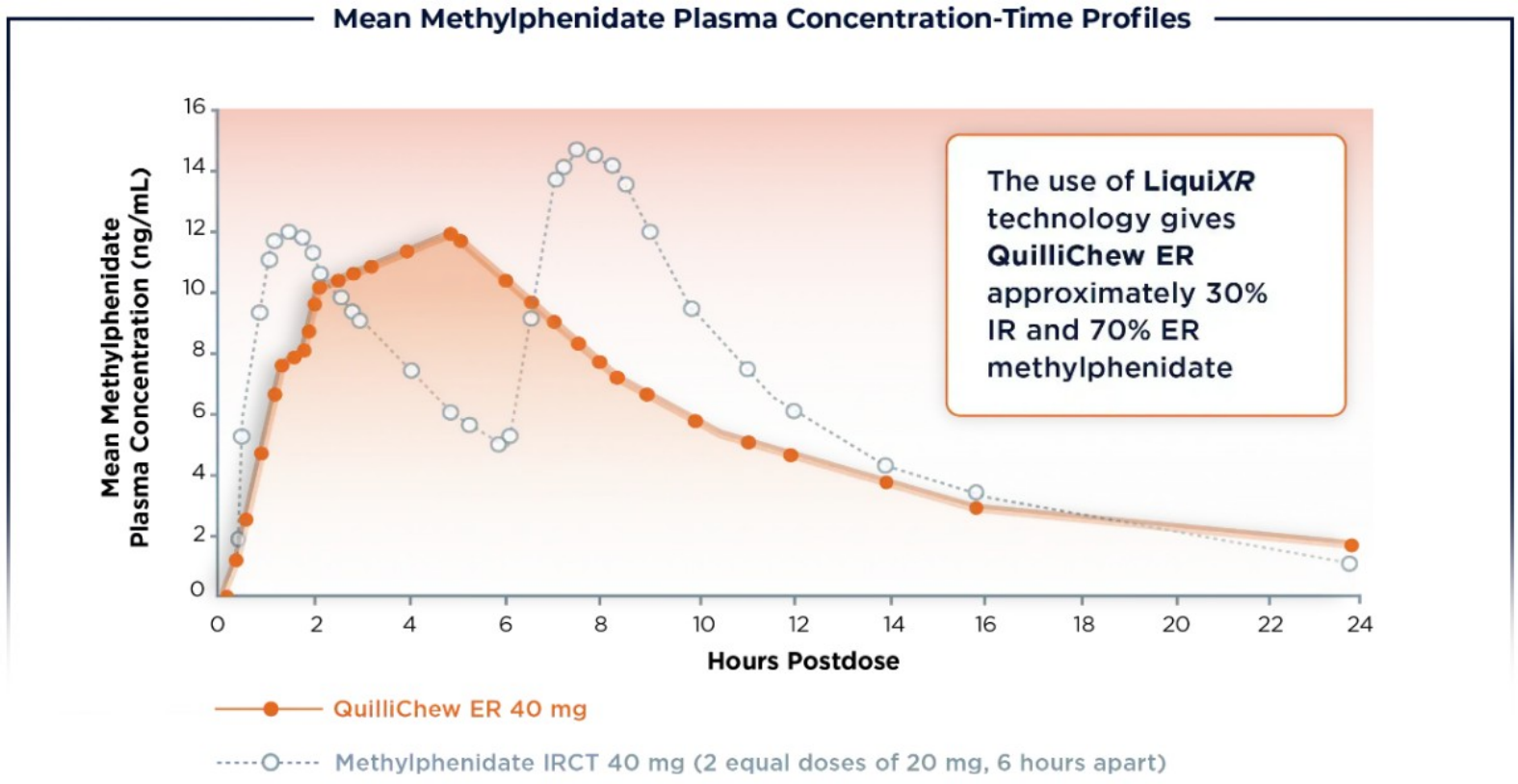
Quillivant XR (methylphenidate HCl) continually releases through the rest of the day—no additional peaks or crashes after initial onset



Methylphenidate (Quillichew XR®) (2015)

- Dosing: 20-60 qAM
- Formulation: **Chewable XR**
- Onset of Action: 20-60 minutes
- Time to Peak: 5 h
- Duration: 8-10 hours
- Can split? Yes
- Age: 6+
- **Liqui*XR*® Technology**
  - 30% uncoated microparticles & 70% film coated ER microparticles

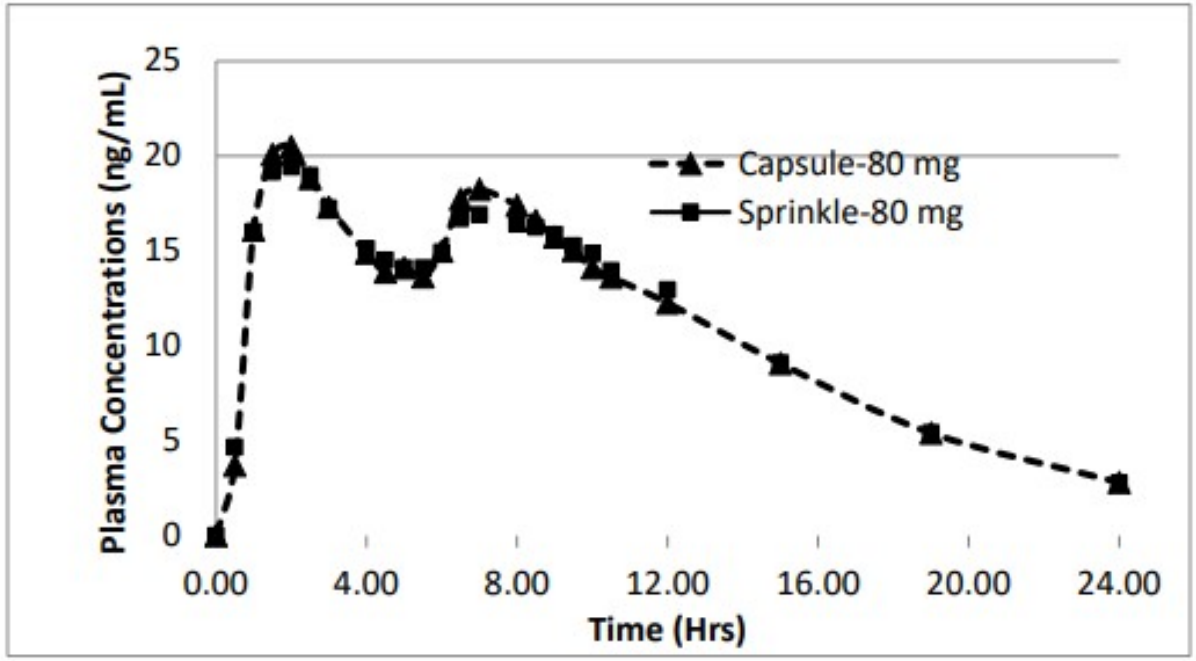
Methylphenidate (Quillichew XR®)

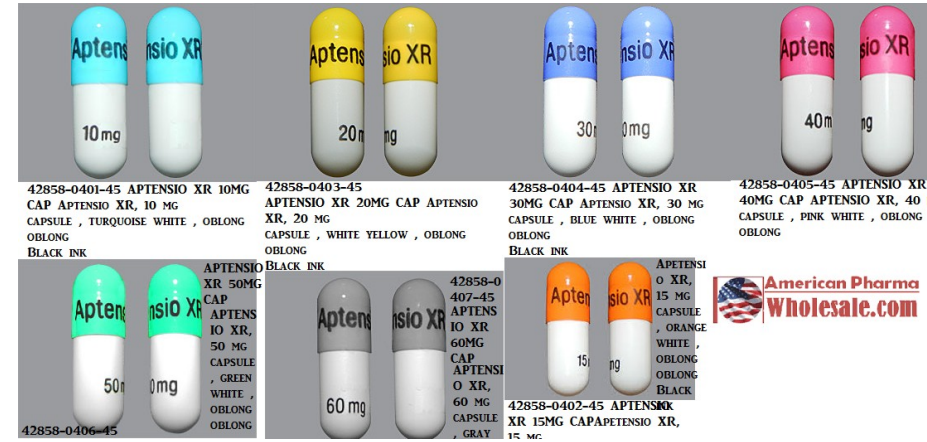


Methylphenidate (Aptensio XR®) (2015)

- Dosing: 10-60 qAM
- Formulation: Capsule
- Onset of Action: 20-60 minutes
- Time to Peak: 2 h, 8 h
- Duration: **<=16 h**
- Can split? Yes
- Age: 6+
- Capsule of 40% IR beads & 60% CR beads

Methylphenidate (Aptensio XR®)

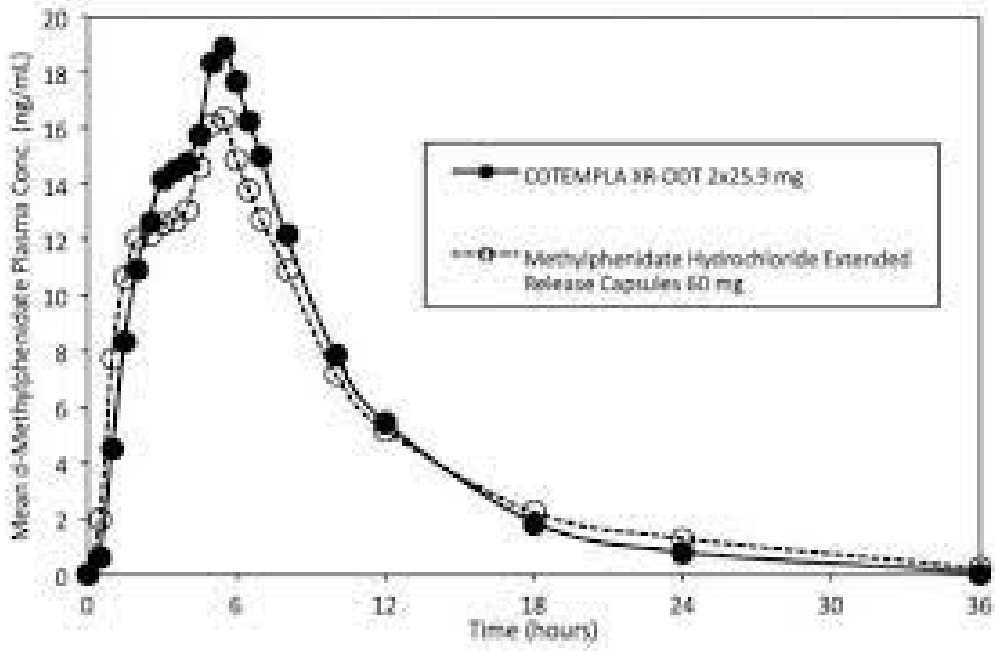




Methylphenidate (Cotempla XR-ODT®) (2017)

- Dosing: 17.3-51.8 qAM
- Dose equivalent of 17.26mg is ~20mg of methylphenidate
- Formulation: **ODT XR**
- Onset of Action: 20-60 minutes
- Time to Peak: 5 h
- Duration: 8-12 h
- Can split? Yes
- Age: 6+
- ODT of 30% IR microparticles & 70% ER microparticles

Methylphenidate (Cotempla ODT-XR®)



INDIVIDUALIZED DOSING OPTIONS TO FIT PATIENT NEEDS

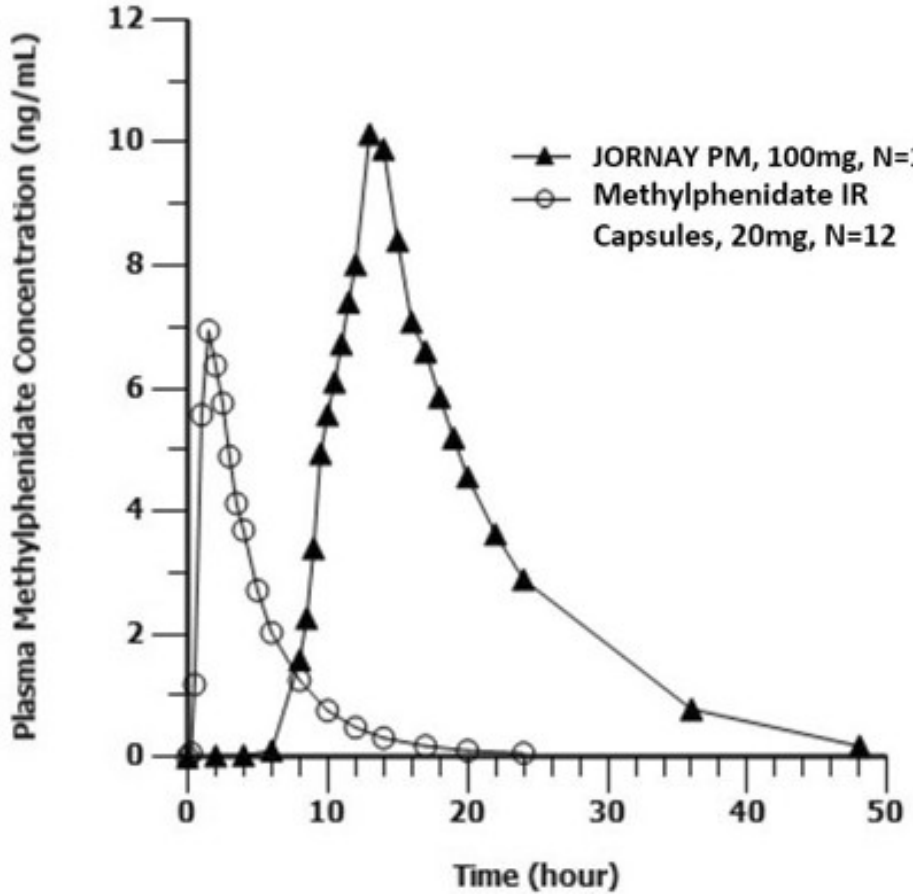
8.6 mg	17.3 mg	25.9 mg	34.6 mg	51.8 mg
T1	T2	T3	T2 + T2	T3 + T3
	Starting Dose		17.3 mg + 17.3 mg	25.9 mg + 25.9 mg

Tablets depicted are not actual size

Methylphenidate (Jornay PM®) (2018)

- Dosing: 20-100 **qPM (1830-2130)**
- Dose equivalent of 33.3mg is ~20mg of methylphenidate
- Formulation: Capsule
- Onset of Action: **10-12 h**
- Time to Peak: **14 h**
- Duration: 8-12 h
- Can split? Yes
- Age: 6+
- Beads have 2 layers, 1st is delayed release 10-12 hours, 2nd is extended release

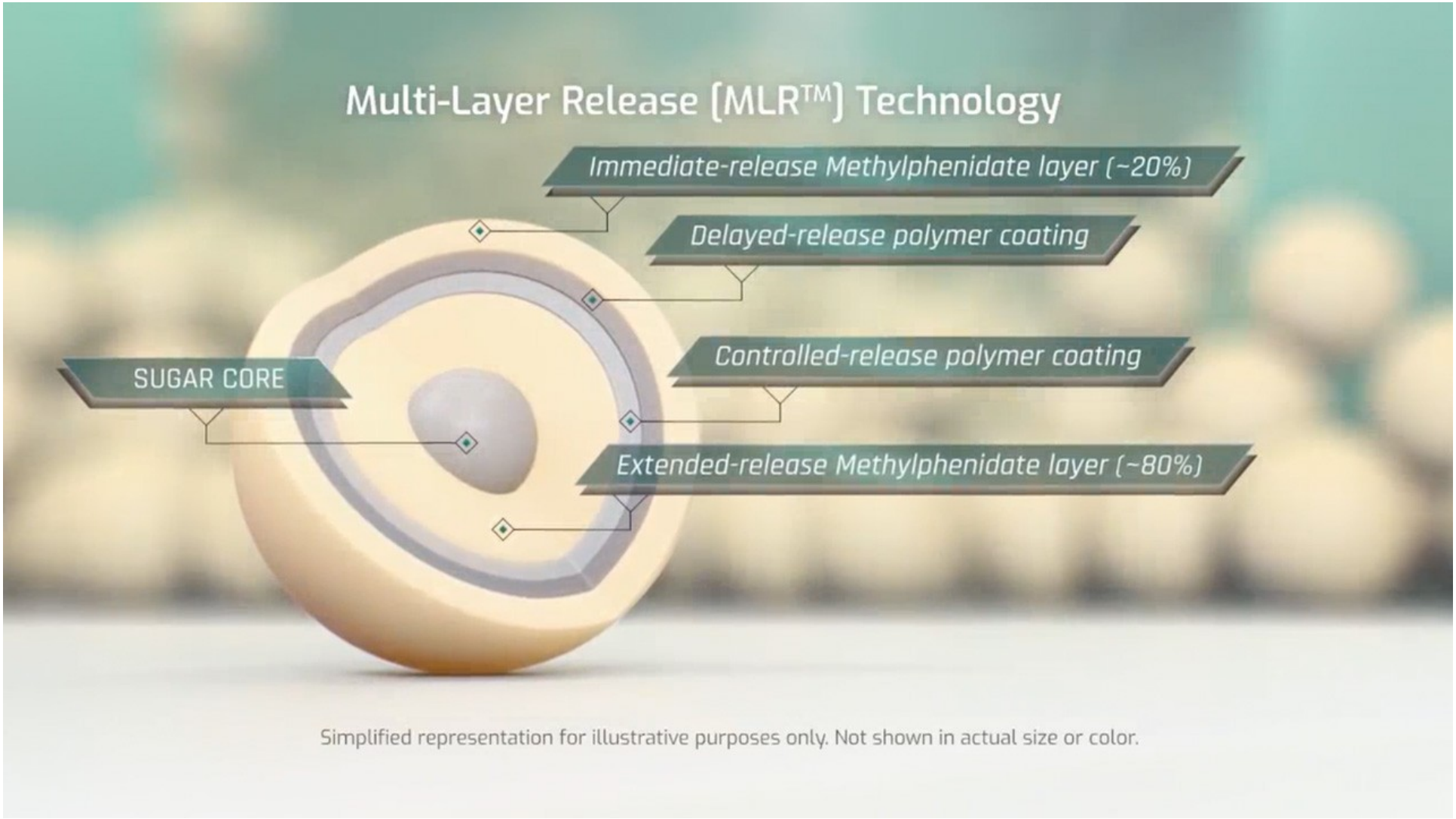
Methylphenidate (Jornay PM®)



