STIMULANTS: A Therapeutic Class Review

Continuing Education Seminar

Saturday, July 11, 2020

Maryland
DEPARTMENT OF HEALTH

OFFICE OF
PHARMACY SERVICES

Notes:

Maryland
DEPARTMENT OF HEALTH

Continuing Medical Education (CME) &
Pharmacy Continuing Education (ACPE) Seminar

Stimulants: A Therapeutic Class Review

Virtual Live Program
on
Saturday, July 11th , 2020

Attendees must pre-register at www.mmppi.com to attend. This program will only be available virtually due to contact precautions related to COVID-19.

8:30 am – Registration	
8:45 am – Introductions	Maryland Department of Health Office of Pharmacy Services
9:00 am – Diagnosis and Management of Attention Deficit Hyperactivity Disorder	Ronald Means, MD Chief Medical Officer Catholic Charities of Baltimore
10:30 am – Break	
10:40 am – Stimulant Pharmacology	Megan Ehret, PharmD, MS, BCPP Associate Professor University of Maryland School of Pharmacy
11:55 am – Break	
12:00 pm – Inappropriate Use of Stimulants	Enrique Oviedo, MD, FASAM Medical Director for SUD Treatment Catholic Charities of Baltimore
1:15 pm – Closing Remarks	Maryland Department of Health Office of Pharmacy Services
1:30 pm - Adjourn	

The views and opinions expressed by the speakers are not necessarily the views and opinions of The State of Maryland Department of Health.

****This event will be recorded for future use. By attending, you agree to participate in audio and/or visual recording****

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This program is co-sponsored by The Maryland Department of Health (MDH) Office of Pharmacy Services (OPS) in collaboration with Health Information Designs, a KEPRO company.

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CME Designation:
MedChi designates this live activity for a maximum of (4) *AMA PRA Category 1 Credit(s)*^{TM}. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Presenter Disclosure:

Dr. Means states that he does not have relevant financial relationship with commercial interests and will be discussing “Off-Label” uses of products or devices. This information is on file with Health Information Designs/KEPRO.

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Program Disclosure:
Support provided by Health Information Designs, LLC.

Activity Type: Knowledge-Based

Diagnosis and Management of Attention Deficit Hyperactivity Disorder

Ronald F. Means, M.D.
Chief Medical Officer – Catholic Charities of Baltimore
Clinical Assistant Professor – University of Maryland
Instructor– Johns Hopkins

1

Disclosures

- No financial relationships with commercial interests
- Off-label use – stimulants for Major Depressive Disorder

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Learning Objectives

- Learn about the history of the diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), typical presentations and differential diagnosis
- Learn about the history of stimulants for the treatment of ADHD and current practices for using stimulants
- Review the use of non-stimulant medications, psychotherapy and adjunctive services for the treatment of ADHD
- Discuss long-term outcomes with ADHD and its impact upon the transition to adulthood

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Outline

- Pre-Test
- History of ADHD
- Diagnosing ADHD
- Stimulants
- Non-stimulants
- Non-psychopharmacologic treatment
- Course of disorder and outcomes

4

Pre-test

A 12 y/o girl presents with her father. His primary concern is her anger and occasional aggression. She has always done poorly in school, but this year, her performance is worse. The girl's mother left the family ten months ago after struggling with recurrent drug problems. When asked how the girl feels about her mother's departure, she expressed apathy and noted that her mother used to hit her. What is her diagnosis?

A. Posttraumatic Stress Disorder
B. Major Depressive Disorder
C. Attention Deficit Hyperactivity Disorder
D. Any or all of the above

5

Pre-test

A 7 y/o boy is brought for assessment by his mother. He is failing the 2nd grade. His mother complains that she is always being called to the school to address his "misbehavior." Upon examination, he is quiet and angry. He is calm with only minor fidgetiness. His mother seems very overwhelmed. What should you do next?

A. A trial of a stimulant medication
B. A trial of a non-stimulant ADHD medication
C. Request that parents and teachers complete rating scales
D. Refer to behavioral therapy

6

Pre-test

A 4 yr 10mo boy presents with both parents for possible treatment. He has just completed his pre-school year but was also in organized child care settings in the past. His teacher raised large concerns about his attention and hyperactivity. The teacher not only provided verbal feedback but completed rating scales that showed many ADHD symptoms. She noted that despite his apparent high intelligence, he is unable to learn much due to being unfocused. His parents noted that he was expelled from daycare in the past. Family members note that, despite the parents good effort, the boy seems totally unmanageable. Upon exam, he is extraordinarily hyperactive and had to be asked several times to stop jumping from the exam table. What should you do next?

A. Get an EKG in order to clear for potential treatment with a stimulant
B. Assuming there is no personal or family cardiac history, initiate treatment with a stimulant
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D. Initiate treatment with a non-stimulant ADHD medication like Strattera or an alpha-agonist

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History of ADHD

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Initial ADHD Presentations

- The emergence of the "troubled" child in the early 20th century
- Problematic behaviors included difficulty with schoolwork, fighting, and failure to obey authority
- Child guidance movement and institutional treatment for misbehavior emerged as a result
- Physician-run residential institutions were created for behavioral and neurological diseases

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DSM

- In 1980, the DSM-III gave the behavioral disorder of hyperactivity its current name

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Genetics and Neurobiology

- Prevalence 1.5 – 6%
- Greater prevalence in boys
- 2x greater rate with 1st degree relatives
- Variations in the dopamine receptors or transporters most studied etiologic mechanisms

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Environmental Factors

- Prematurity
- Intrauterine toxins
  - alcohol
  - cocaine
- Lead poisoning

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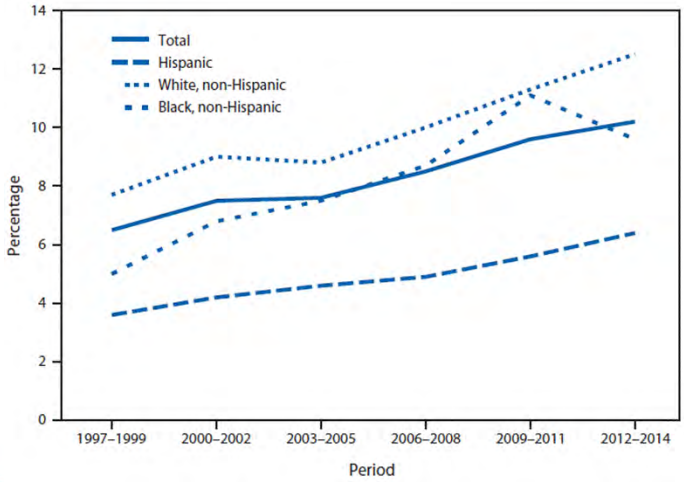
Prevalence Trends

Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD)



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ADHD Debate

- Claims of disorder being a new creation due to societal demands
- Variability in diagnosis
- Parents seeking treatment as a substitute for parenting or to improve kid's normal baseline
- Misdiagnosis in minority populations, especially impoverished African-American boys or the foster care population
- Avoidance of diagnosis or treatment

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Diagnosing ADHD

15

DSM – V Criteria

- Inattention (6+)
  - Fails to give close attention to details
  - Difficulty sustaining attention
  - Does not listen
  - Does not follow through
  - Difficulty organizing
  - Reluctance to engage in tasks that require attention
  - Loses things
  - Easily distracted
  - Forgetful

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DSM – V Criteria

- Hyperactivity and Impulsivity (6+)
  - Fidgets
  - Leaves seat
  - Runs about
  - Unable to play quietly
  - On the go
  - Talks excessively
  - Blurts out answers
  - Difficulty waiting turn
  - Interrupts

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DSM – V Criteria

- Present in two or more settings
- Not caused by other disorders
- Several symptoms before age 12

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Specifiers

- Combined
- Predominantly inattentive
- Predominantly hyperactive/impulsive
- In partial remission
- Mild/Moderate/Severe

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Typical presentations – Combined Type

- Kindergarten/1st grade
- Prior reports of parents of hyperactivity that became problematic upon entering school
- Impairment across settings
  - church
  - extracurricular
  - parents
  - family members
  - teachers/school
- Visible hyperactivity upon examination

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Typical presentations – Predominantly Inattentive

- Later onset – often middle school
- Poor academic performance
- Poor organizational skills across settings
- Not typically a behavioral problem

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Associated Features

- Low frustration tolerance
- Irritability
- Mood lability
- Aggression/outbursts/volatility

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Differential Diagnosis

- Learning Disorder
- Intellectual Disability
- Hearing/Vision problems
- Disruptive Mood Dysregulation Disorder
- Bipolar Disorder
- Anxiety disorders – including trauma-related
- Behavioral disorders