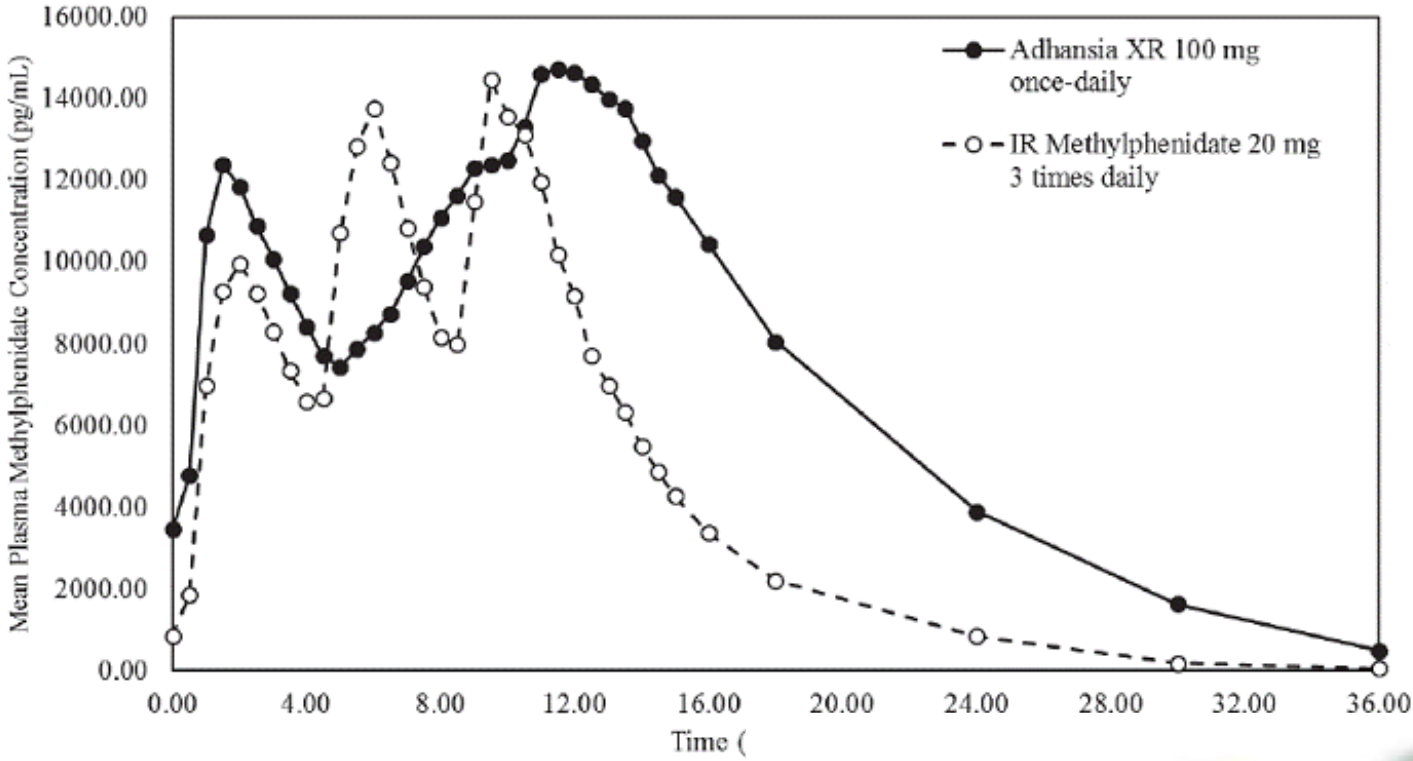
Methylphenidate (Adhansia XR®) (2019)

- Dosing: 20-**100** qAM
- Dose equivalent of 25mg is ~20mg of methylphenidate
- Formulation: Capsule
- Onset of Action: 20-60 minutes
- Time to Peak: 1-4 h, 8-14 h (adult: 1-2.5 h, 8.5-16 h)
- Duration: **10-16 h**
- Can split? Yes
- Age: 6+
- **Multi-Layer Release (MLR®) Technology**
  - 20% IR layer & 80% CR layer

Methylphenidate (Adhansia XR®)



Methylphenidate (Adhansia XR®)

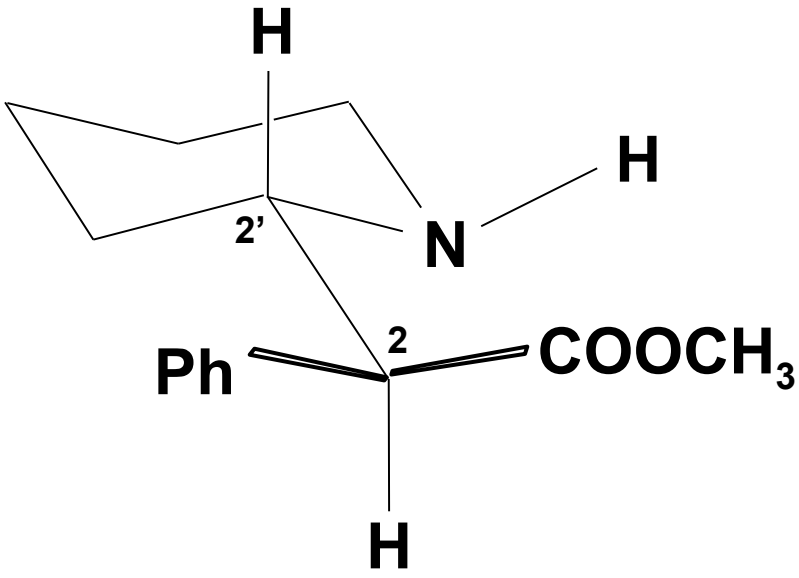


Dexmethylphenidate (Focalin®) (2001)

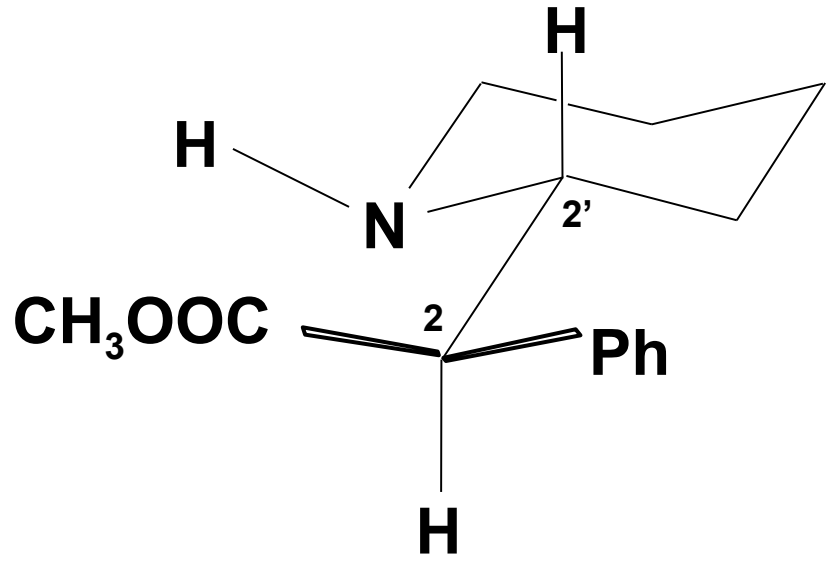
- Dosing: 2.5-20 BID
- Dose equivalent of 5mg is 10mg of methylphenidate
- Formulation: Tablet
- Onset of Action: 20-60 minutes
- Time to Peak: 1-2 h
- Duration: 3-4 hours
- Can split? Yes
- Age: 6+
- Immediate release **d-enantiomer** of methylphenidate

Dexmethylphenidate (Focalin®)

Dexmethylphenidate



l (-) Methylphenidate

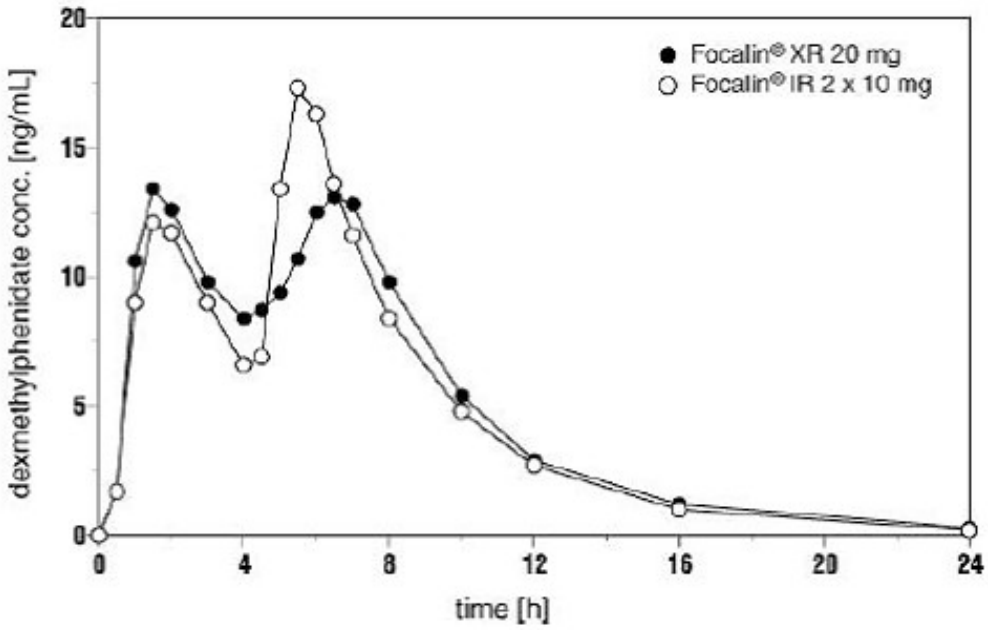


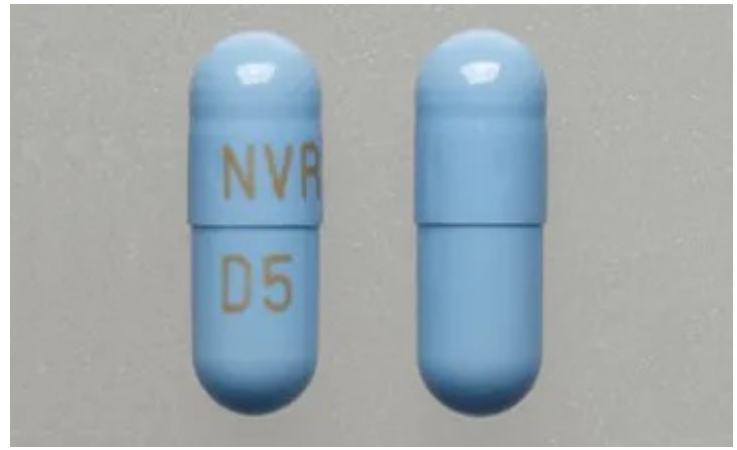
d (+) Methylphenidate

Dexmethylphenidate ER (Focalin XR®) (2005)

- Dosing: 5-30 qAM (10-**40** qAM for adults)
- Dose equivalent of 5mg is 10mg of methylphenidate
- Formulation: Capsule
- Onset of Action: 20-60 minutes
- Time to Peak: 1-2 h
- Duration: **8-12** hours
- Can split? Can be sprinkled, do not crush or chew
- Age: 6+
- 50% IR beads & 50% delayed release beads

Dexmethylphenidate (Focalin®)

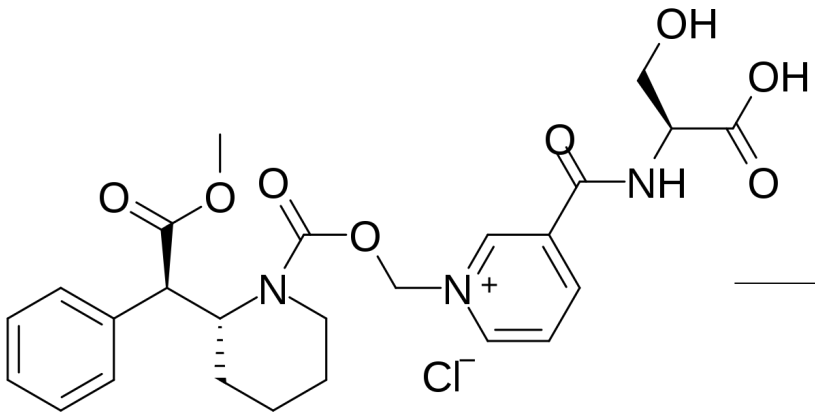




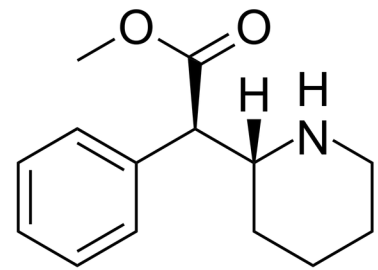
Serdexmethylphenidate/dexmethylphenidate (Azstarys®) (2021)

azstarys®
serdexmethylphenidate and dexmethylphenidate
26.1/5.2mg • 39.2/7.8mg • 52.3/10.4mg capsules

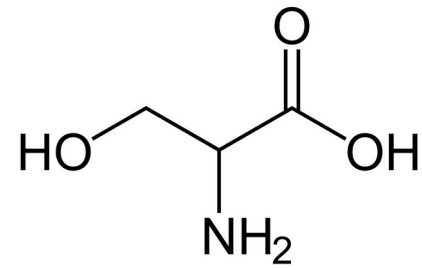
Contains prodrug that is therapeutically inactive until converted to active *d*-methylphenidate in the lower gut



serdexmethylphenidate



dexmethylphenidate



serine

?

FDA indicated for Children 6 years & Older

Serdexmethylphenidate/dexmethylphenidate (Azstarys®)

- Dosing: 26.1-5.2 – 52.3-10.4 qAM
- Dose equivalent of 15.65mg is ~20mg of methylphenidate
  - 26.1-5.2 = 20mg dexmethylphenidate / 40mg MPH
  - 39.2-7.8 = 30mg dexmethylphenidate / 60mg MPH
  - 52.3-10.4 = 40mg dexmethylphenidate / 80mg MPH
- Formulation: Capsule
- Onset of Action: **30** minutes
- Time to Peak: ~2 h
- Duration: **13 h**
- Can split? Yes
- Age: 6+
- Capsule of 30% IR beads & **70% beads that are slowly metabolized in the lower gut**

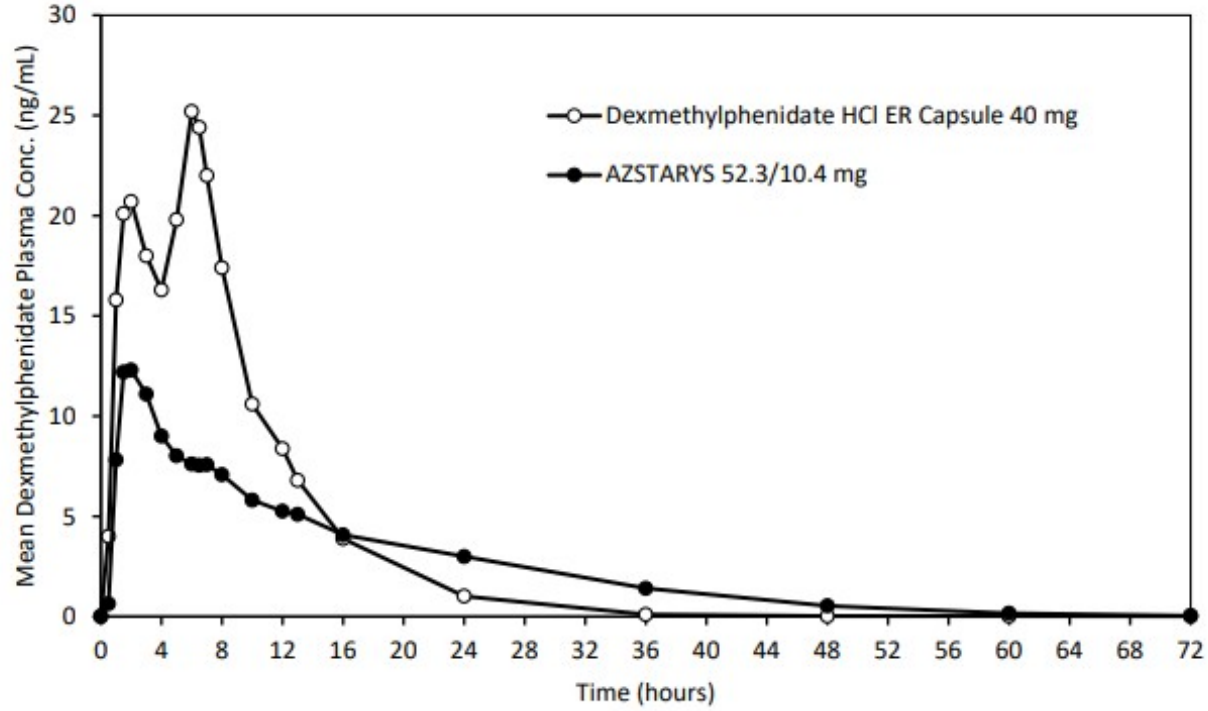
Serdexmethylphenidate/dexmethylphenidate (Azstarys®)