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Pre-test

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Standardized Scales

- Best to acquire before and after initiating treatment
- Teacher's version tend to be more useful
- National Institute for Children's Health Quality Vanderbilt Assessment Scales – https://www.nichq.org/sites/default/files/resource-file/NICHQ_Vanderbilt_Assessment_Scales.pdf
- Conners Rating Scales

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Psychological testing

- Not necessary for diagnosis
- May aid in diagnostic clarification, especially in diagnostically complicated cases
- Something other than ADHD needed to qualify

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Laboratory testing

- No lab testing needed for diagnostic or treatment purposes
  - Watch for masquerading illnesses
- Lead testing might be indicated if past testing status not known or a new exposure
- Pharmacogenomic testing is not typically needed

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Pre-test

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Stimulants

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Emergence of Stimulants

- Synthesized in 1887, amphetamine (alpha-methylphenethylamine) initially as an artificial replacement for epinephrine
- Not studied clinically until 1927 as a bronchodilator
- In1935 the pharmaceutical company Smith, Kline & French acquired the amphetamine Benzedrine Sulfate

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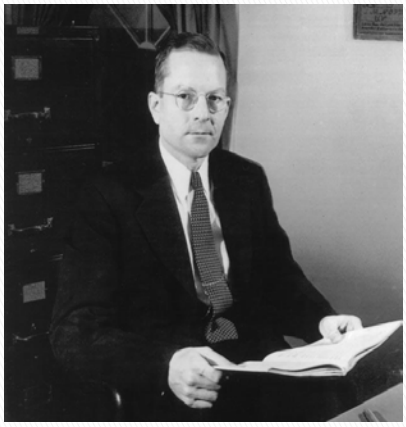
1937 – American Journal of Insanity



Charles Bradley, MD

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Initial Studies

- Initially, Bradley sought treatment for post-spinal tap headaches
- In 1937, the effects of Benzedrine sulfate treatment were first documented in thirty children in a residential setting with a variety of behavioral problems
- Expanded to one hundred patients in 1941

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Slow Progress

- Tranquilizers flourished as the predominant drug treatment for behavioral disorders because they produced distinct and reproducible responses
- Amphetamines for mental performance enhancement garnered public criticism
- 1950s psychiatrists began to focus on the specific behavioral disorder of hyperactivity
- 1956 psychiatrists began to prescribe Ritalin (methylphenidate), a stimulant drug similar to Benzedrine with known benefits for children's behavior and fewer side effects

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Current Stimulants

- Adhansia XR
- Aptensio XR
- Concerta
- Cotempla XR-ODT
- Daytrana
- Focalin (XR)
- Jornay PM
- Metadate (ER, CD)
- Methylin (ER)
- Quillichew
- Quillivant
- Ritalin (LA, SR)

Methylphenidate-Based

- Adderall (XR)
- Adzenys (ER, XR-ODT)
- Desoxyn
- Dexedrine
- Dyanavel XR
- Evekeo (ODT)
- Mydayis
- ProCentra
- Vyvanse
- Zenzedi

Amphetamine-Based

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ADHD Medication Guides

https://chadd.org/wp-content/uploads/2019/07/Medication-Chart-July-2019.pdf

http://www.adhdmedicationguide.com/

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What to expect

- Stimulants work fast
- Stimulants work well
- Stimulants all have the same side effect potential
- Stimulants can be used in the young
- Stimulants work differently based on the individual being treated
- Stimulants get a bad rap

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What to consider

- Preparation
- Prior Authorizations
- Long-acting vs. Short-acting
- Availability

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Preparation Differences

- **Openable Capsules**
  - Focalin
  - Adderall
  - Metadate
  - Vyvanse (dissolvable in liquid)
  - Adhansia
  - Aptensio
  - Jornay
  - Mydayis
  - Ritalin LA
- **Liquids**
  - Adzenys
  - Dyanavel
  - Methylin
  - ProCentra
  - Quillivant
- **Disintegrating**
  - Cotempla
  - Evekeo
  - Adzenys
- **Chewable**
  - Quillichew
- **Patch**
  - Daytrana

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Dosing

- Start low, especially when younger
- Do not overdose or underdose
- Warn of possible over-treating and ability to reduce
- Know FDA maximum dosing
- Consider weight based-dosing (isomer exceptions)
  - 1-2mg/kg of methylphenidate
  - 0.5-1mg/kg of amphetamine
- Watch for rapid metabolizers
- Adjustments likely needed with growth
- Booster dosing

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Typical Side Effects

- Appetite suppression
- Abdominal pain
- Insomnia
- Exacerbation of tics
- Rebound
- Cardiac effects/Black Box

"Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug"

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The Zombie-Effect

- Worse in the past when disorder was treated more aggressively or incorrectly
- Some emotional dulling might happen – warn preemptively
- Discussion with patient/guardian about the benefit vs. some decrease in emotional output

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Atypical Side Effects

- Emotional sensitivity
- Tactile hallucinations
- Priapism

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Monitoring

- Cardiac work-up prior to treatment if personal or family cardiac history
- BP and Pulse – regularly
- Weight
  - Drugs Holidays

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Alternative Indications for Stimulants

- Narcolepsy
- Obesity
- Binge-Eating Disorder
- Treatment-resistant depression (off-label)

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Pre-test

A 4 yr 10mo boy presents with both parents for possible treatment. He has just completed his first pre-school year but was also in organized child care settings in the past. His teacher raised large concerns about his attention and hyperactivity. The teacher not only provided verbal feedback but completed rating scales that showed many ADHD symptoms. She noted that despite his apparent high intelligence, he was unable to learn much due to being unfocused. His parents noted that he was expelled from daycares in the past. Family members note that, despite the parents good effort, the boy seems totally unmanageable. Upon exam, he is extraordinarily hyperactive and had to be asked several times to stop jumping from the exam table. What should you do next?

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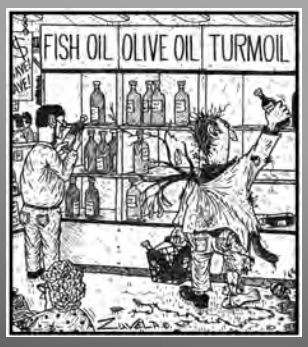
Non-stimulants



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Strattera (atomoxetine)

- FDA max dose of 80mg daily
- Weight based dosing of 1.2mg/kg
- Limitations:
  - need daily use for full effectiveness
  - 2-4 weeks needed for full effectiveness to be achieved
  - tends to be better with inattentive symptoms

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Alpha-Agonists

- Guanfacine -1-4mg divided
  - Intuniv
- Clonidine – 0.05 – 0.4mg divided
  - Kapvay

Often added as adjunctive treatment after reaching a ceiling with the stimulant due to maximum dosing or problematic side effects. Particularly good for residual impulsivity

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Third-Line Treatments

- bupropion
- venlafaxine

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Diet Modification and Complimentary Approaches

- Diet modifications
  - Dyes
  - Sugars
- Herbals targeting calm and inattention
- Exercise
- Sleep
  - Hygiene
  - Sleep aides

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Non-Psychopharmacologic Treatment

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Psychotherapy

- Individual therapy
  - Anger management
  - Organizational skills
- Family therapy
  - Parental management training
  - Psychoeducation
    - No accountability
    - No understanding
  - Family support groups

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Adjunctive Services

- Psychiatric Rehabilitation Program
  - Social skills training – group or individual
  - Life skills training
- Therapeutic Behavioral Services
- Case Management

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Educational Accommodations

- Student Support Team
- 504 plan
- Individualized Education Program

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Course of ADHD

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Multimodal Treatment Study of Children with ADHD (MTA)

- Four treatment arms
  - TAU
  - Intensive behavioral therapy
  - Medication only
  - Combination
- Combination superior but only slightly to medication alone
- Numerous follow-up studies with long-term outcomes examined after first fourteen months

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Substance Use and ADHD

- MTA revealed likelihood of protection against substance use problems with medication management
- Dependence to stimulants only at high dose thus requiring taper
- Misuse is limited in younger populations

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Resolution with Age

- Generally thought that majority resolve completely with adulthood transition
- Hyperactivity almost always resolves but inattention might remain in minority
- Discontinuation of treatment common in late adolescence but should be weighed carefully with college and new jobs
- Driving should be discussed due to increase accident rates

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"New" Adult Cases

- Childhood history should be demonstrable – ideally a history of treatment
- Adult cases with no prior treatment history require higher scrutiny
- Collateral information from parent, teachers or employer often useful
- Standardized scales can also be useful for assess symptoms
  - Adult ADHD Self-Report Scale

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Notes:

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Stimulant Pharmacology

Megan J. Ehret, PharmD, MS, BCPP
Associate Professor
mehret@rx.umaryland.edu

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Objectives

- Describe the pharmacology of the currently available stimulant and wakefulness promoting medications
- Outline the pharmacokinetic differences between the stimulant and wakefulness promoting medications
- Identify drug-drug interactions and adverse effects of stimulant and wakefulness promoting medications
- Select an appropriate stimulant or wakefulness promoting medication for a patient based on patient specific variables

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Stimulant Pharmacology

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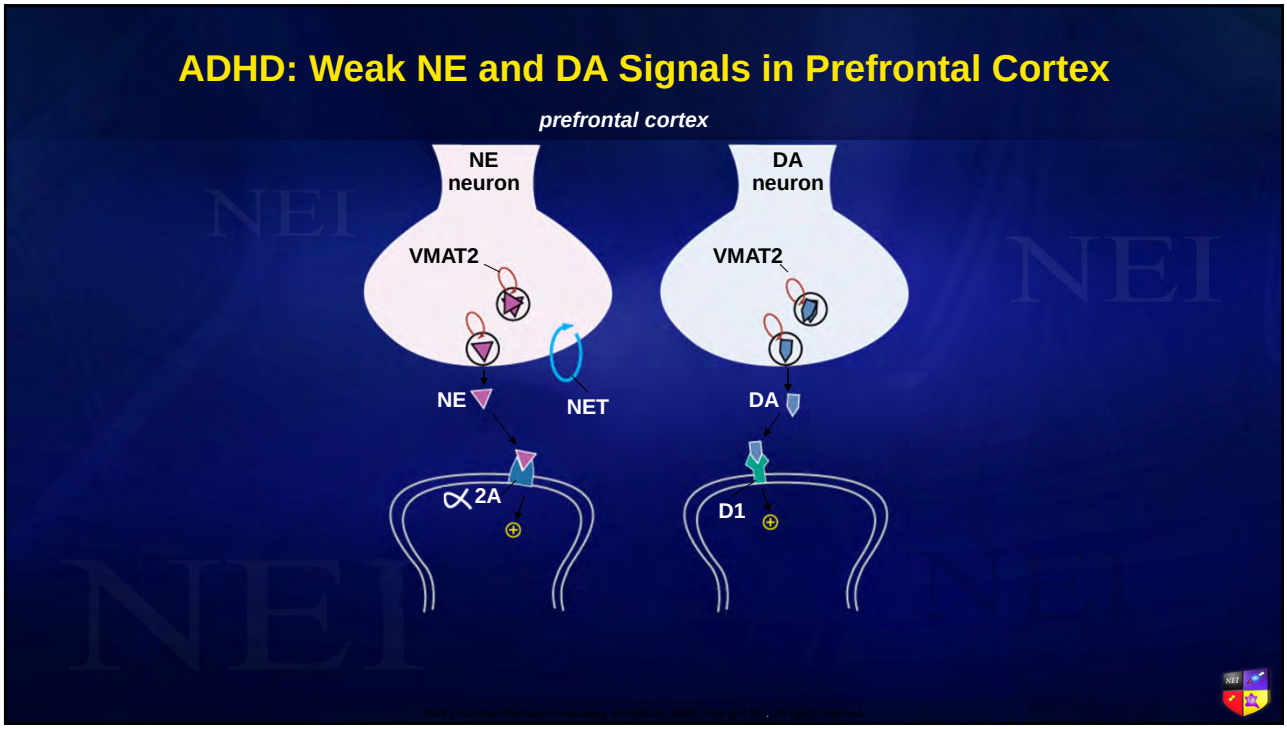
ADHD: Weak NE and DA Signals in Prefrontal Cortex
prefrontal cortex
NE neuron
DA neuron
VMAT2
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NE
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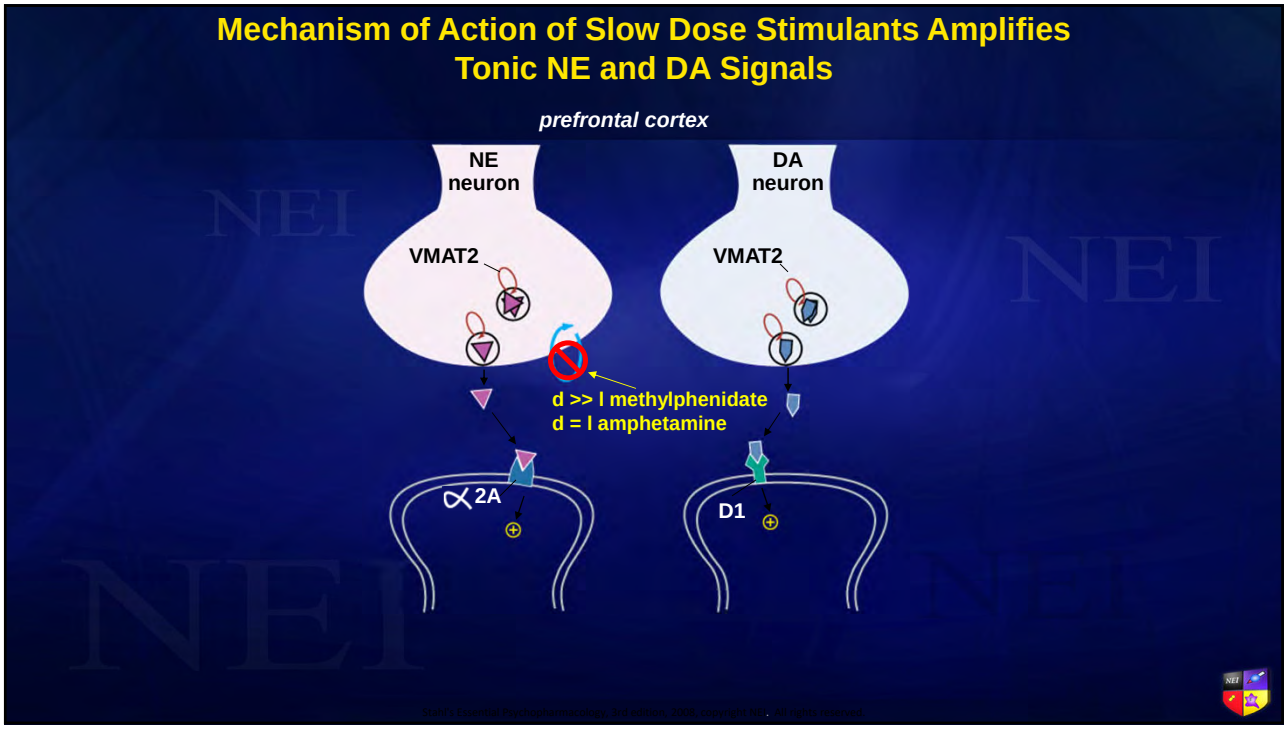
Mechanism of Action of Slow Dose Stimulants Amplifies Tonic NE and DA Signals
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NE neuron
DA neuron
VMAT2