- Ser-dexmethylphenidate (70%)
  - Novel compound that is inactive until metabolized by unknown enzymes in the gut into dexmethylphenidate
  - **Has very low activity if insufflated or injected**
  - **Only stimulant which is a Schedule IV controlled substance**
  - Compared to other stimulants
    - Longer onset of action
    - Longer duration of action
- Dexmethylphenidate (30%)
  - Short-acting compound added due to delayed onset of action of serdexmethylphenidate
- Due to addition of dexmethylphenidate, Azstarys® is a schedule II controlled substance
- Research being done on ser-dexmethylphenidate for other indications

Serdexmethylphenidate/dexmethylphenidate (Azstarys®)

- Concentration of Azstarys® and dexmethylphenidate ER are the same at 16 hrs
- Maximum dose of Azstarys® peak plasma levels are lower than dexmethylphenidate ER
- Azstarys® plasma concentration lasts longer

Figure 1: Mean Dexmethylphenidate Plasma Concentration-Time Profiles After A Single Dose Administration of AZSTARYS or Dexmethylphenidate Hydrochloride Extended-Release (ER) Capsule in Healthy Adults Under Fasted Conditions



Other Stimulants

Modafinil (Provigil®) (1998)

- Not FDA approved for treatment of ADHD
  - MOA: DRI, activates release of orexin and histamine
  - Promotes alertness > concentration
  - Studies demonstrated effect at 400 mg
  - Trials showed effectiveness, however a few participants got a rash (13/1585), one SJS (1/1585)
    - FDA Pediatric Advisory Committee declined use in pediatric ADHD
    - No warning for adults (0 cases per 4,264 individuals)
- FDA approved
  - Narcolepsy-related or OSA-related excessive daytime sleepiness
  - Shift work sleep disorder-related excessive daytime sleepiness
- Schedule IV Controlled Substance
- Off-label
  - Cancer-related fatigue
  - MDD
  - Multiple sclerosis-related fatigue
  - Parkinson disease-related excessive daytime sleepiness
  - Myotonic dystrophy-related excessive daytime sleepiness
  - Idiopathic hypersomnia
  - TBI-related fatigue
  - ADHD

*Alert for healthcare professionals. Modafinil. March 2006.

Armodafinil (Nuvigil®) (2007)

- Not FDA approved for treatment of ADHD
- (R)-enantiomer of modafinil
- Similar effects
- Same FDA indications
- Levels are smoother than modafinil
- Slightly longer acting than modafinil

Stimulant Adverse Effects

Stimulant Side Effect Profile

- Insomnia: 10-30%
  - However insomnia may also be a part of the disorder; some improve with small stimulant dose at night
- Loss of appetite: 20-30%
- Weight loss: 5-10%
- Rebound phenomena
- Irritability/Anxiety: 5-10%
- Potential suicide ideation
- Headache: 20-30%
- Increased blood pressure
- Circulation problems in fingers and toes
- Tics (prior history): 7%
- Seizures (uncontrolled)
- Priapism (rare)

Appetite Suppression

- Administer the medication at or after a meal
- Encourage the child to eat nutrient dense foods before those with “empty calories”
- Offer food that the child likes for the noon meal, which is often affected
- When making these changes, an important caveat is that meals with high fat content may delay the time to peak concentration of some extended-release mixed amphetamine salts
- Choose high protein foods rather than carbohydrate-rich foods
- Use protein powder or anything to get them to eat higher calories while avoiding excessive carbohydrates

Meals and Methylphenidate

- Food may increase oral absorption of immediate release tablet and chewable tablet: administer 30-45 minutes before meals
- High-fat meal may delay time of onset and increase peak concentration (Focalin, Quillivant, long-acting)
- Children with decreased GI absorption or intestinal resection may not receive the full benefit (Concerta)
- Should not be taken with antacids or other drugs that decrease gastric acidity (long-acting)
- Gastrointestinal acidifying agents (acidic food, juices, or Vit C) and urinary acidifying agents lower amphetamine plasma levels
- Gastrointestinal alkalinizing agents (Sodium Bicarb, etc) and urinary alkalinizing agents (acetazolamide, some thiazides) increase amphetamine plasma levels and potentiate amphetamine‘s actions
- Avoid: caffeine

Irritability/Anxiety

- If mood lability occurs at the time of peak concentration
  - Try reducing the dose or switching to a longer acting preparation
- Irritability, sadness, and increased activity as the medication wears off is particularly common when short-acting medication is used on a morning and noon twice-a-day schedule
  - Try adding an afternoon dose or switching to long-acting formulation
- Coexisting or solitary mood disorder or anxiety disorder may be present
  - Consider SSRI

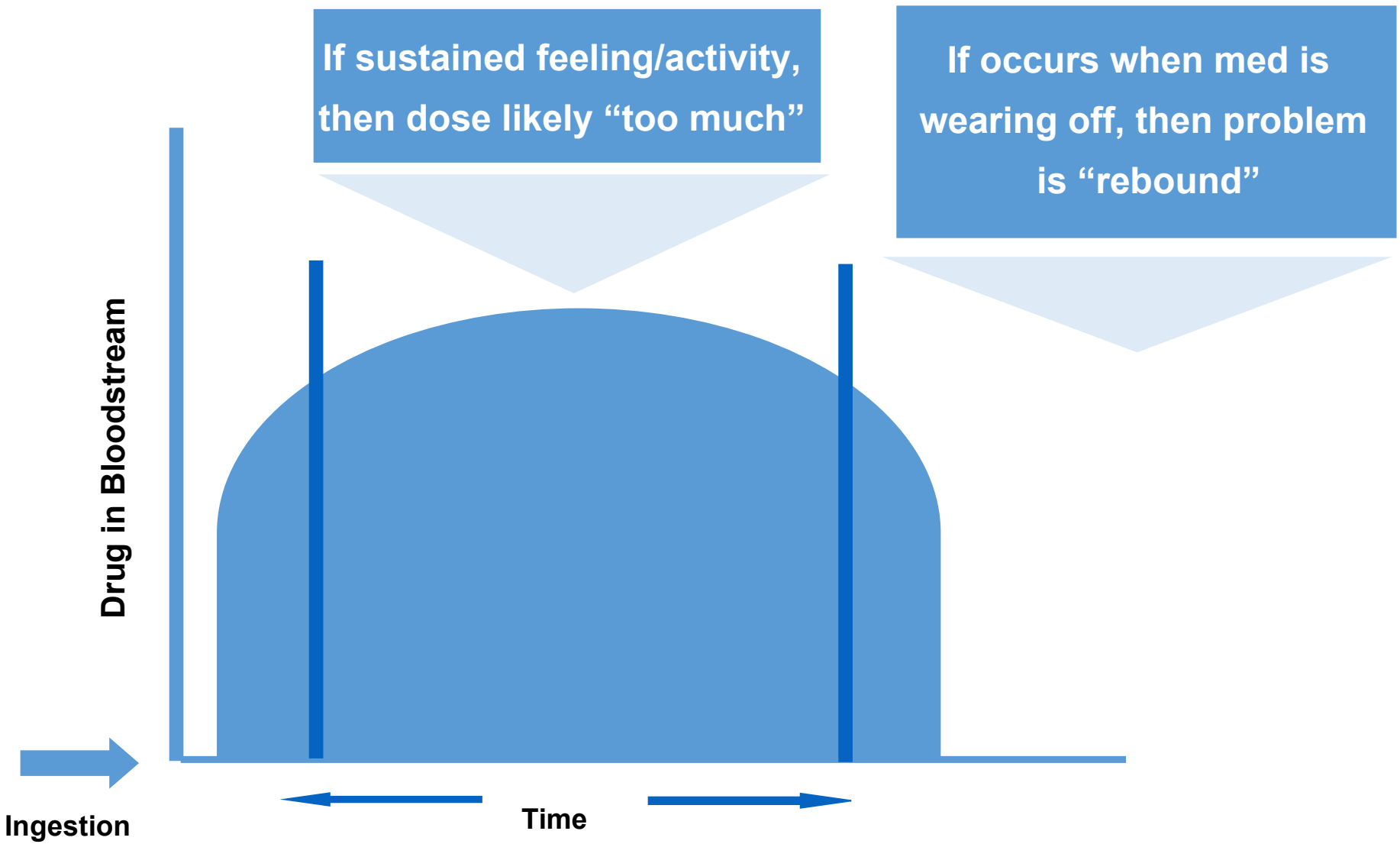
Dizziness

- Monitor blood pressure and pulse
- Ensure adequate fluid intake
- If associated only with peak effect, try a longer-acting preparation

Rebound

- “Rebound” refers to symptoms or adverse effects that occur as the medication is wearing off
- Rebound effects may improve by increasing the dose of the long-acting agent administered in the morning or adding a smaller dose of short-acting medication at the end of the day

Stimulant Time Frames & Rebound



Tic Disorder

- FDA warning of use of psychostimulants for those with tics is based on limited data from the 1970s and 1980s
- Recent studies have not demonstrated link between psychostimulants and tics, however there is a link between ADHD and tics (they are comorbid, up to 50% of children with tic disorders also have ADHD regardless of psychostimulant use)
- Conduct a drug trial at different doses, including no medication, to be sure that tics are drug-related
- If tics abate on no medication, reconsider the risks and benefits of treatment with the patient and family
- Psychostimulants may actually treat the tics along with ADHD
  - Methylphenidate has more data for treating both conditions than amphetamines
  - Consider use of alpha-2 agonist with/without psychostimulant
  - Atomoxetine does not worsen or increase tics

Contraindications for Stimulants

- Untreated CV disease including moderate to severe HTN
- Uncontrolled seizures
- Hyperthyroid
- Known hypersensitivity to sympathomimetic amines
- Uncontrolled Glaucoma
- Agitated states
- Motor tics or Tourette syndrome (questionable)
- Untreated bipolar disorder
- Recent or unstable substance abuse
- Concurrent use or use within 14 days of MAOi

Growth Delay

- Two-year, prospective multimodal treatment of ADHD with stimulant showed 1 cm per year growth deceleration
- Another study showed small but significant differences in height were found between children with and without ADHD but differences were no longer apparent by late adolescence
- Prospective studies following children into adulthood has found no significant impairment in attained height

Typically ~2 cm + 2.7 kg less/ 3 years

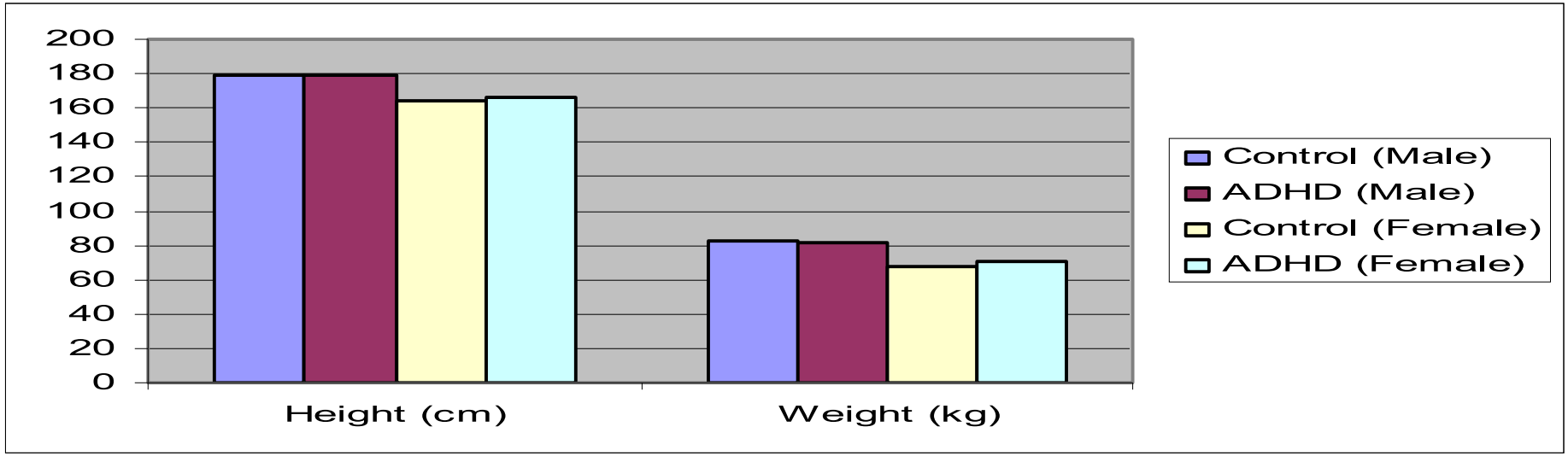
Spencer T et al. Pediatrics 102 (2 pt. 3): 501-06, 1998; NIMH Multimodal Treatment. Pediatrics. 113:762-69, 2004;

Mannuzza S et al. Arch Gen Psychiatry 48:77-83, 1991

Peyre H et al. Long-Term Effects of ADHD Medication on Adult Height: Results from the NESARC. J Clin Psychiatry 2013;74(11):1123-1124

Growth Delay

- 10-year prospective study on weight & height in children with ADHD
  - Two identical, longitudinal case-studies of female & male +/- ADHD
    - Control (N=124) ADHD (N=137)
  - Used linear growth curve models to estimate the effect of time on change in height



Biederman J et al. A Naturalistic 10-Year Prospective Study of height and Weight in Children with Attention-Deficit Hyperactivity Disorder Grown Up: Sex and Treatment Effects. J Pediatr 2010;157:635-40.

Weight Loss

- Drug holidays may be beneficial for children in whom stimulant therapy is associated with a growth trajectory that crosses two major percentiles (ie, the 5th, 10th, 25th, 50th, 75th, 90th, and 95th)
- Drug holidays should only be undertaken if they can be tolerated without marked impairment in functioning

Stimulants & Cardiovascular Risk

Cardiovascular Effects

- Twelve cases of sudden death associated with Adderall XR reported to the FDA between 1999-2003
  - Health Canada (like FDA) suspended sale of product due to sudden death in February 2005 (Canada; NOT the FDA)
  - Health Canada reevaluated data and reintroduced sale of product in October 2005
  - More than 20 clinical trials involving 5,200 patients with Adderall XR
  - Risk of sudden death with stimulant use is markedly lower than expected in general public without stimulant (1.3-8.5 per 100,000 patient years)
- FDA warns about the risk in children with underlying cardiovascular defects (February 2006)
- **Black Box Warning:** MAS and Evekeo only

Nissen SE. NEJM 2006;354(14):1445-48.

FDA Center for Drug Evaluation & Research. Alert for healthcare professionals. Adderall and Adderall XR. Sept 2005.

AHA Recommended Cardiovascular Monitoring

Medication	Class I, Level C Evidence	Class IIa, Level C Evidence
Stimulant	BP, HR	Baseline EKG
NRI	BP, HR	Baseline EKG
Alpha Adrenergic Agonists	BP, HR	Baseline EKG
Tricyclic Antidepressant	BP, HR	Baseline EKG & Dose increase
Bupropion	BP, HR	Baseline EKG

Committee on Congenital Cardiac Defects, Council on Cardiovascular Disease in the Young, American Heart Association Circulation. 1999;99:979-982.

Davis WB et al. J Am Acad Adolesc Psychiatry. 2008;47(2):189-98.