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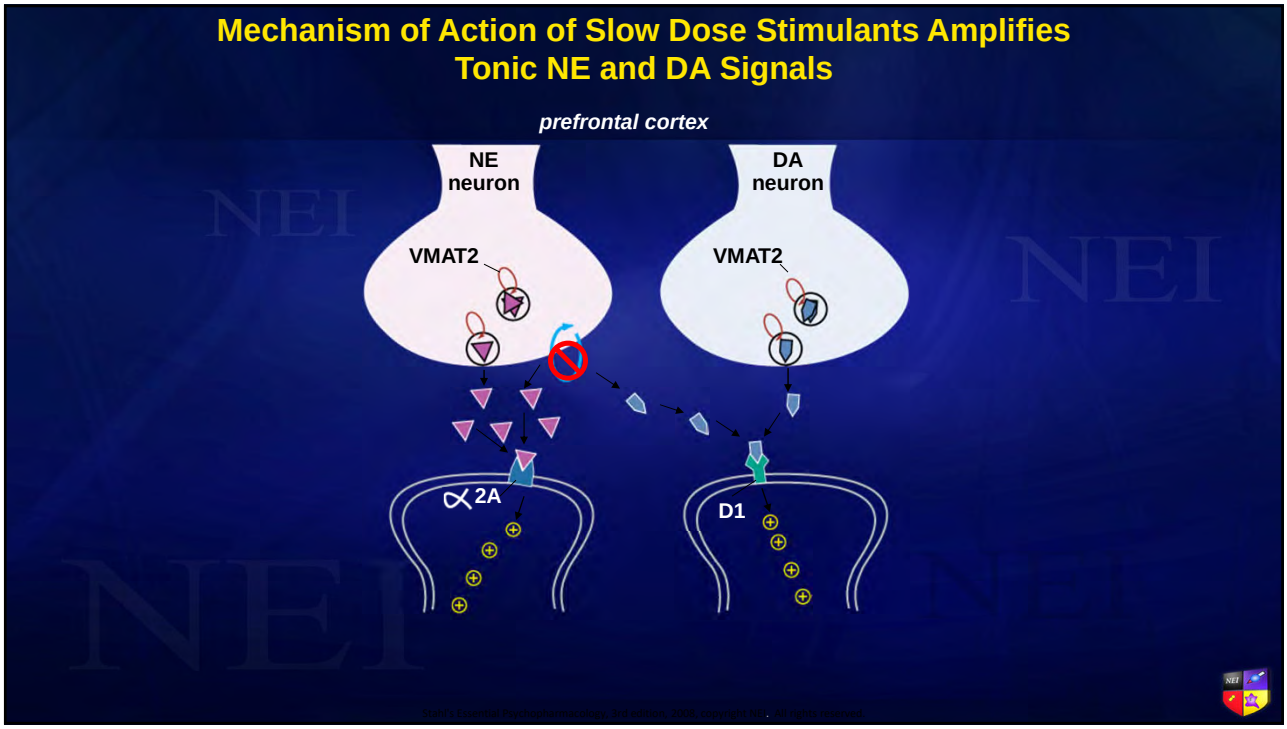
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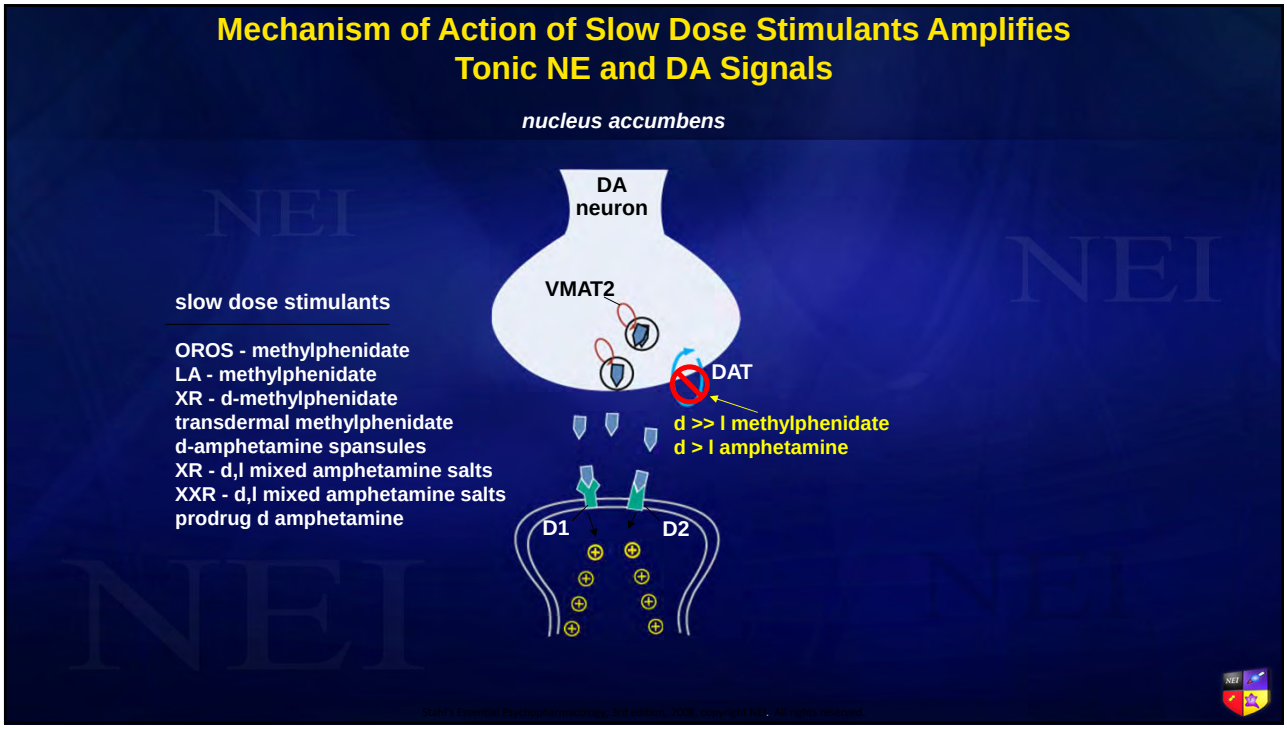
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DA neuron
VMAT2
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d >> l methylphenidate
d > l amphetamine
D1
D2
slow dose stimulants
OROS - methylphenidate
LA - methylphenidate
XR - d-methylphenidate
transdermal methylphenidate
d-amphetamine spansules
XR - d,l mixed amphetamine salts
XXR - d,l mixed amphetamine salts
prodrug d amphetamine