NICE Guidelines

- EKG not recommended
- Q3 months & after each dose change
  - Heart rate
  - Blood pressure
  - Atenolol may be useful if HR/BP are elevated as it only acts peripherally unlike propranolol and will blunt this effect of the stimulant

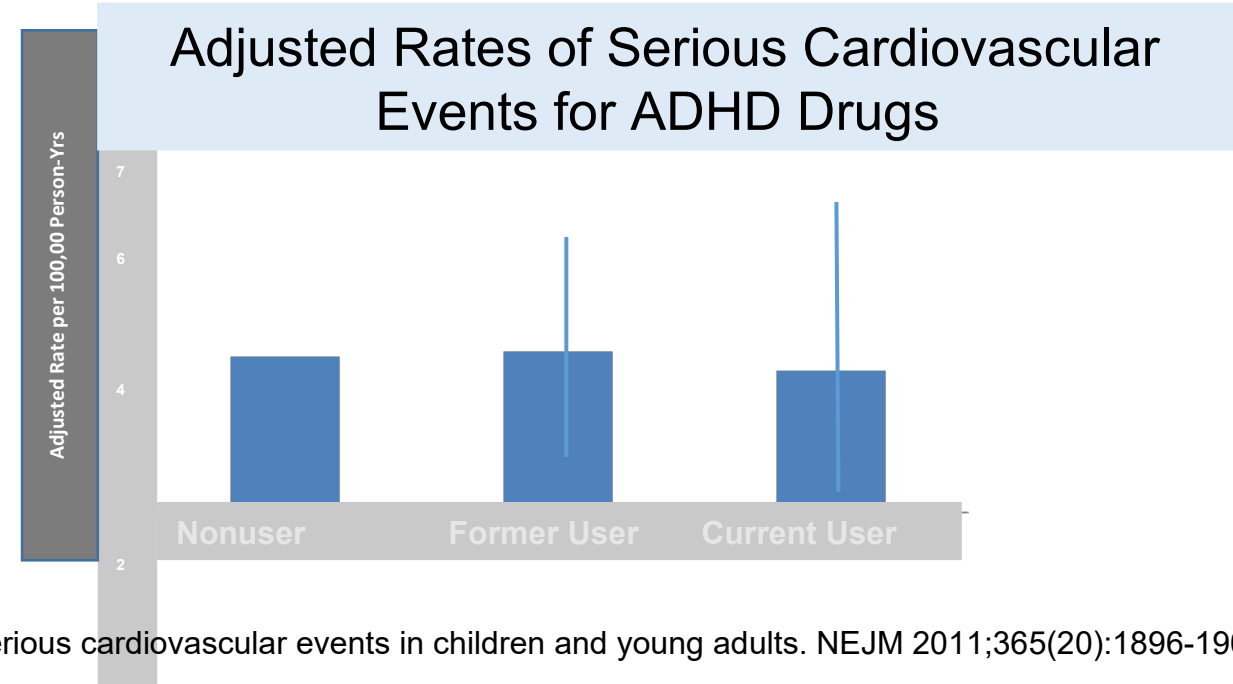
Similarities & Differences Between the AHA & AAP Guidelines

- Similarities
  - History & exam focused on cardiovascular disease
    - Individual & family
- Differences
  - AHA
    - EKG prior to stimulant therapy but not mandatory
    - Heart rate & blood pressure
    - Monitoring for stimulants & nonstimulants
  - AAP: EKG not recommended (stimulants)

Committee on Congenital Cardiac Defects, Council on Cardiovascular Disease in the Young, American Heart Association *Circulation.* 1999;99:979-982; Davis WB et al. J Am Acad Adolesc Psychiatry. 2008;47(2):189-98; Perrin JM, Friedman RA, Knilans TK; Black Box Working Group, Section on Cardiology and Cardiac, Surgery.Cardiovascular monitoring and stimulant drugs for attention-deficit/hyperactivity disorder. Pediatrics 2008 Aug;122 (2): 451-3; American Academy of Pediatrics /American Heart Association.American Academy of Pediatrics/American Heart Association clarification of statement on Cardiovascular evaluation and monitoring of children and adolescents with heart disease receiving medications for ADHD: May16, 2008. J Dev Behav Pediatr 2008 Aug; 29 (4): 335.

ADHD Drugs & Serious Cardiovascular Events in Children & Young Adults

- Cohort study, 4 health plans
  - Children & young adults (2 – 24 years) (N=1,200,438)
    - Current users of ADHD medications (N=373,667)
  - Serious Cardiovascular events (N=81) – Sudden cardiac death, stroke, acute MI
    - Users not at increased risk (Hazard Ratio = 0.75, CI= 0.31 – 1.85)
    - Current vs. former users not at increased risk (Hazard Ratio = 0.70, CI= 0.29 – 1.72)



Cooper WO et al. ADHD drugs and serious cardiovascular events in children and young adults. NEJM 2011;365(20):1896-1904.

Cardiovascular Effects

- 2022 study shows no statistically increased risk of ADHD medication and CV risk[1]
- Another 2022 study shows that ADHD is a risk factor for cardiovascular disease[2]
  - 5.3M adults from Swedish register
  - Born between 1941 and 1983
  - Looking at incidence from 2001-2013
  - 2.05x higher risk for all
  - After adjusting for many factors risk was 1.65x higher
  - Risk was similar with or without medication and family hx of CV disease
  - Strongest associations for
    - Cardiac arrest
    - Hemorrhagic stroke
    - Peripheral vascular disease/atherosclerosis
  - There is also an increased incidence of migraine headaches with ADHD

[1]Zhang L, Yao H, Li L, et al. Risk of Cardiovascular Disease Associated With Medications Used in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022;5(11):e2243597.

[2]Lin L, Chang Z, Sun J, Garcia-Argibay M, et al. Attention-deficit/hyperactivity disorder as a risk factor for cardiovascular diseases: a nationwide population-based cohort study. World Psychiatry. 2022;21(3);452-459.

Stimulants in Pregnancy

- Risk is low but studies are sparse
- Slight increased risk
  - Premature labor and delivery
  - Pre-eclampsia
- Mild to moderate symptoms: likely better to not take stimulants
- Severe symptoms: benefit may outweigh risk
  - Risk of traffic accident
  - Leaving the stove on
  - Getting fired from work
  - Starting smoking, alcohol, substances
  - Other children injured due to carelessness

Stimulants in Pregnancy

- 2023 Danish registry study of over 1M pregnancies from 1998 to 2015 followed until 2018
  - In utero exposure to ADHD medication and long-term offspring outcomes
  - Methylphenidate, amphetamine, dexamphetamine, lisdexamphetamine, modafinil, atomoxetine, clonidine users and discontinuers were compared
    - 898 exposed, 1270 mothers discontinued
  - Outcomes: neurodevelopmental psychiatric disorders, impairments in vision or hearing, epilepsy, seizures, growth impairment
  - No increased risk found (aHR 0.97, CI 0.81-1.17)
- 2021 Danish registry study over 360K pregnancies from 2007-2014
  - Associates Between ADHD Medication Use in Pregnancy and Severe Malformations Based on Prenatal and Postnatal Diagnoses: A Danish Registry-Based Study
  - Methylphenidate exposure not associated with increased risk of malformations overall (prevalence ratio 1.04)
  - Increased risk of cadiac malformations with NNH of 92 based on 12 cases (PR 1.65)

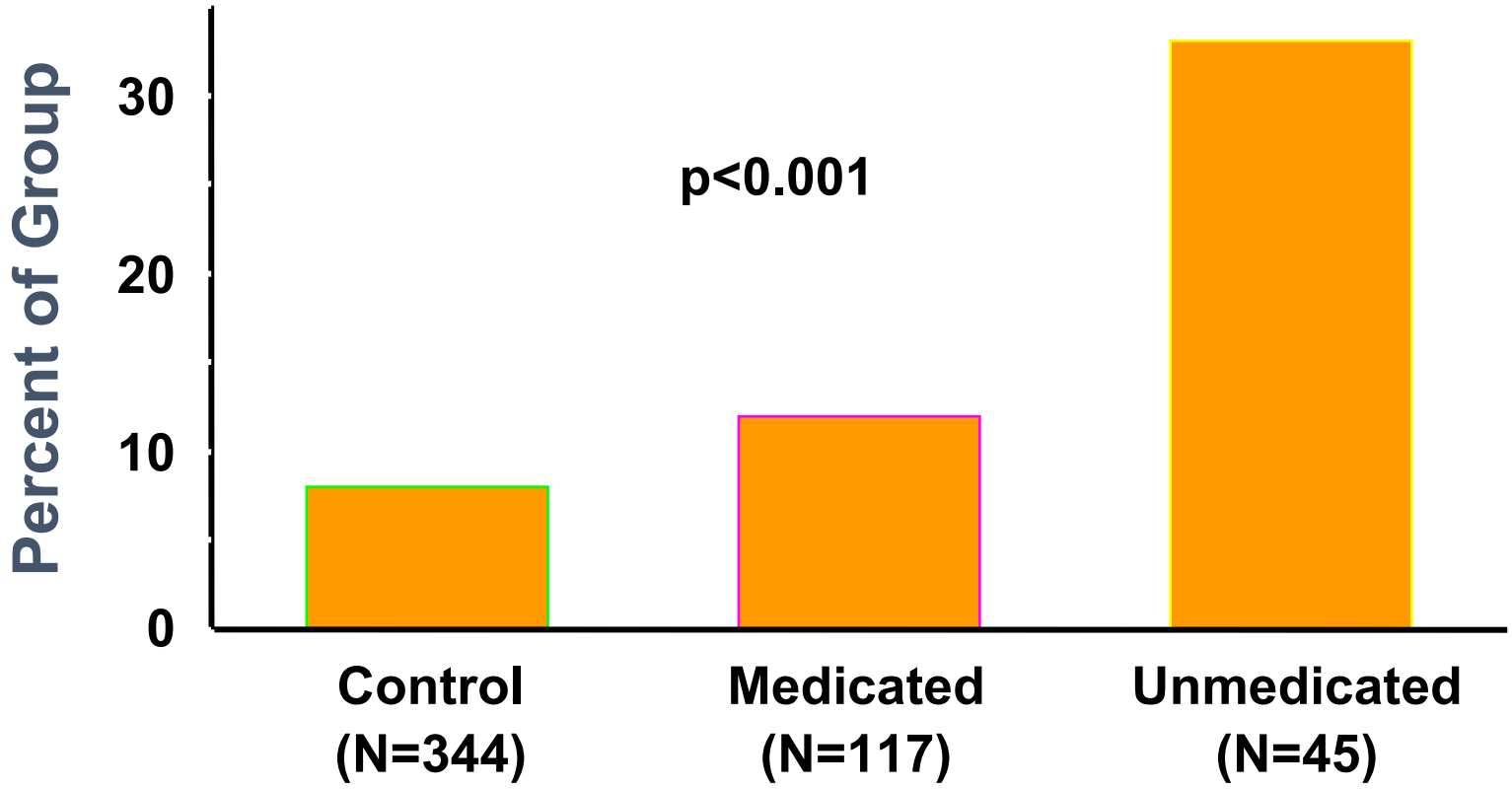
Suicidal Ideation

- FDA Warning (April 2015)
- Not a Black Box Warning
- Black Box Warning is a class warning for any medication that is FDA approved as an antidepressant
- While these medications are similar in action (especially with bupropion), they are not FDA approved as antidepresants and do not carry the same warning
- However, they do work in a similar way and can cause suicidal ideation, so please advise your patients and be vigilant
- In that same vein they can be helpful with depression symptoms

Substance Abuse & Black Box Warning

Abuse, Misuse, and Addiction

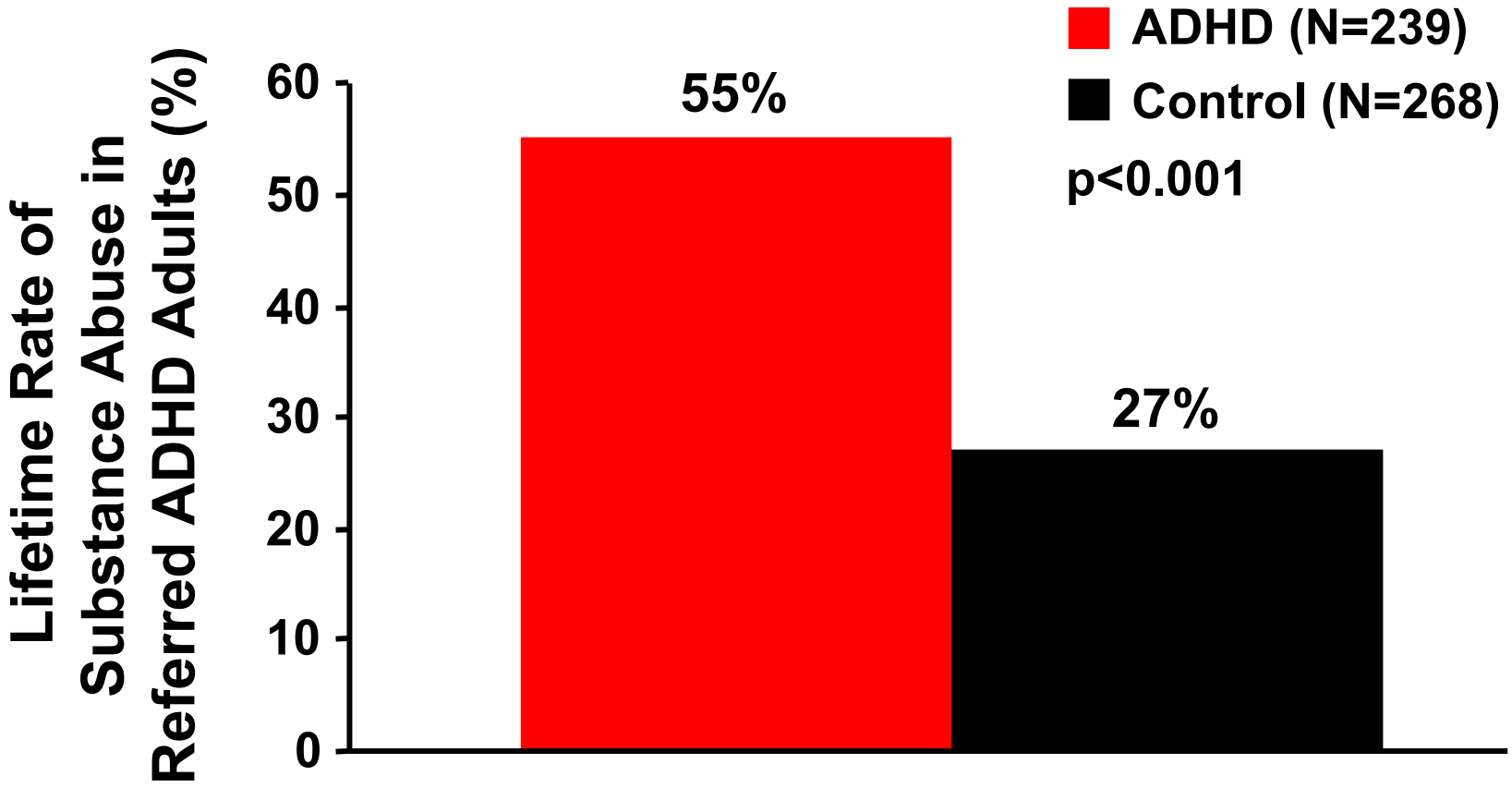
SUD in ADHD Youth Growing Up: Overall Rate of SUD



SUD = substance use disorder

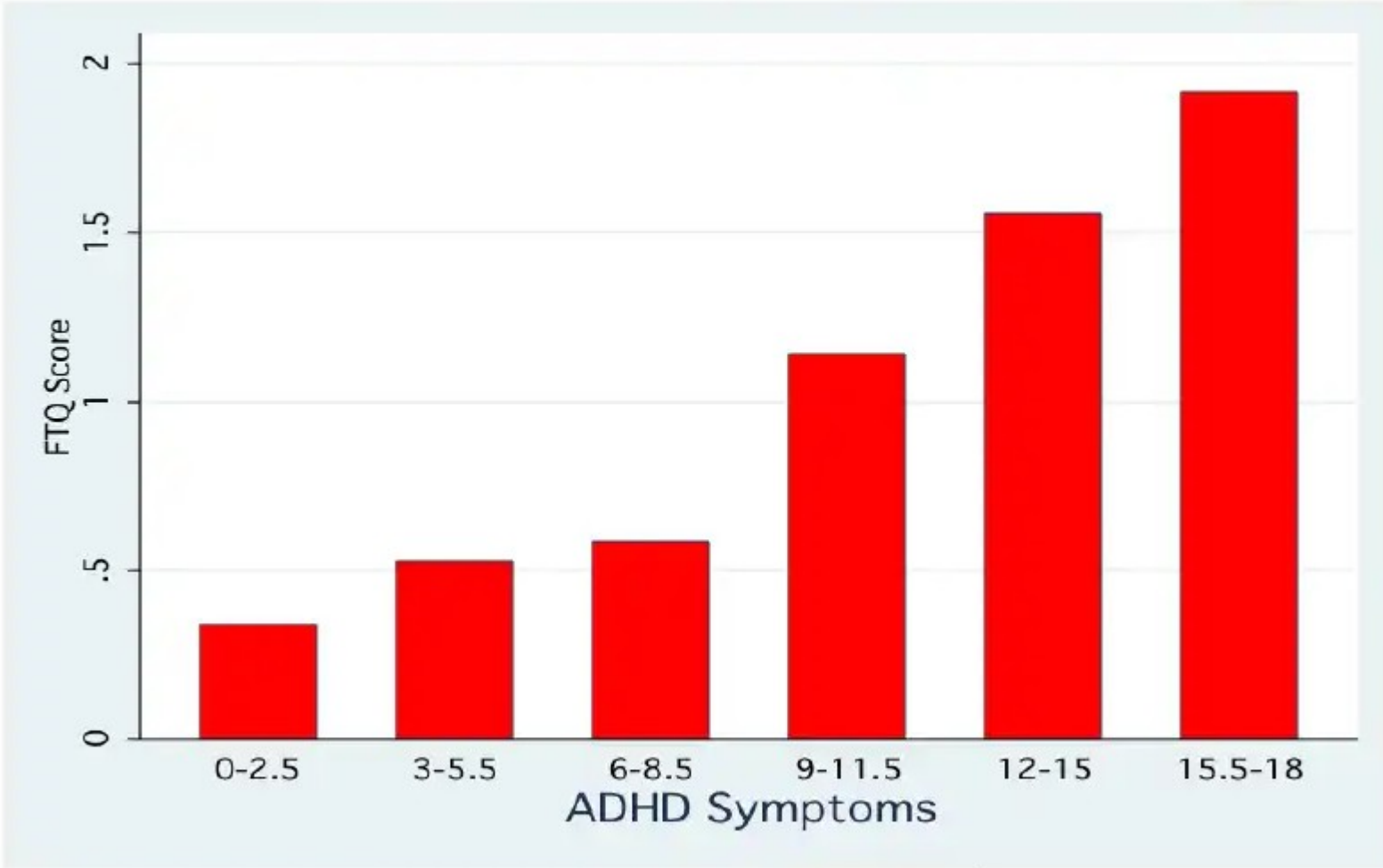
Biederman J, Faraone S, Milberger S, et al. J Am Acad Child Adolesc Psychiatry. 1996;35(3):343-351

Increased Lifetime Substance Abuse in Untreated Adults with ADHD



Biederman J, Wilens TE, Mick E, et al. Biol Psychiatry. 1998;44(4):269-273

ADHD Symptoms are Directly Related to Higher Smoking Scores



FTQ = Fagerström Tolerance Questionnaire.

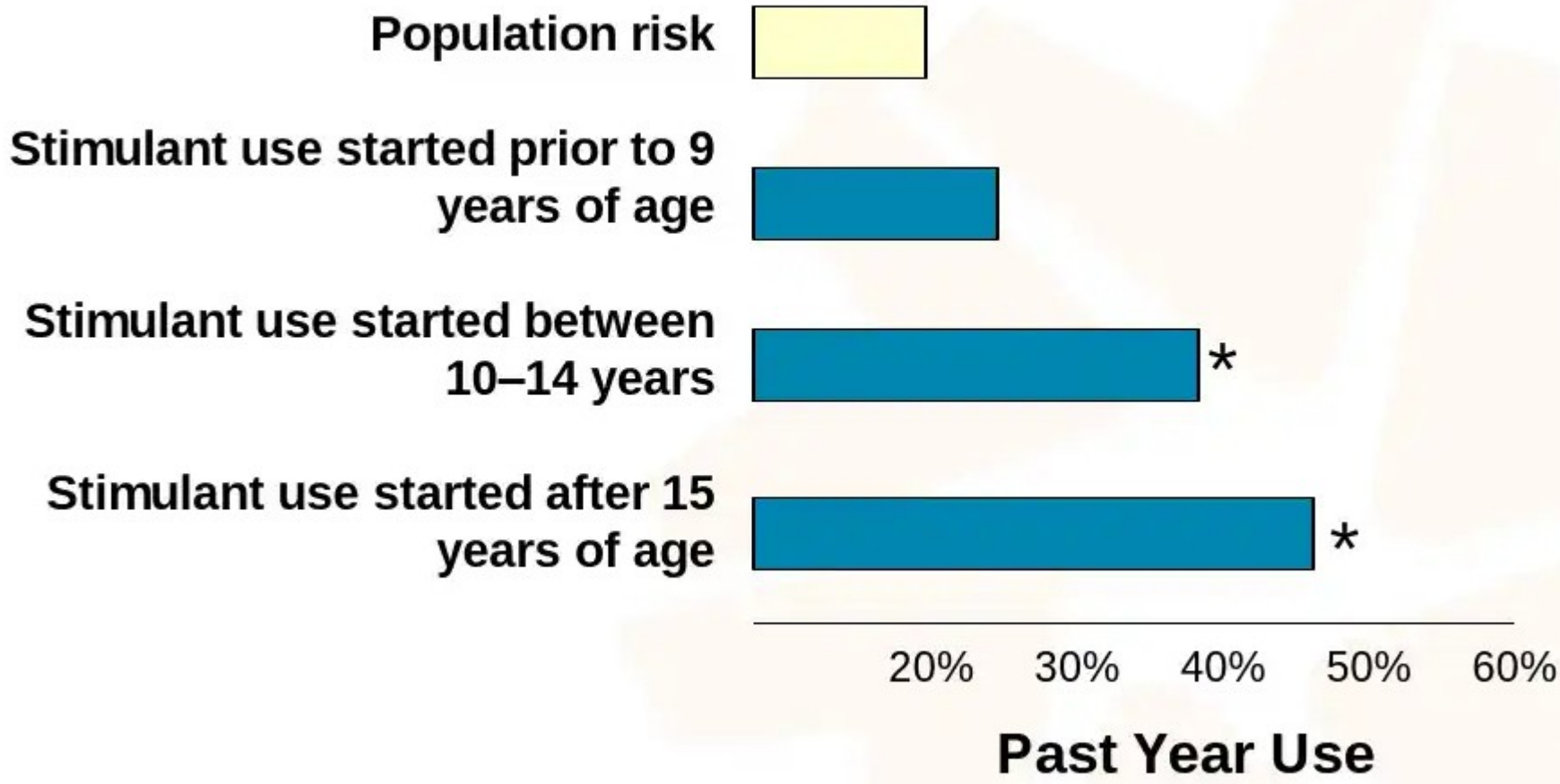
Wilens TE, et al. *J Pediatr*. 2008;153(3):414-419.

t = 5.00, $P < .001$

Long-Term Studies of ADHD: Stimulant Treated vs. Untreated and Subsequent Substance Use Disorders

Study	Country	Total: N	ADHD: N	Age	Main Findings Tx vs UnTx
Quinn et al., 2017	USA	146,000,000	2,993,887	15–42 yrs	Within group 
Sundquist et al., 2015	Sweden	551,164	9,424	Mean 15 yrs	Between group 
Chang et al., 2014	Sweden		38,753	8–46 yrs	Between group 
Steinhausen et al., 2014	Denmark		20,742	11–20 yrs	Between & within groups 

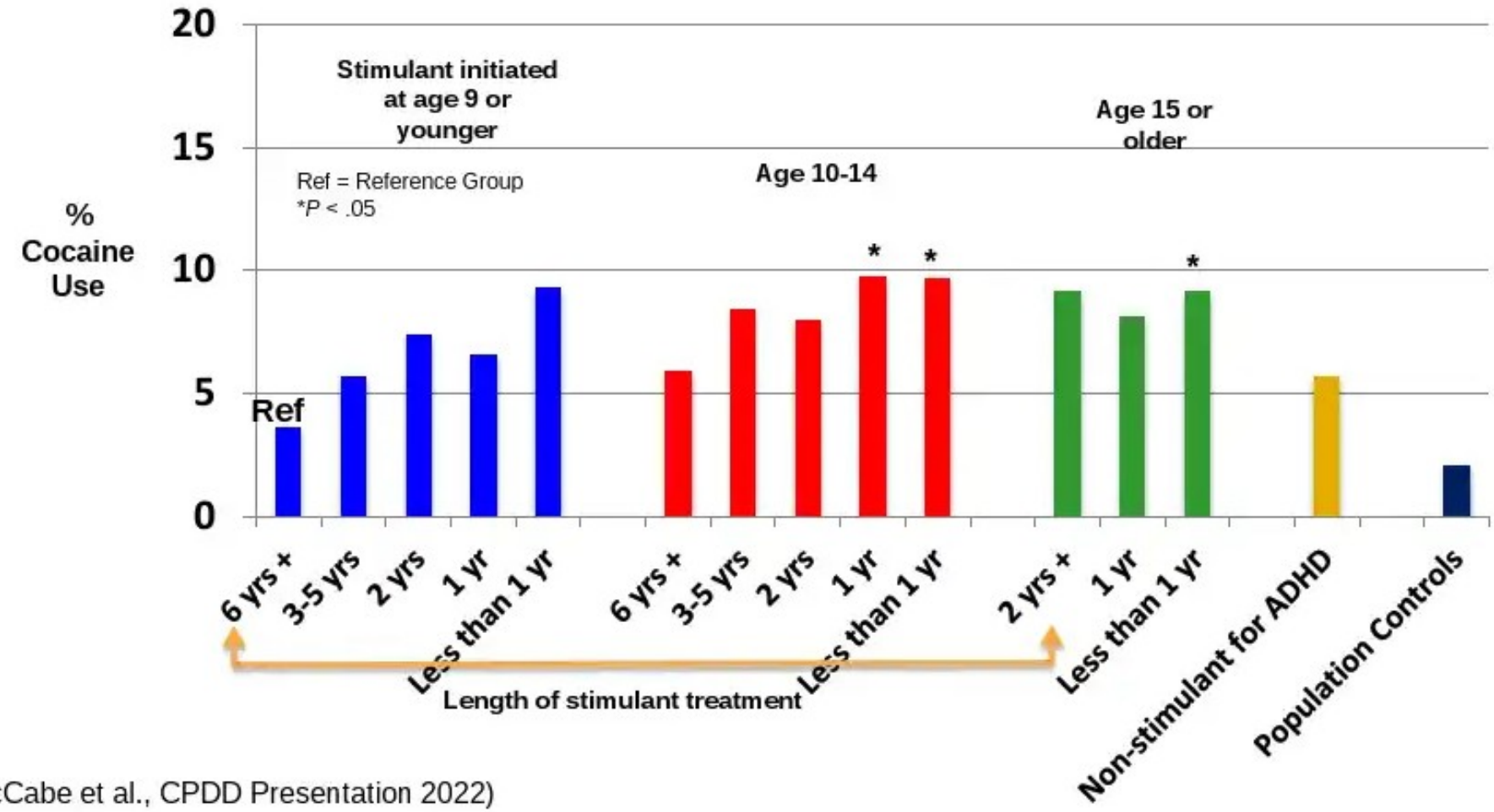
Early ADHD Treatment Reduces Marijuana Use



10 Cohorts of high school seniors 2005 to 2014 (N = 40,358; ~10% with ADHD).
*P < .001 vs controls.
McCabe SE, et al. *J Am Acad Child Adolesc Psychiatry*. 2016;55(6):479-486.

Early Onset ADHD Medication Treatment Does Not Increase Risk for Cocaine Use

(N = 132,164: Monitoring the Future Survey, 16 Cohorts of Secondary School Students 2005 to 2020)



(McCabe et al., CPDD Presentation 2022)

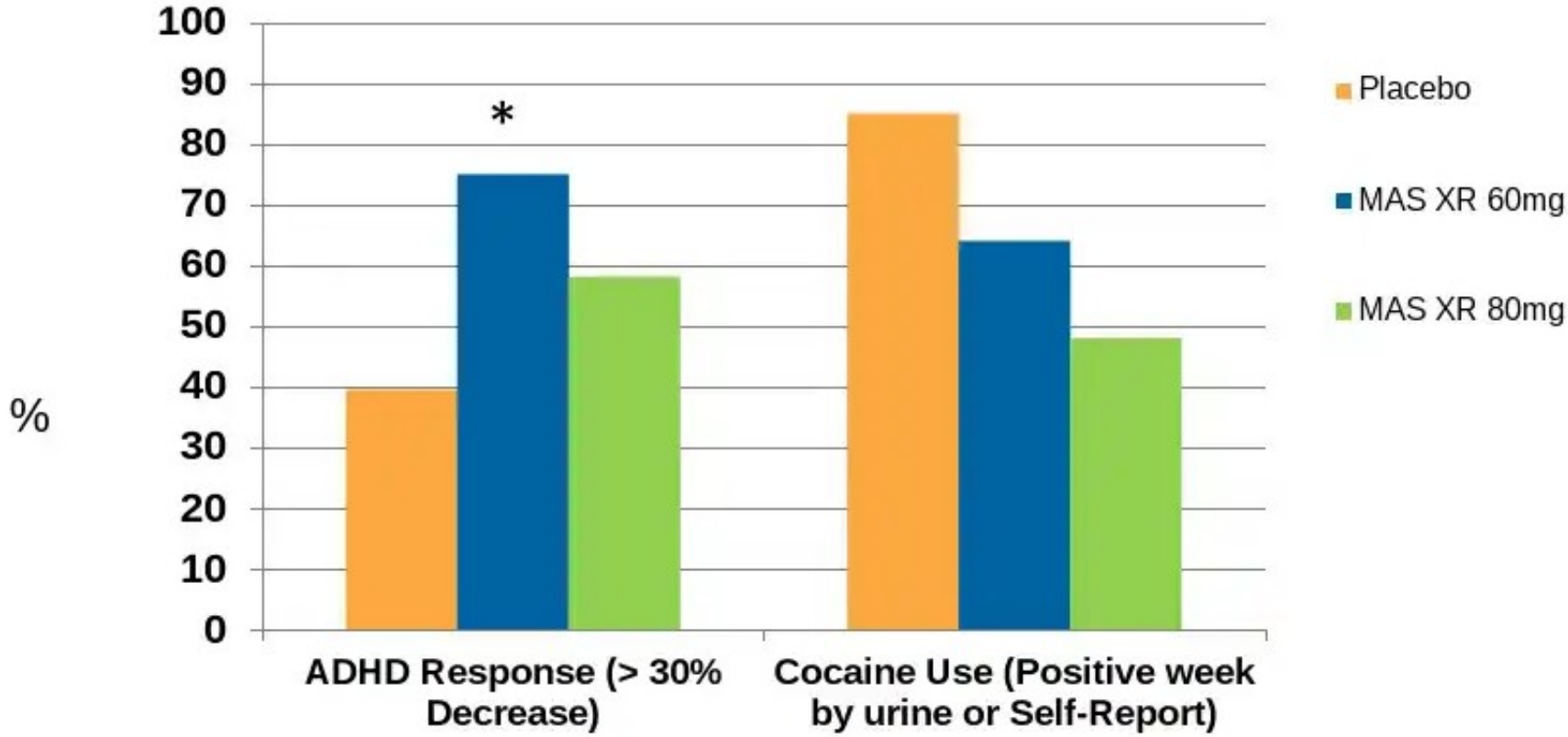
Diagnostic Dilemmas in ADHD and SUD

- Overlap symptoms of SUD in ADHD
  - Intoxication or withdrawal (30% worsening of ADHD)
  - Neuropsychological deficits (transient/permanent)
  - SUD "traits" misinterpreted as ADHD (eg, impulsive traits/risk-taking, harm avoidance)
- Other comorbidity (eg, anxiety, disruptive disorders)
- Reliability of retrospective report
- Subthreshold ADHD vs full ADHD
  - Age-of-onset criteria (NOS)
  - Effected domains, inadequate number of symptoms
- Concerns of drug-seeking behavior/rationalization
- Use of rating scales for ADHD helpful (eg, ASRS)

ASRS = Adult ADHD Self-Report Scale; NOS = not otherwise specified.

Levin FR, et al. *Drug Alcohol Depend*. 1998;52(1):15-25. Riggs PD. *Sci Pract Perspect*. 2003;2(1):18-29. Kaminer Y, et al. *Am J Addict*. 1999;8(2):114-119. Wilens TE, et al. *Curr Opin Psychiatry*. 2011;24(4):280-285. Faraone SV, et al. *Am J Psychiatry*. 2006;163(10):1720-1729. Faraone SV, et al. *Am J Addict*. 2007;16 Suppl 1:24-32.

Higher Dose MAS XR Is Helpful in ADHD and Cocaine Use Disorder in Patients with OUD

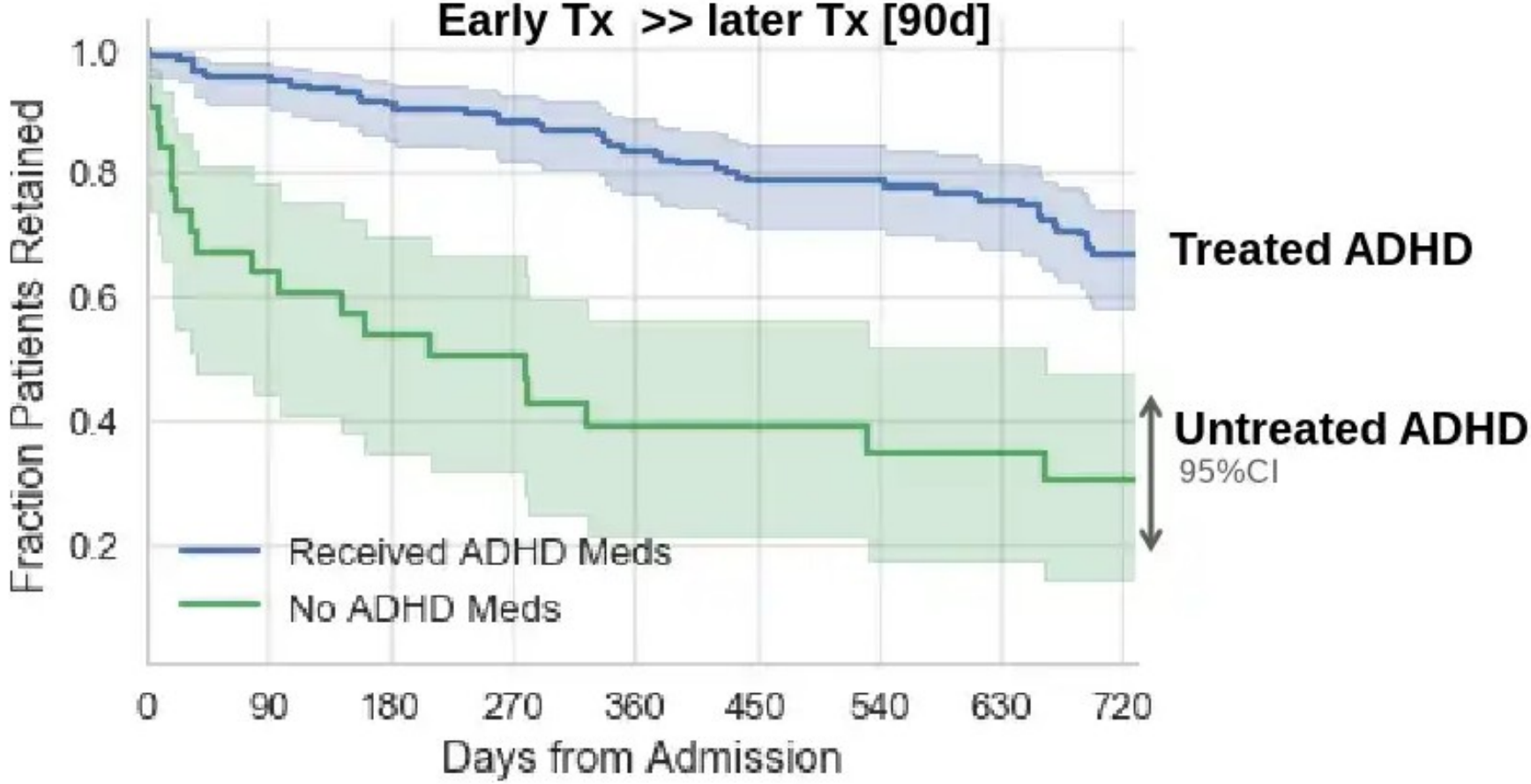


13-week RCT
Diagnosis: Cocaine Use Disorder and ADHD
Treatment: CBT +/- MAS XR

N = 126. *$P < .05$.
Levin FR, et al. *JAMA Psychiatry*. 2015;72(6):593-602.