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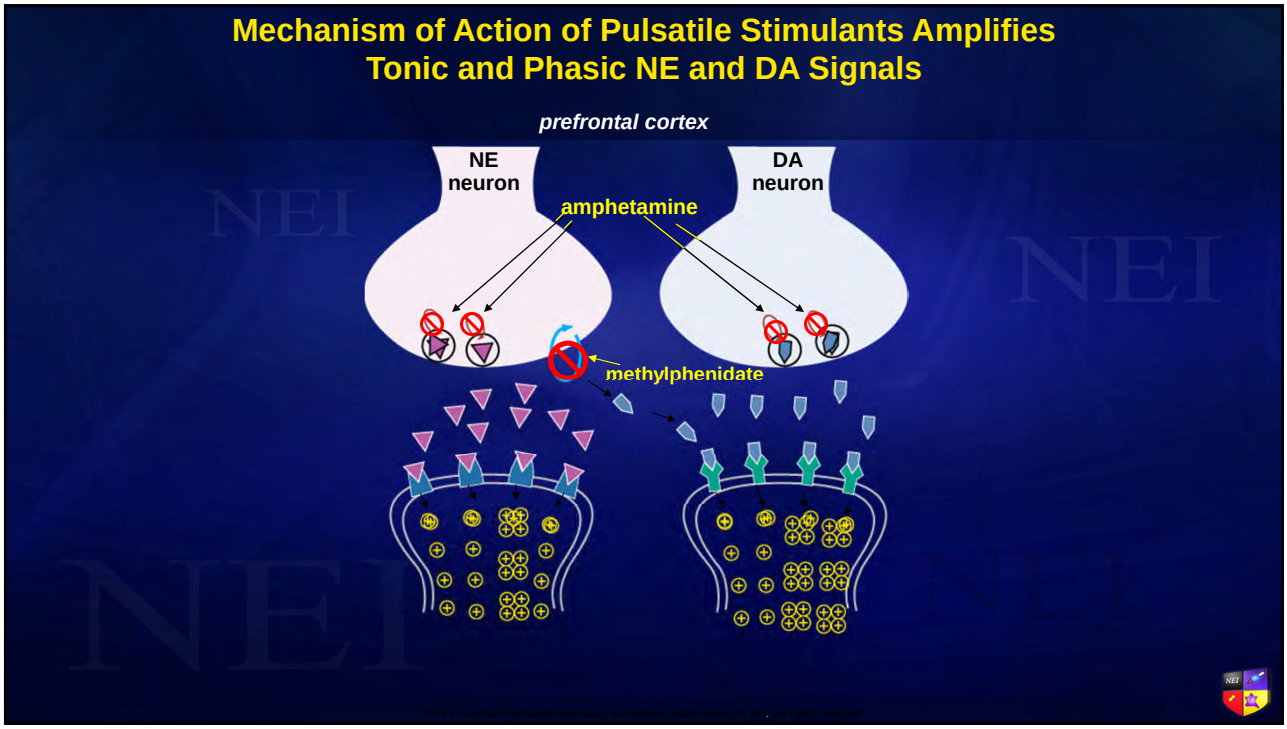
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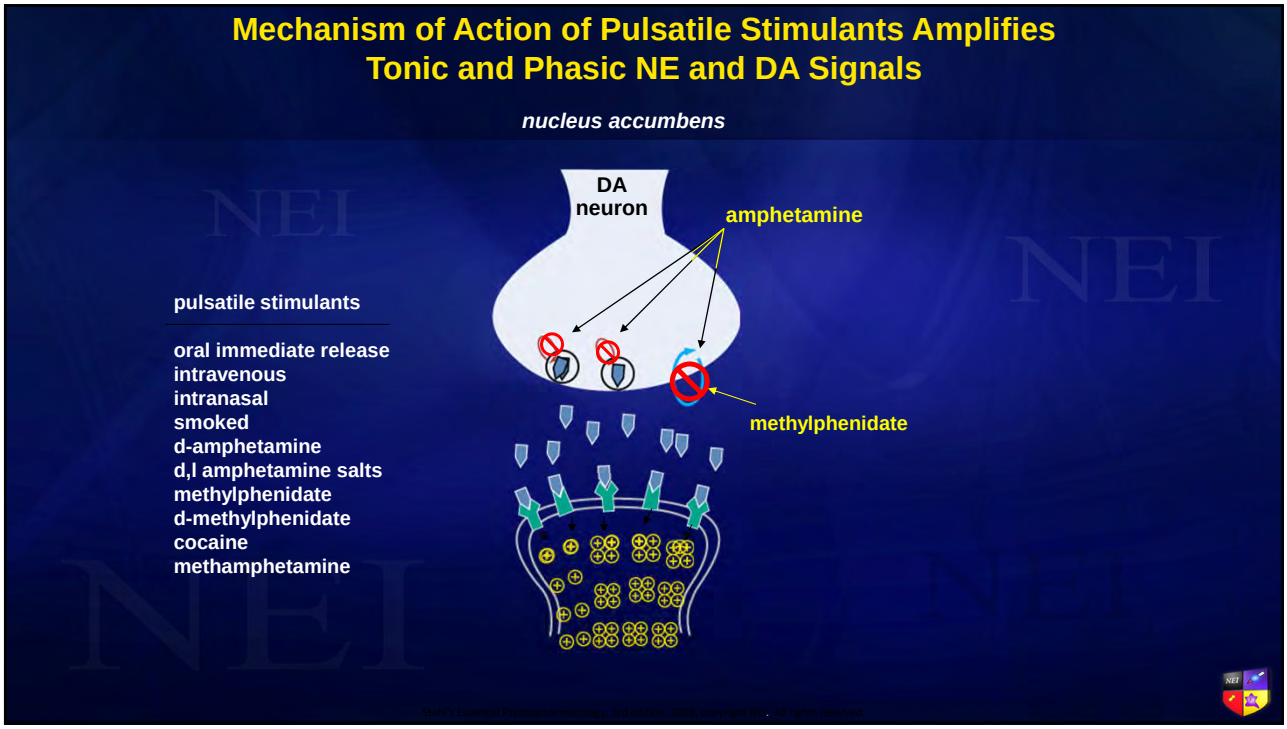
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nucleus accumbens
DA neuron
amphetamine
methylphenidate
pulsatile stimulants
oral immediate release
intravenous
intranasal
smoked
d-amphetamine
d,l amphetamine salts
methylphenidate
d-methylphenidate
cocaine
methamphetamine
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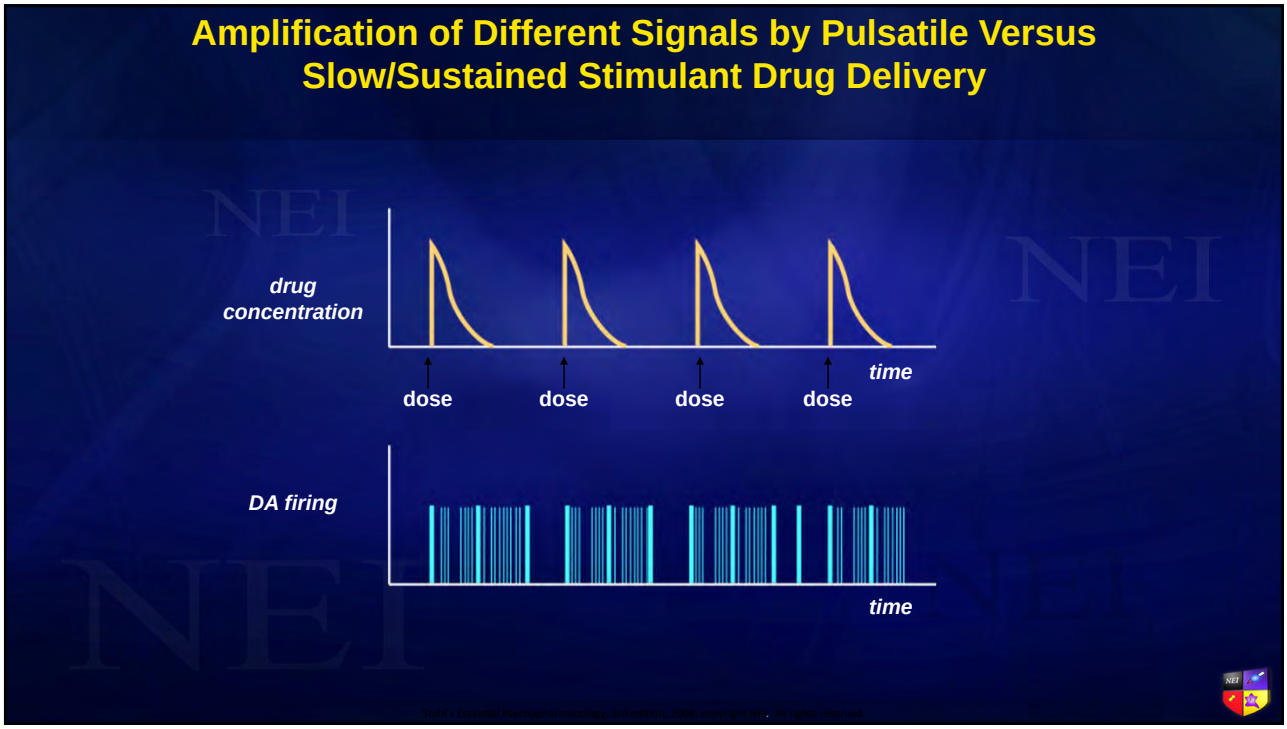
Amplification of Different Signals by Pulsatile Versus Slow/Sustained Stimulant Drug Delivery