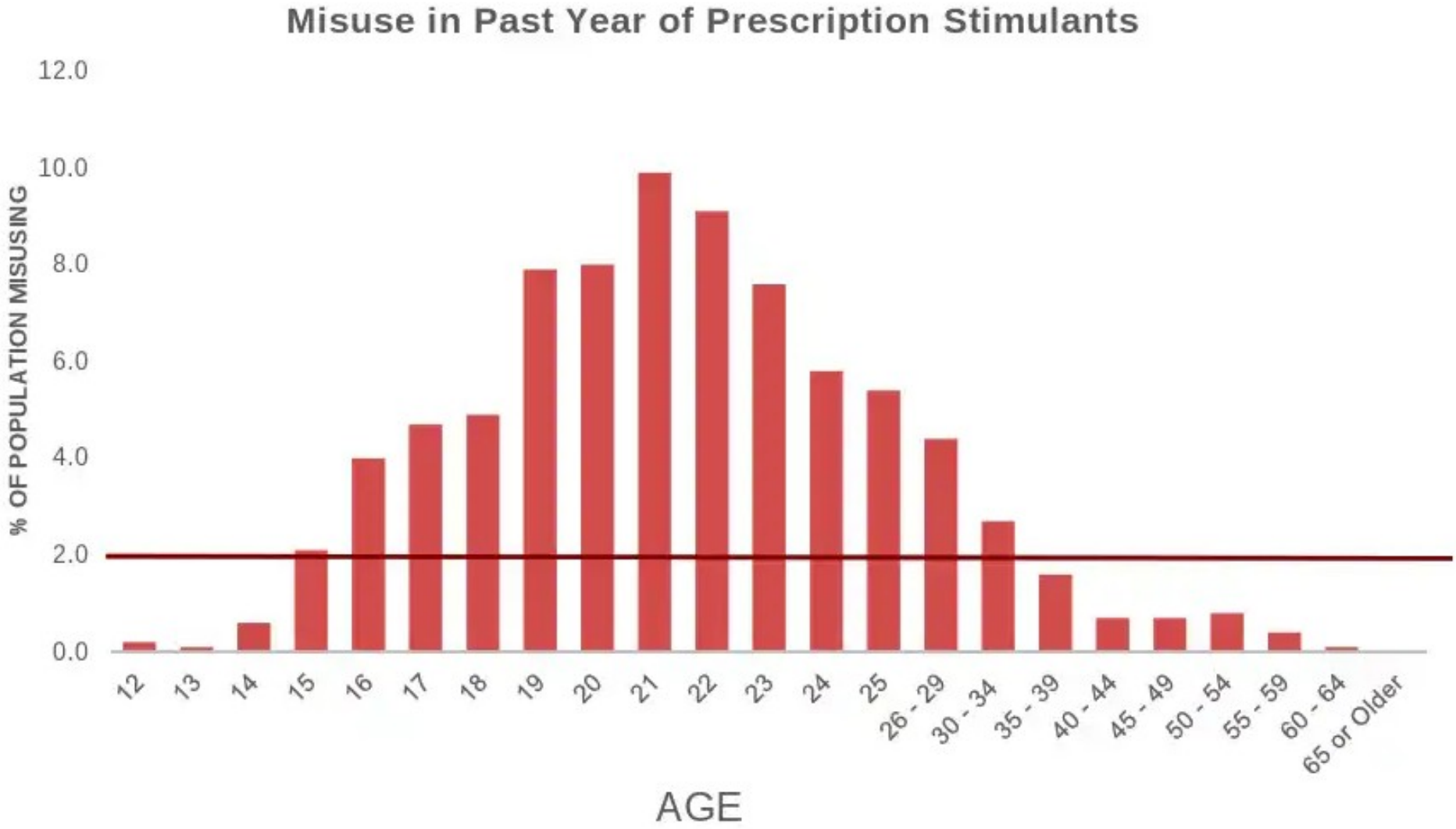
MGH Study: Treatment of ADHD Improves Retention in SUD Treatment

N=171 Treated ADHD
N=32 Untreated ADHD
Early Tx >> later Tx [90d]



(Kast K, Rao V, Wilens T. J Clin Psych: 2021)

Stimulant Misuse Peaks at Age 21
10% of the Population Reporting Lifetime Stimulant Misuse



Source: SAMHSA, Center for Behavioral Health Statistics & Quality, National Survey on Drug Use and Health, 2015

Stimulant Misuse and Diversion

- N > 120 studies; mostly survey studies in college students (80%)
- 10% to 20% prevalence of nonmedical use of stimulants
- 65% to 85% of stimulants diverted from “friends”
  - Majority not “scamming” local doctors
  - Not seen as potentially dangerous

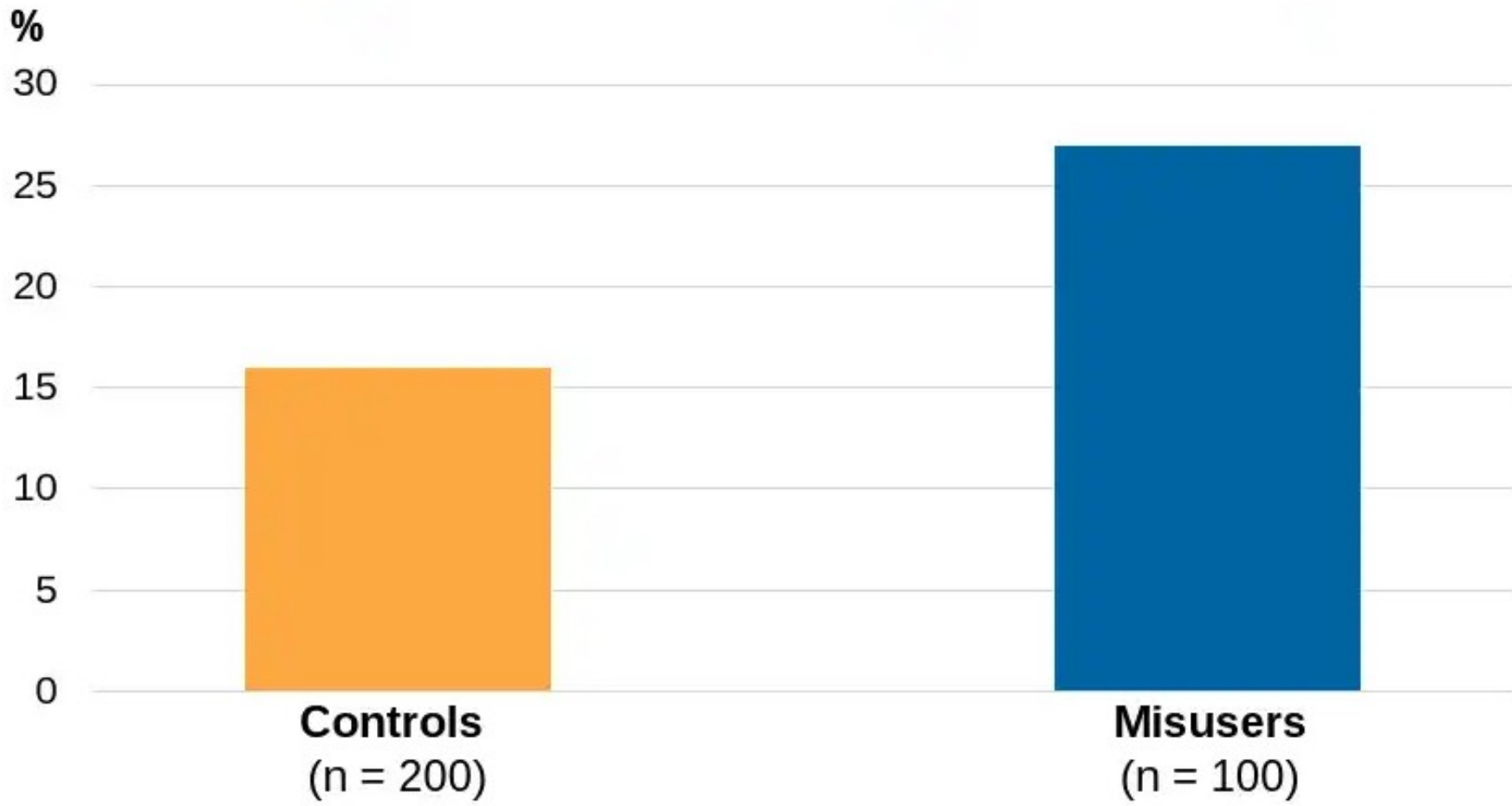
McCabe SE, et al. *Addiction*. 2005;100(1):96-106. Arria AM, et al. *Subst Abus*. 2008;29(4):19-38. Wilens TE, et al. *J Am Acad Child Adolesc Psychiatry*. 2006;45(4):408-414. Wilens TE, et al. *J Am Acad Child Adolesc Psychiatry*. *J Am Acad Child Adolesc Psychiatry*. 2008;47(1):21-31. Wilens TE, et al. *J Clin Psychiatry*. 2016;77(7):940-947. : Faraone et al. J Am Acad Child Adoles Psych, 2020).

Reasons for Misusing Stimulants (N=100)

To help concentrate or focus better	79%
To stay awake	62%
To reduce distraction	56%
To get more energy	48%
To experiment – to see what it's like	42%
To have a good time with my friends	22%
To feel good or get high	21%
To get through the day	12%

(Wilens et al. Am J Addictions 2020)

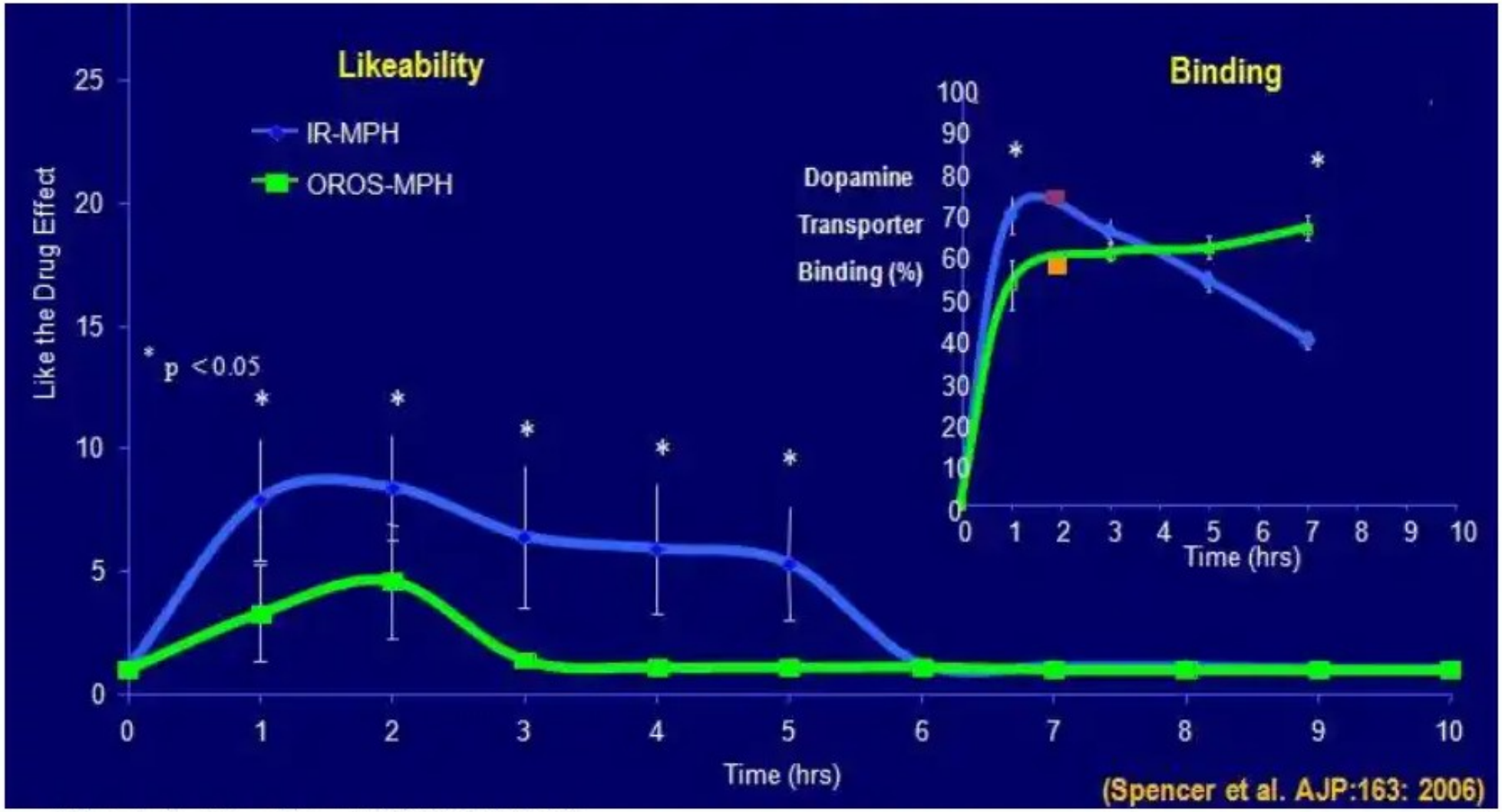
Rates of ADHD are Higher in College Students Who Misuse Stimulants Compared to Controls



N = 300. *Subthreshold + full diagnosis of ADHD.
Wilens TE, et al. *J Clin Psychiatry*. 2016;77(7):940-947

Immediate Release Stimulants Linked to Dopamine Transporter Binding and More "Drug" Likeability

40 mg IR-MPH vs 90 mg OROS MPH



Spencer TJ, et al. *Am J Psychiatry*. 2006;163(3):387-395.

Pharmacotherapy for ADHD and SUD Risk

- 2022 meta-analysis of 21 studies examining the impact of pharmacotherapy and later SUD in ADHD
- 14 studies showed reduced risk of SUD
- 10 studies showed no effects
- 2 studies showed enhanced effects
- Studies reported that earlier-onset and longer-duration treatment was associated with the largest risk reduction for later SUD
- Overall reduced risk of SUD by 30%
- Caution in high-risk populations
  - Current substance use disorder
  - 1st degree relative with substance use disorder

Wilens TE et al. The Impact of Pharmacotherapy of Childhood-Onset Psychiatric Disorders on the Development of Substance Use Disorders. Journal of child and Adolescent Psychopharmacology. 2022;32(4):200-214.

Things Practitioners and Parents Can Do to Curtail Prescription Drug Misuse

- It is important to monitor symptoms and prescription refills for evidence of misuse or diversion of ADHD medication
- Consider non-stimulants and extended-release or prodrug stimulants in higher risk groups
  - Lisdexamfetamine, serdexmethylphenidate are prodrugs
  - OROS capsule is extremely difficult to release all at once
- Don’t overprescribe quantity (ie stockpile, reservoir)
- It is also helpful to have an open discussion about stimulant diversion and misuse with patients and parents so that students can be prepared if they are approached by peers to sell or misuse medications and so that parents can remain vigilant in monitoring medications

Things Practitioners and Parents Can Do to Curtail Prescription Drug Misuse

- Discussion points include
  - Taking the medication exactly as prescribed (both the dose and the frequency)
  - Letting the clinician know if the medication does not seem to be working
  - Avoiding alcohol, tobacco, marijuana, and other illicit substances (may interact with stimulants and exacerbate attention problems)
  - Learn and communicate the medical, psychological, addictive, legal issues of prescription drug misuse
  - Administering medication at school in a safe location with adult supervision (eg, school nurse's office)
  - Safe storage (not in medicine cabinets)
  - Not being coerced/tempted into selling it or giving it away
  - Confidentiality: "Don't advertise you are on stimulants"
  - A plan for transition of responsibility for administering stimulant medication from the parent to the child or adolescent

Non-Stimulants

Why Nonstimulant Treatments for ADHD?