drug concentration
dose
dose
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DA firing
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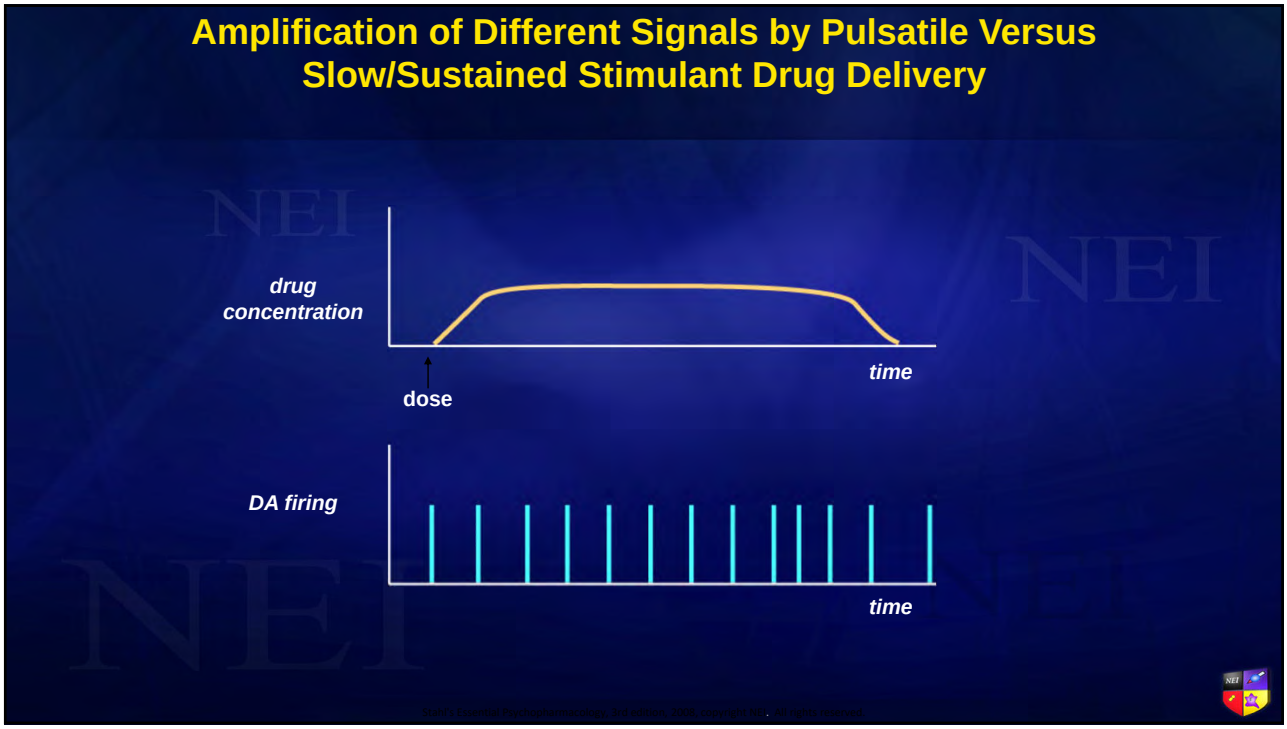
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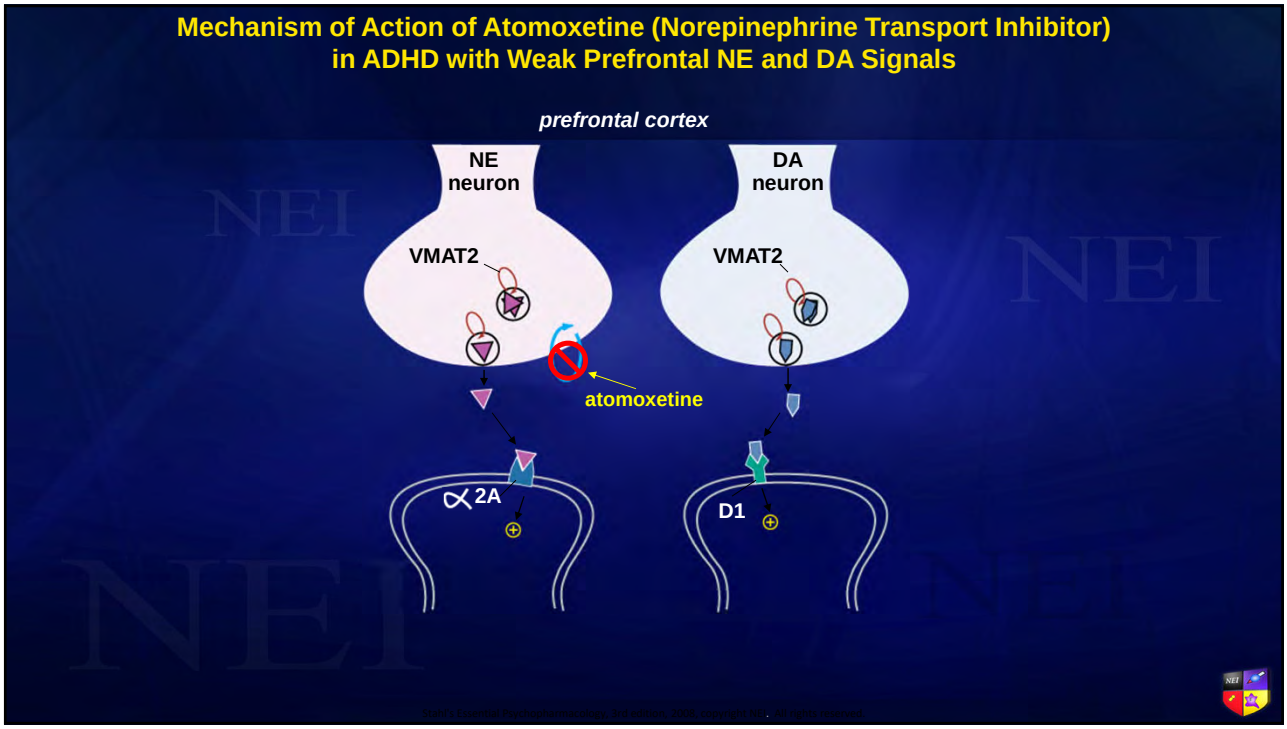
Mechanism of Action of Atomoxetine (Norepinephrine Transport Inhibitor) in ADHD with Weak Prefrontal NE and DA Signals
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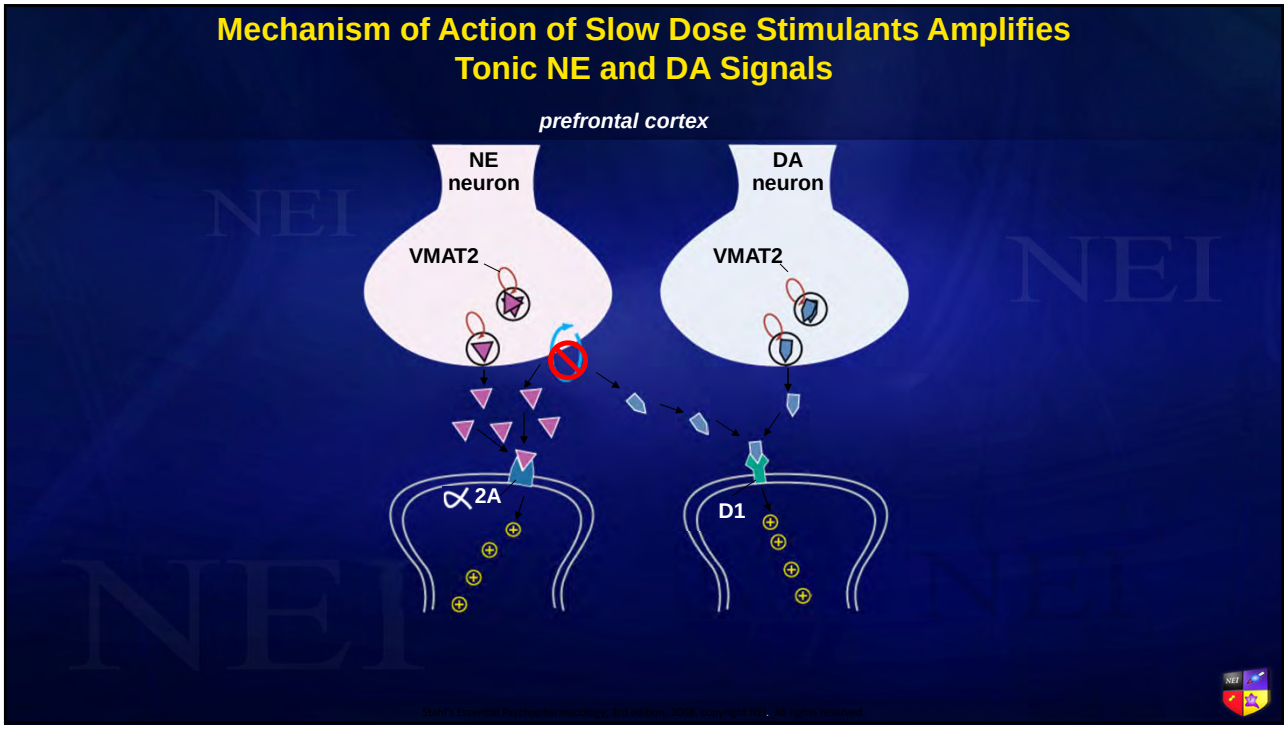
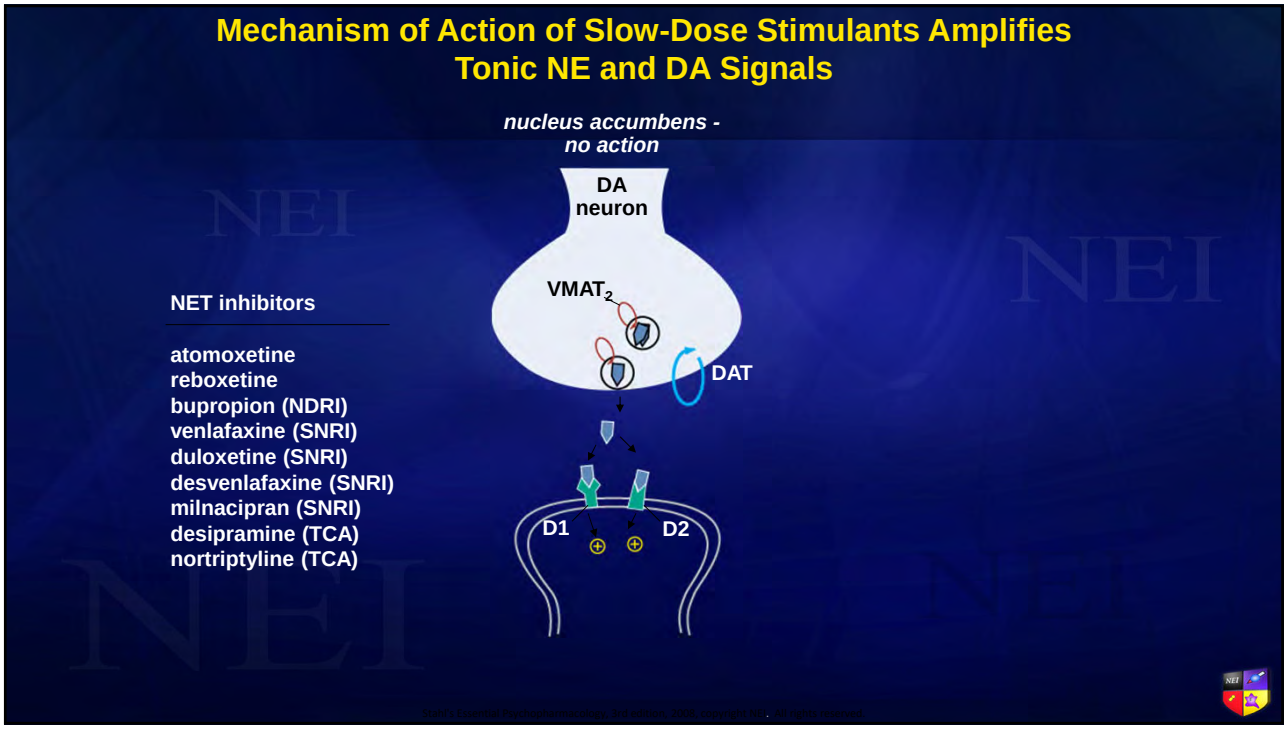
NE neuron
DA neuron
VMAT2
VMAT2
atomoxetine
2A
D1