Problems with the Stimulants

- Schedule II drugs (abuse liability, diversion, medical legal concerns) but potentially less with lisdexamfetamine and serdexmethylphenidate
- 10-20% do not adequately respond or cannot tolerate stimulant treatment
- Short duration of action (compliance, embarrassment)
- Side-effect profile adversely impacting sleep, appetite, mood and anxiety
- Concerns about growth suppression and tic development

Spencer T, Biederman J. J Atten Disord. 2002;6(suppl 1):S109-S119

Non-Stimulants

- Selective Norepinephrine Reuptake Inhibitors
  - Atomoxetine (Strattera®)
  - Viloxazine (Qelbree®)
- Alpha (α_{2A}) Adrenergic Agonists
  - Clonidine: binds α_{2A} and α_{2C} more equally
    - IR: Catapres® (1966) [off-label] (branded product discontinued) (BID/TID/QID)
    - XR: Kapvay® (2010) (BID)
    - XR: Onyda XR (2024) (available in liquid) (QHS)
  - Guanfacine: more selective to α_{2A} receptor
    - IR: Tenex® (2002) [off-label]
    - XR: Intuniv® (2009)
- Antidepressants
  - Tricyclic Antidepressants: Imipramine, Desimpramine [off-label]
- NDRI
  - Bupropion (Wellbutrin®) [off-label]
  - Solriamfetol (Sunofi®)[off-label]
- Saffron

Non-Stimulant Treatments for ADHD

Atomoxetine and Viloxazine

- Selective Norepinephrine Reuptake Inhibitors
  - Increases NE and DA in prefrontal cortex
  - Does not increase DA in the pleasure center
- FDA approved for ADHD in children/adults 6 years or older
- **BBW** added in 2005 similar to that for antidepressant
  - Subsequent studies have failed to replicate the finding
- Dosing guidelines
  - Weight based for atomoxetine
  - Age based for viloxazine
- Metabolized in liver
  - Cytochrome P450 2D6 pathway
    - Caution with use of atomoxetine in poor metabolizers and with 2D6 inhibitors; consider genomic testing
- Effect size
  - Atomoxetine: ~0.7 (children), 0.44 (adolescents and adults)
  - Viloxazine: ~0.6
- Monitor BP, HR, (BL EKG ?)

Non-Stimulant Treatments for ADHD

Atomoxetine (Strattera®) (2002)

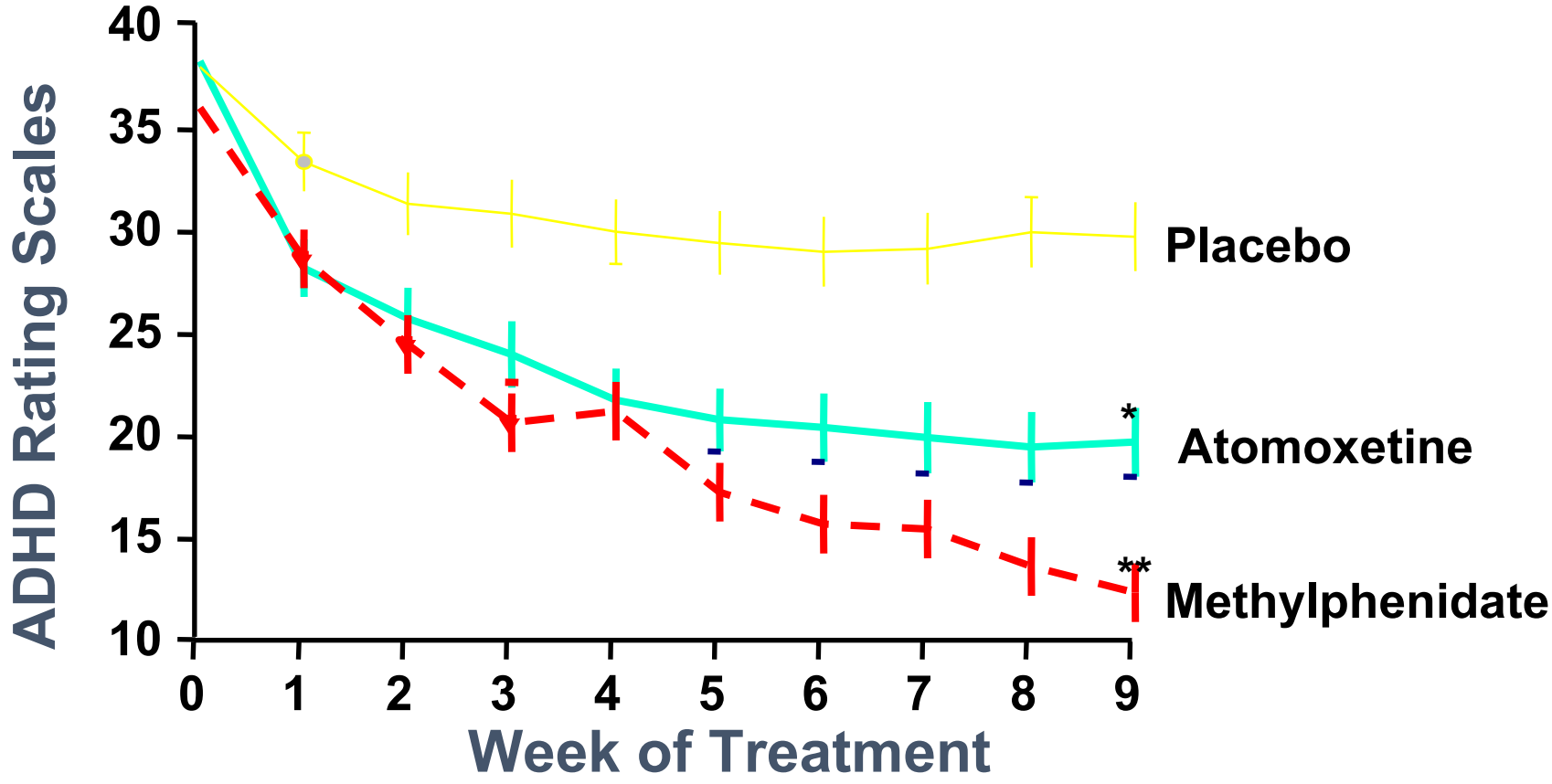
- May be used 1st line if patient or household member has history of substance abuse
- May be useful with tics
- May be used 2nd line if severe side effects to stimulants
  - Mood changes, >5% weight loss compared to baseline, abnormal blood pressure, agitation, psychosis
- More time to steady state
  - Up to two weeks for initial response, up to eight weeks for maximal effect
- "Drug holidays" are not an option due to loss of effect
- Requires dosing adjustment if administered with agents that inhibit the cytochrome P450 2D6 enzyme (ie fluoxetine, paroxetine, bupropion)
- Use caution in patients who may have bipolar disorder
  - However does not affect serotonin

ADHD Atomoxetine Dosing*

	Initial Dose	Target Dose	Maximum Dose
≤ 70 kg	0.5 mg/kg/day	1.2 mg/kg/day	1.4 mg/kg/day (Max 100 mg/day)
≥ 70 kg	40 mg/day	80 mg/day	100 mg/day

* Daily or BID Dosing

Pooled Results: Effect on Conner's Adult ADHD Rating Scale



P<0.05 for atomoxetine vs. PBO Weeks 1 through 9; **p<0.05 for MPH vs. PBO Weeks 3 through 9 atomoxetine vs. methylphenidate not statistically significantly different at any visit; Michelson et al.
Biol Psychiatry. 2003 (Jan 15); 53(2):112-120

Non-Stimulant Treatments for ADHD

Viloxazine ER (Qelbree®) (2021)

- Mechanism of action
  - Modest NRI properties
  - 5-HT2B antagonism (antidepressant?)
  - 5-HT2C agonism (antidepressant?)
  - 5-HT7 antagonism (antidepressant?, pro-cognitive?)
  - Increases levels of 5-HT, NE, and DA in prefrontal cortex
- **Strong inhibitor of CYP1A2 and weak for CYP3A4**
- May work a little quicker than atomoxetine
- Viloxazine was used in Europe since 1974 for depression dosed TID
- Discontinued in 2002 unrelated to efficacy or safety
- Initiate 200mg daily, may increase by 200mg weekly to max of 600mg

Atomoxetine/Viloxazine Side-effect Profile

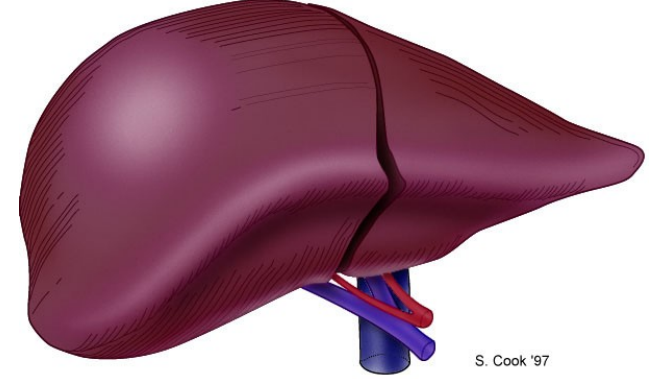
Common

- **Children**
  - Abdominal pain
  - Anorexia
  - Nausea/Vomiting
  - Fatigue/Somnolence
  - Mood swings

Adults

- Increased BP
- Constipation
- Dry mouth
- Nausea/Vomiting
- Anorexia
- Dizziness
- Insomnia
- Decreased libido
- Urinary problems
- Menstrual cramps

Risk of Hepatotoxicity for Several Common Medications



- Valproic Acid (Polytherapy) 1 : 12,000
- Valproic Acid (Monotherapy) 1 : 50,000
- Felbamate 1 : 25,000
- Pemoline 1 : 100,000
- Atomoxetine
  - Hepatic events associated with atomoxetine treatment for ADHD
    - 7961 patients treated with atomoxetine in trials
    - 41 had hepatobiliary events requiring analysis
    - Most were mild increases in ALT and AST
    - No cases of liver failure
    - In the 4 years after FDA approval there were 3 cases identified as probable cause of liver injury
      - 1 case had a positive rechallenge; all 3 recovered
    - Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted
      - No adjustment for Child-Pugh class A; reductions for B and C

Non-Stimulant Treatment of ADHD

Alpha-2-Adrenergic Agonists

- MOA: Unclear. Low level or excessive level of release of norepinephrine may disrupt cognitive functioning
- Effect size as much as 1.3 if optimized
- Useful in combination with stimulants for sleep disturbances, aggression, conduct disorder, and those with partial response to stimulants
- May be useful in over-aroused, easily frustrated, highly active, or aggressive individuals
- Addition of guanfacine/clonidine to stimulant therapy
  - May help offset some of the common stimulant side effects (wakefulness, BP/HR)
  - May help with stimulant off time
- Can be used for tic disorders including Tourette's
- No known abuse potential
- More time to steady state (up to two weeks for initial response)
- "Drug holidays" are not an option
- May take without regards to food
- Patch applied in a different area every 7 days
- Requires taper as it affects blood pressure

Non-Stimulant Treatment of ADHD

Alpha-2-Adrenergic Agonists

- Guanfacine (Intuniv®)
  - More selective for α_{2A}-receptor as compared with clonidine
    - α_{2A}-receptor agonism can help with attention and cognition
  - Less sedation
  - Once daily guanfacine (Intuniv®) available
  - High-fat meal taken with Intuniv® can raise C_{max} by 75% and AUC by 40%
  - Can lead to fatigue and hypotension
  - Few reports of sudden death in children seen with clonidine + methylphenidate
    - Not contraindicated
    - Need to screen patient, family hx of cardiac issues, BP, HR, EKG

Non-Stimulant Treatment of ADHD

Alpha-2-Adrenergic Agonists

- Clonidine (Kapvay®, Onyda®)
  - More equal binding of α_{2A}- and α_{2C}-receptor as compared with guanfacine
    - α_{2C}-receptor agonism has more effect on blood pressure
    - May help with impulsivity and hyperactivity
  - May block the autonomic symptoms in anxiety and panic disorders and improve subjective anxiety as well
  - May be useful in decreasing the autonomic arousal of PTSD
  - May be useful as an as needed medication for stage fright or other predictable socially phobic situations
  - May improve social relationships, affectual responses, and sensory responses in autistic disorder
  - Kapvay® is often used for insomnia in children; still BID needed for 24 hr coverage
  - Longer-acting (Onyda XR®) form is just dosed once a day at night

ADHD Alpha-2-Adrenergic Agonist Dosing

	Initial Dose	Target Dose	Maximum Dose
Kapvay®	0.1 mg Daily	0.1 mg Daily to BID	0.4 mg Daily (divided)
Onyda XR®	0.1 mg QHS	0.1-0.2 mg QHS	0.4 mg QHS
Intuniv®	1 mg Daily	1 to 7 mg Daily	7 mg Daily

Non-Stimulant Treatment of ADHD
Alpha-2-Adrenergic Agonists: Adverse Effects

- Common
  - CNS: Sedation, drowsiness, depression, nervousness, agitation, headache, weakness, fatigue
  - GI: Dry mouth, constipation, weight gain
  - Cardiac: orthostatic hypotension
  - Skin: rash
  - Genitourinary: Nocturia, sexual dysfunction
  - Hepatic: Abnormal LFTs
- Rare
  - Cardiac: Palpitations, tachycardia, bradycardia, CHF
  - CNS: Vivid dreams, nightmares, insomnia, delirium
  - GU: Urinary retention; blurred vision; gynecomastia (ie stimulates growth hormone release)

Non-Stimulant Treatments for ADHD

Tricyclic Antidepressants

- MOA: mediated by 5-HT and NE reuptake blockade but more selective for NE
  - Imipramine, desipramine
  - No abuse potential, less sleep problems, no growth suppression
  - Baseline BP, HR, EKG needed in children & at maintenance
    - Consider alternative Therapy & cardiology consult if
      - PR >200 ms, QRS >120 ms, or QTc >460 ms
      - if symptoms such as palpitations, near syncope, or syncope develop
  - Takes 4-6 weeks to see effect
  - Can also use SNRI

Non-Stimulant Treatments for ADHD
Bupropion

- MOA: NE and DA reuptake inhibitor
- Metabolized to an active metabolite that has more powerful NE reuptake blocking effects than bupropion
- Takes 4-6 weeks to see effect
- Take without regards to food

Non-Stimulant Treatment of ADHD
Bupropion

- Advantages
  - May decrease hyperactivity and aggression
  - Beneficial in comorbid depression/anxiety and avoidance of sexual dysfunction
  - Other: Cardiac issues in adults, smoker wanting to quit
  - May improve cognitive performance
  - Low abuse potential
- Disadvantages
  - May decrease seizure threshold (> 6 mg/kg/dose)
  - May exacerbate tics
  - Avoid in patients with eating disorders
  - Relative-contraindication: Headaches
  - Monitor BP, HR, EKG in children
  - Minimal to modest benefit

ADHD Practice Parameters. J Am Acad Child Adolesc Psychiatry. 1997;36:85S; Biederman. J Clin Psychiatry. 1998;59(suppl 7):4

Non-Stimulant Treatments for ADHD
Solriamfetol

- MOA
  - NE and DA reuptake inhibitor
  - Some TAAR1 agonism
  - Likely has strong action on DAT than bupropion
- Takes 3-6 weeks to see effect
- Solriamfetol for Attention-Deficit/Hyperactivity Disorder in Adults: A Double-Blind Placebo-Controlled Pilot Study. J Clin Psychitry. 2023
  - 60 adults, 6 week, 75mg or 150mg
  - No significant effects on BP or HR
  - 45% vs 6.9% placebo reduced AISRS scale

Future Treatment of ADHD

Centanafadine

- Currently undergoing Phase III clinical trials for ADHD in adults
- Would be the first approved SNDRI
  - Inhibits reuptake of norepinephrine, dopamine, and serotonin in ratio of 1:6:14
- Considered to be a stimulant with non-stimulant characteristics
- Effect size range for adults: 0.24-0.4
  - Comparable to bupropion and atomoxetine
- Reported effect within 1 week
- Reported low risk for dependence
  - May be due to dose tolerance effects of SRI activity
  - Tentatively to be Schedule IV due to DAT activity but likability is very low

"Efficacy, Safety, and Tolerability of Centanafadine Sustained-Release Tablets in Adjults With Attention-Deficit/Hyperactivity Disorder." J Clin Psychopharmacol. 2022 Sep-Oct; 42(5): 429-439.