13


Mechanism of Action of Slow Dose Stimulants Amplifies Tonic NE and DA Signals
prefrontal cortex
NE neuron
DA neuron
VMAT2
VMAT2
2A
D1

14


Mechanism of Action of Slow-Dose Stimulants Amplifies Tonic NE and DA Signals
nucleus accumbens - no action
DA neuron
VMAT2
DAT
D1
D2
NET inhibitors
atomoxetine
reboxetine
bupropion (NDRI)
venlafaxine (SNRI)
duloxetine (SNRI)
desvenlafaxine (SNRI)
milnacipran (SNRI)
desipramine (TCA)
nortriptyline (TCA)

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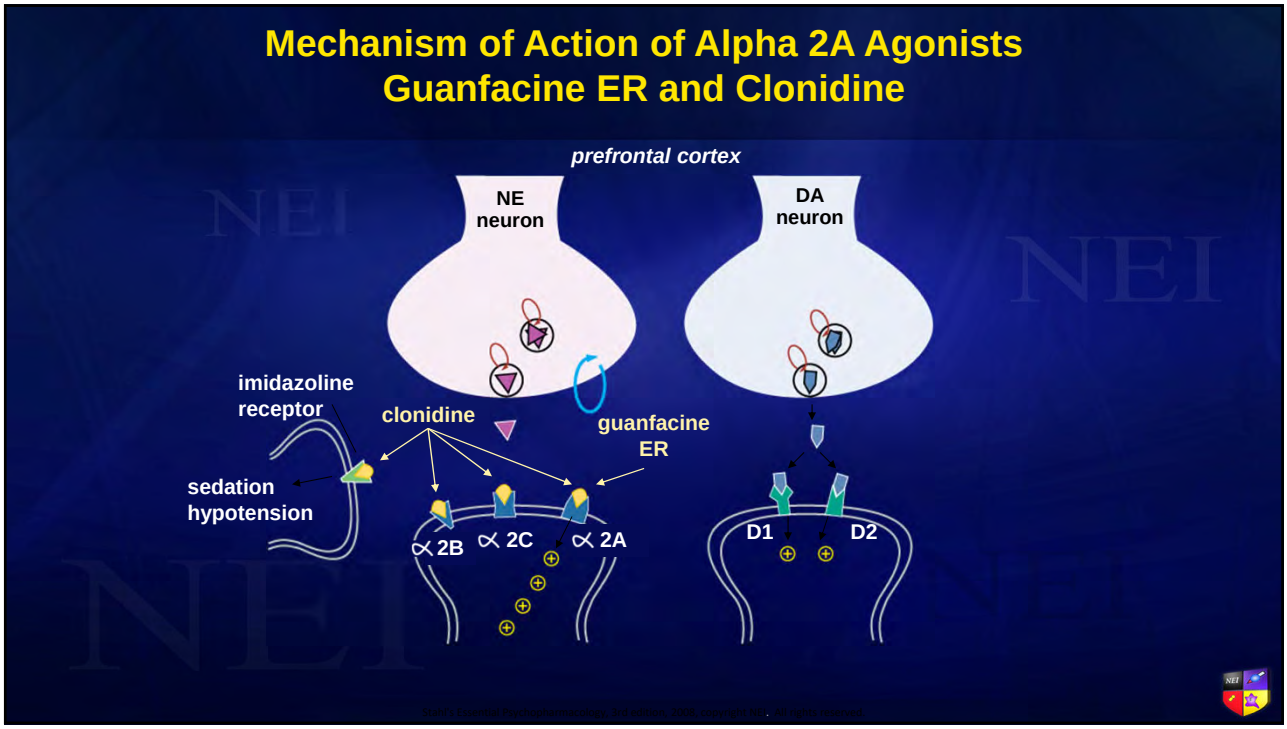
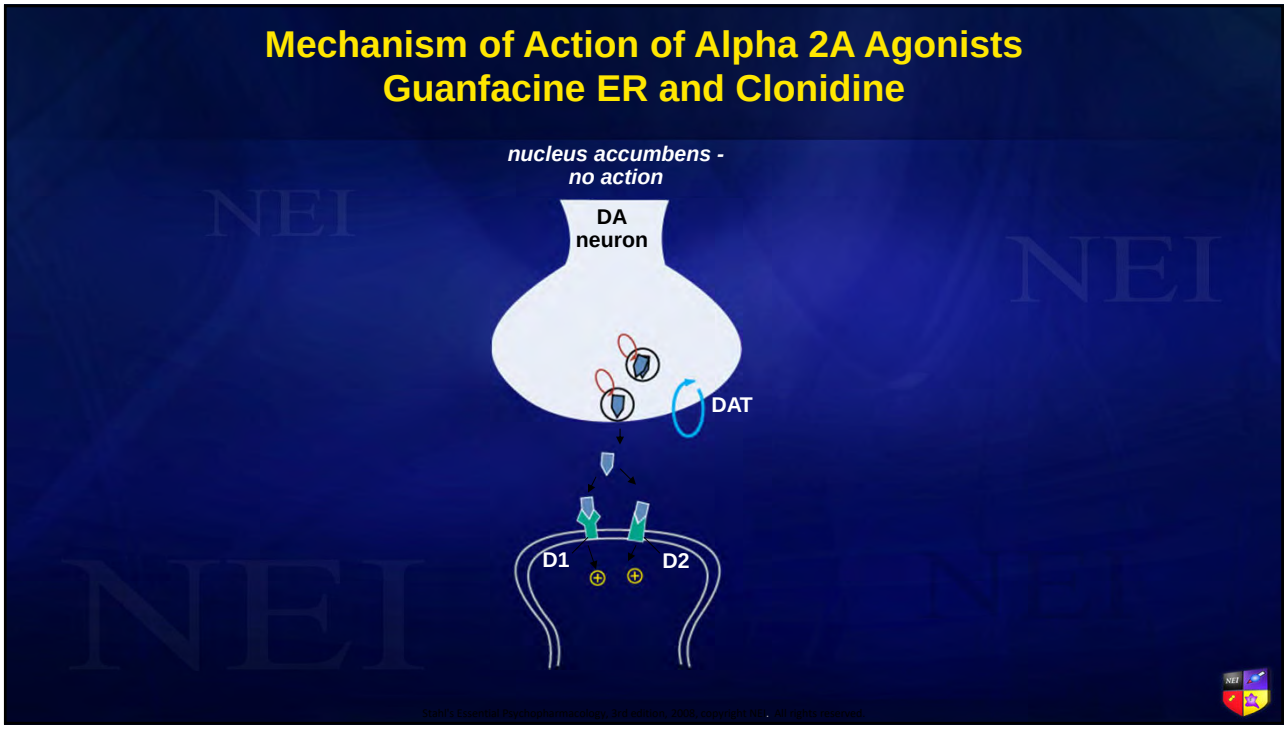

Mechanism of Action of Alpha 2A Agonists Guanfacine ER and Clonidine
prefrontal cortex
NE neuron
DA neuron
imidazoline receptor
clonidine
guanfacine ER
sedation hypotension
∝2B
∝2C
∝2A
D1
D2