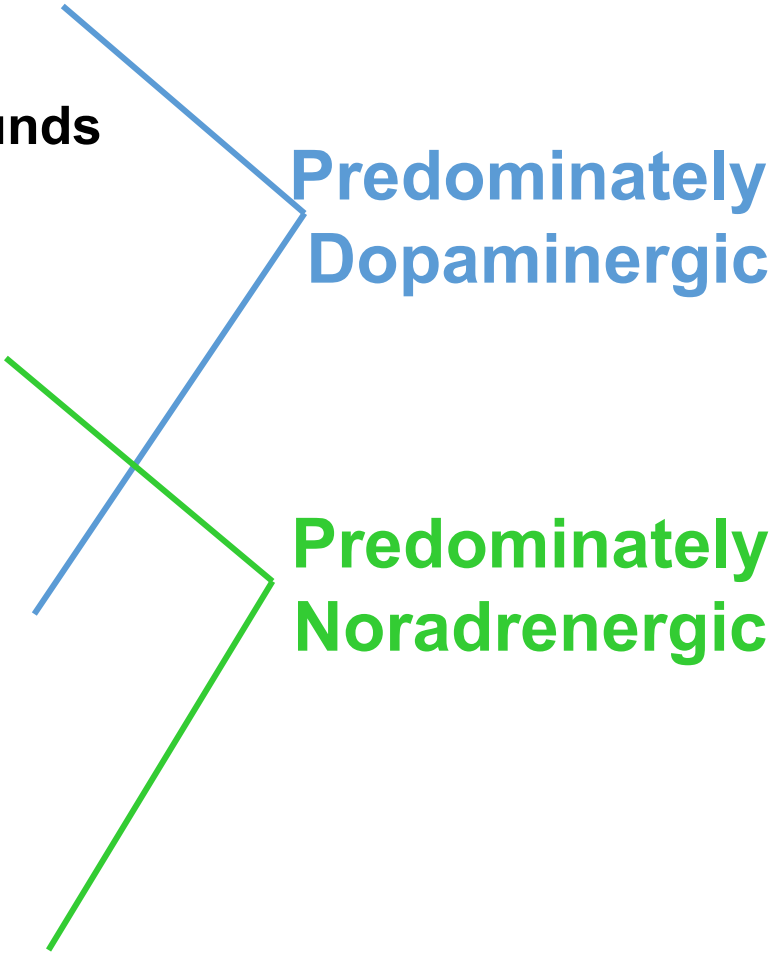
Pharmacologic Agents Used in Treatment of ADHD

Stimulants
- **Methylphenidate**
- **Amphetamine compounds**
- **Modafinil/Armodafinil**
- ***Magnesium pemoline***

Antidepressants
- **Bupropion**
- **Tricyclics**

Antihypertensives
- **Clonidine**
- **Guanfacine**

Other
- **Atomoxetine**



Wilens TE, Biederman J, Spencer TJ. Annu Rev Med. 2002;53:113-131

Nonstimulant Treatments for ADHD

Saffron

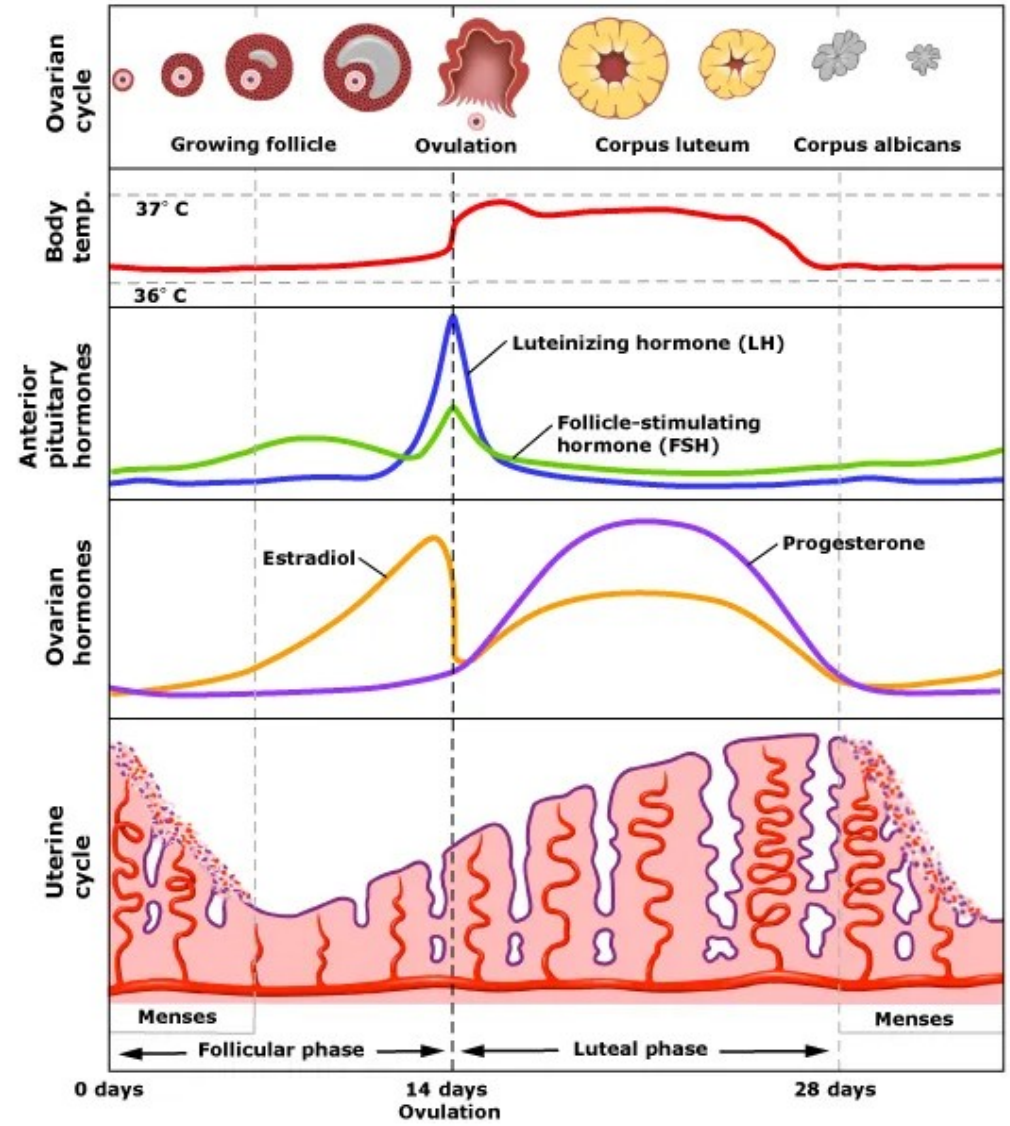
- NDRI
- NMDA antagonism
- $GABA_A$ agonism
- May be as effective as methylphenidate for ADHD

Blasco-Fontecilla H et al. Effectivity of Saffron Extract (Saffr'Activ) on Treatment for Children and Adolescents with Attention Deficit/Hyperactivity Disorder (ADHD): A Clinical Effectivity Study. Nutrients. 2022 Sep 28;14(19):4046.

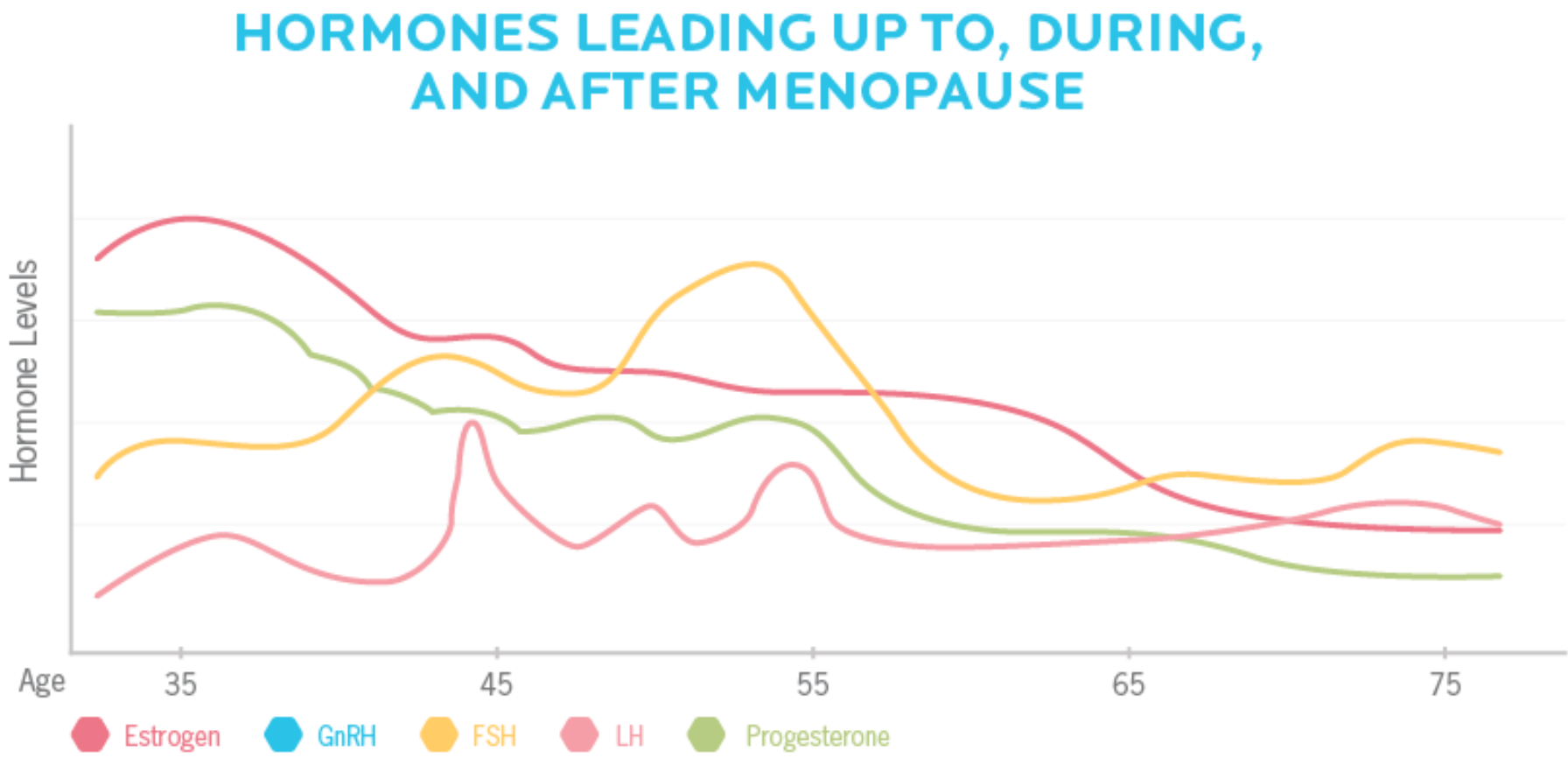
Effects of Estrogen on ADHD

Effect of Estrogen on ADHD Symptoms

- Follicular Phase
  - Estrogen levels steadily increasing
  - ADHD symptoms at their lowest
  - Possibly more responsive to ADHD medications (experienced as more stimulating by NT females)
- Luteal Phase
  - Progesterone increasing while estrogen decreases
  - ADHD symptoms increase
  - PMDD worse than NT females
  - Possibly decreasing effectiveness of ADHD medications
- Menses
  - Estrogen at its lowest
  - ADHD symptoms at their worst



Hormone Levels over the Lifetime



Estrogen Level Fluctuations over the Lifetime

- Perimenopause
  - Cycle irregular
  - Average age: 47
  - Duration: 4-10 years
- Menopause
  - Moment of final cycle
  - 12 months after last cycle
  - Average age: 51
- Postmenopause
  - Time after menopause

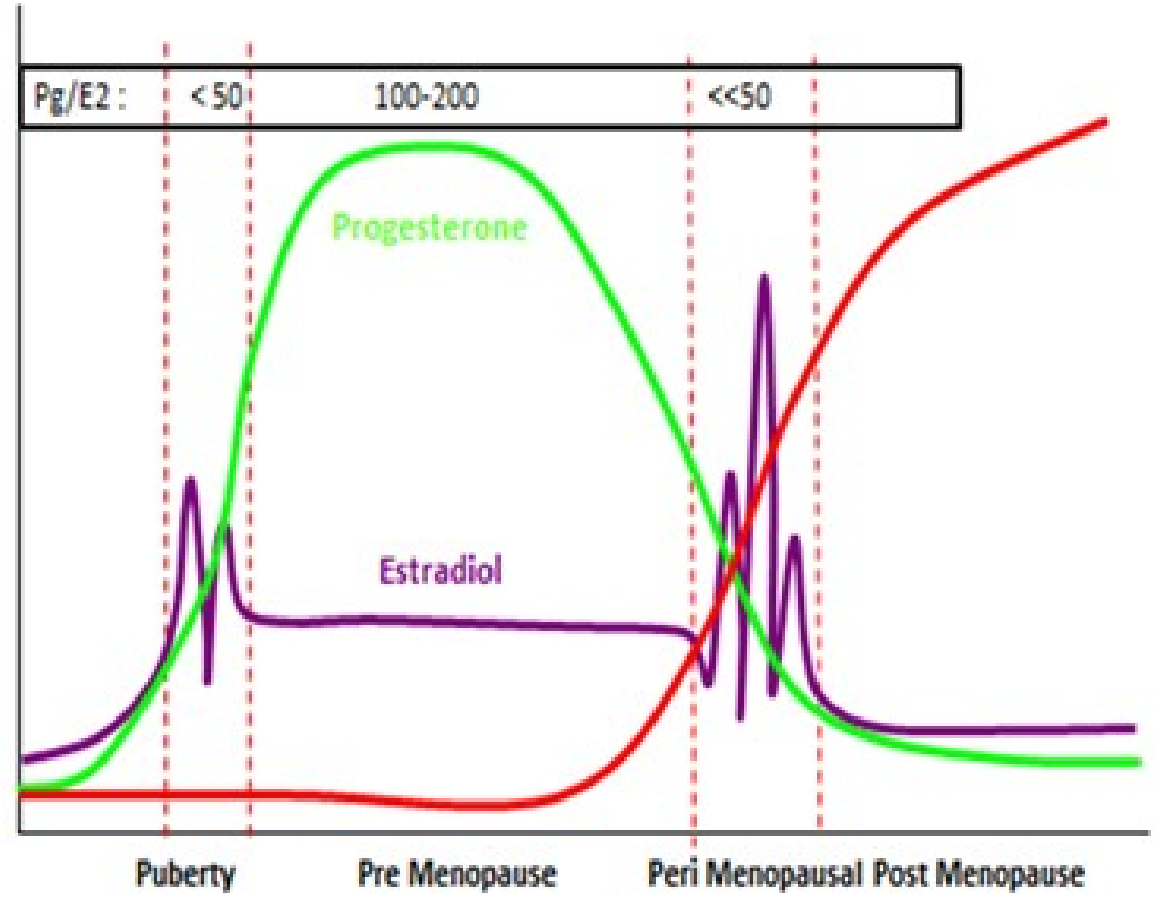


Fig. 1 Fluctuations in estradiol and progesterone across the female lifecycle.

Overlap in Menopause and ADHD Symptoms

- Symptoms of menopause
  - Hot flashes, night sweats
  - Irregular periods
  - Sleep problems
  - Weight gain
  - Mood lability, anxiety
  - Loss of libido, vaginal dryness
  - Impaired attention, concentration, memory
  - Bone loss*
  - Depression*
  - Urinary infections*
  - Heart disease*
  - Breast cancer risk*

- Symptoms of ADHD
  - Mood lability
  - Sleep disturbances
  - Work inefficiency
  - Temper outbursts
  - Depression
  - Financial impulsivity
  - Procrastination
  - Inattention, impulsivity, hyperkinesis

*Postmenopause

Estrogen's Effects on Neurotransmitters

- Estrogen modulates neurotransmitters
  - Dopamine
    - Attention
    - Executive functioning
    - Many women come in with either worsening or pre-existing ADHD, or what appears to be new onset of symptoms
  - Acetylcholine
    - Memory (link to Alzheimer's disease)
  - Serotonin
    - Mood and anxiety

Hormone Replacement Therapy

- There is flexibility in how estrogen and progesterone are dosed
- Progesterone must be given with estrogen in patients with a uterus but neither must be taken every day
- Estrogen replacement
  - Helps with symptoms of menopause
  - Increased risk of endometrial cancer
  - Increased risk of thrombosis
- Progesterone replacement
  - Decreases risk of endometrial cancer which is increased by estrogen alone
  - Increased risk of breast cancer after 5 years
  - Helps with symptoms of menopause (hot flashes, sleep, anxiety)
  - Progesterone may not be well tolerated in some patients
    - May take for only 2 weeks every 3 months

Contraindications of HRT

- Cancer (progesterone)
  - Breast cancer (current, hx within 5 years)
- Coagulation (estrogen)
  - CVD disease (hx of DVT/PE, poorly controlled HTN, Ischemic heart disease, hx of stroke)
    - Multiple risk factors for atherosclerotic disease (>35, smoking, DM, HTN, HLD)
    - Complicated valvular heart disease
  - Major surgery or medical condition with prolonged immobilization
  - Thrombogenic mutations
  - <21 days postpartum (relative for 21-42 days postpartum)
  - Lupus
  - Migraine with aura (risk is relatively low at current estrogen doses)
  - Indications that estrogen is too high (ACHES)
    - Abonminal pain
    - Chest Pain
    - Headaches
    - Eye problems
    - Swelling or severely painful legs
    - If these symptoms are severe it is a signal to stop medication

Contraindications of HRT

- Pharmacokinetics
  - History of bariatric surgery with malabsorptive procedures
  - Drug interactions (ie anticonvulsants, immunosuppressants, rifampin, fosamprenavir)
- Liver disease (severe cirrhosis, hepatoma (malignant and hepatocellular adenoma))
- Gallbladder disease (stones) (current or medically treated) (progesterone and estrogen)
  - Hx of cholestasis related to combined oral contraceptive
- Diabetes with nephropathy/retinopathy/neuropathy/other vascular disease

ADHD: Personalized Medicine
Pharmacogenetic Testing

- Examines effects of metabolism & efficacy of medications
  - CYP2B6, CYP2D6, ADRA2A, and COMT
- Medications
  - Stimulants, atomoxetine, alpha-2-agonists, bupropion
- Harmonyxdiagnostics.com
  - ~ $100/mouth swab test
  - Results within 24 – 72 hours
- Testing that claims to be able to pick medications is not terribly effective other than checking P450 phenotypes

HarmonYX®
In harmony with human health.