16


Mechanism of Action of Alpha 2A Agonists
Guanfacine ER and Clonidine
nucleus accumbens -
no action
DA
neuron
DAT
D1
D2
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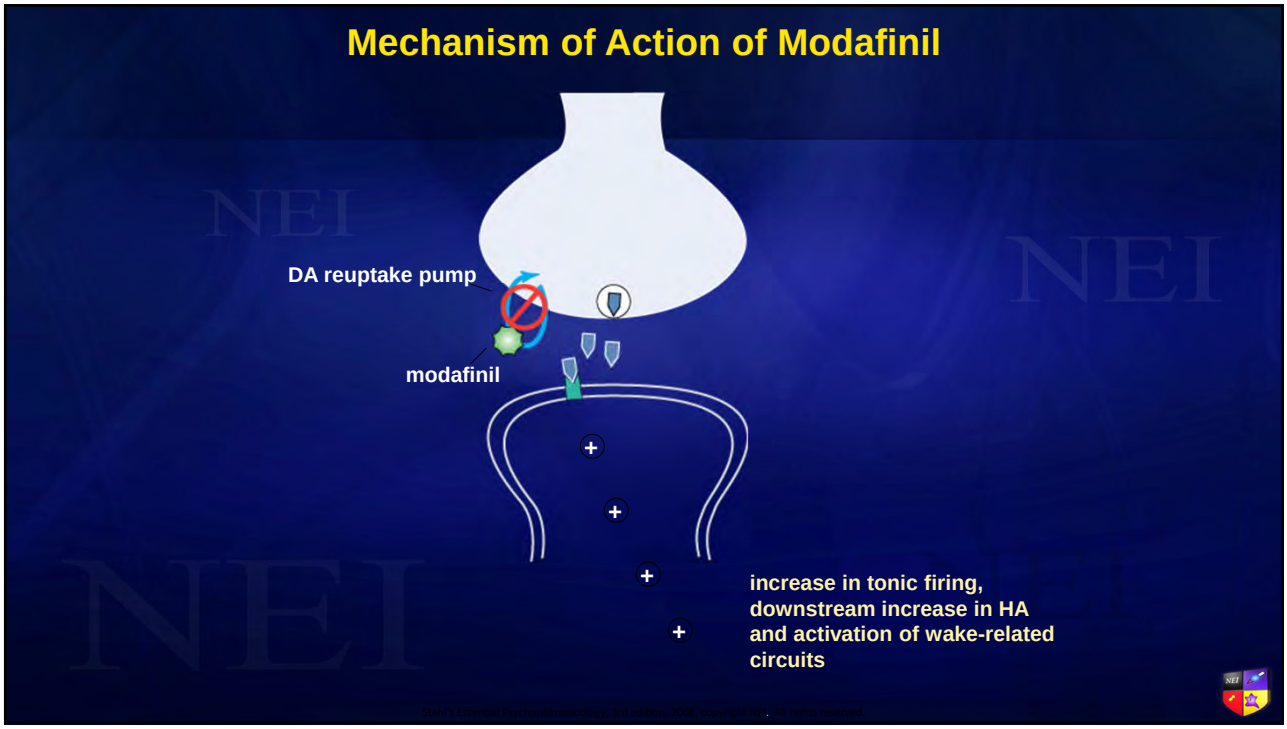
Mechanism of Action of Modafinil
DA reuptake pump
modafinil
increase in tonic firing,
downstream increase in HA
and activation of wake-related
circuits
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Stimulant Pharmacokinetics

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Short and Intermediate Acting Methylphenidate Products

Product	Delivery Mechanism	Time to Peak (hr)	Number of Doses per day	Duration of Action (hr)	Comments
Ritalin		1-2	3	3-4	May be split
Methylin Oral Soln.		1-2	3	3-4	Grape flavor
Methylin Chewable		1-2	3	3-4	Grape flavor
Ritalin SR	Wax-based matrix	~4-5	1-2	8	Swallowed whole
Metadate ER	Wax-based matrix	~4-5	1-2	3 to 8	Swallowed whole
Ritalin LA	50% IR, 50% DR	1^{st}: 2 2^{nd}: 5.5-6.5	1-2	6 to 8	May be opened
Metadate CD	30% IR, 70% ER	1^{st}: 1.5 2^{nd}: 4.5	1-2	6 to 8	May be opened

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Long-Acting Methylphenidate

Product	Delivery Mechanism	Time to Peak (hr)	Number of Doses per day	Duration of Action (hr)	Comments
Concerta	Osmotic 22% IR, 78%CR	1st: 1 2nd: 6-10	1	10-12	Swallow whole; tablet
Relexxii	Osmotic 22% IR, 78% CR	1st: 1 2nd: 6-10	1	10-12	Swallow whole; tablet
QuilliChew ER	Coated MP 30%IR, 70% ER	5	1	10-12	Don't sub on mg to mg basis;cherry
Quillivant XR	Coated MP 20%IR, 80% ER	5	1	12	Shake; banana/fruit
Aptensio XR	ML beads 40% IR, 60% CR	1st: 2 2nd: 8	1	12	Doesn't equivalent to PO MPH
Cotempla XR-ODT	ODT 25% IR, 75% CR	5	1	12	Allow to disintegrate on tongue; grape

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Extended-Release/Transdermal Methylphenidate

Product	Delivery Mechanism	Time to Peak (hr)	Number of Doses per day	Duration of Action (hr)	Comments
Adhansia XR	ML Beads 20% IR, 80% CR	1st: 1.5-2 2nd: 10-12	1	13	Doesn't equivalent to PO MPH
Jornay PM	2 functional film coated beads	14	1	24-36	Take in PM: 6:30-9:30PM
Daytrana	Continuous release from multipolymeric Adhesive	10	1	10-12	Apply to hip; Remove after 9 hours; doesn't equivalent to PO MPH

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Dexmethylphenidate

Product	Delivery Mechanism	Time to Peak (hr)	Number of Doses per day	Duration of Action (hr)	Comments
Focalin IR		1-1.5	2-3	3-6	High fat meal may delay peak
Focalin XR	50% IR, 50%DR	1st: 1.5 2nd: 6.5	1	9-12	May be opened

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Short Acting Amphetamine Products

Product	Delivery Mechanism	Time to Peak (hr)	Number of Doses per day	Duration of Action (hr)	Comments
Adderall	D-AMP: L-AMP- 3:1	3	2-3	5-8	
Evekeo	D-AMP: L:AMP- 1:1	~4	1-2	4-6	
Evekeo ODT	ODT; D-AMP: L-AMP- 1:1	~4	1-2	10	Don't sub on mg to mg; bitter taste
Dexedrine		3	2-3	4-6	Dextro isomer
Zenzedi	100% D-AMP	3	2-3	4-6	
ProCentra	100% D-AMP	3	2-3	4-6	Bubble gum oral soln.

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Intermediate Amphetamine Products

Product	Delivery Mechanism	Time to Peak (hr)	Number of Doses per day	Duration of Action (hr)	Comments
Dexedrine Spansule	50%IR, 50%DR	8	1-2	6-10 (highly variable)	Timed release

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Long-Acting Amphetamine Products

Product	Delivery Mechanism	Time to Peak (hr)	Number of Doses per day	Duration of Action (hr)	Comments
Adderall XR	D-AMP:L-AMP- 3:1; 50%IR; 50% DR	7	1	10-12	50% IR; 50% DR
Adzenys ER		~5	1	10-12	Don't sub on mg to mg
Adzenys XR-ODT	ODT	~5	1	10-12	Don't sub on mg to mg; orange
Dyanavel XR	D-AMP:L-AMP- 1:1	~4	1	8-10	Bubblegum soln.
Mydayis	D-AMP: L-AMP: 3:1; IR and 2 types of DR beads	8	1	16	Three releases throughout the day

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Long Acting Amphetamine Products

Product	Delivery Mechanism	Time to Peak (hr)	Number of Doses per day	Duration of Action (hr)	Comments
Vyvanse		~1 Lisdexamfetamine 3.5 dextroamphetamine	1	8-14	Pro-drug converted to active drug
Vyvanse Chewable					Strawberry-flavored

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Wakefulness Medications Pharmacokinetics

28

Wakefulness Medications

Product	Delivery Mechanism	Time to Peak (hr)	Number of Doses per day	Duration of Action (hr)	Comments
Provigil		2-4 fasted; 3-5 with food		15	
Nuvigil		2 fasted 4-6 with food		15	R-enantiomer of racemic modafinil

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Stimulant Drug-Drug Interactions

30

MPH and AMP Interactions

Other Psychostimulants • Effects can be additive	**Antihypertensive** • May counteract antihypertensive effect	**MAOIs** • May increase BP and lead to hypertensive crisis
TCAs • MPH may increase TCA concentration	**Antacids, PPIs, H2 Antagonists** • Can affect absorption of MPH	**Opioid analgesics** • AMP serum concentrations may be increased
Ascorbic Acid and fruit juices • Lower the absorption of amphetamines	**CYP 2D6 Inhibitors** • Increase exposure to mixed amphetamine salts	**Chlorpromazine, haloperidol, lithium** • May inhibit the stimulatory effect of amphetamines

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Wakefulness Medications Drug-Drug Interactions

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Drug-Drug Interactions

- CYP3A4 inducers and inhibitors
- Modafinil induces CYP3A4
- Cyclosporine
- CYP2C19 inhibitors
- Increase TCAs in CYP2D6 poor metabolizers
- Prazosin
- MAOIs

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Stimulant Warnings/Precautions and Adverse Effects

34

Black Box Warnings

- High potential for abuse
- Sudden cardiac death

35

Warnings/Precautions

- Priapism
- Patch
- MPH-OROS
- MPH-Suspension
- AMP sulfate
- HTN/Tachycardia
- Psychiatric AE
- Seizures
- Visual Disturbances
- Tics
- Peripheral Vasculopathy
- Long-term growth suppression
- Additive Ingredients
- Visual Disturbances
- Serotonin Syndrome
- Pressor Agents

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Adverse Effects

- Decreased appetite
- Insomnia
- GI Distress
- Irritability
- Headache
- Mild Erythema- patch

- Less Common:
  - Dysphoria
  - Tics or abnormal movements
  - HTN or BP fluctuations
  - Hallucinations
  - Aggression
  - Zombie-like state

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Wakefulness Medications Warnings/Precautions and Adverse Effects

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Warnings and Precautions

- Serious rash
- Angioedema and anaphylaxis
- Multi-organ hypersensitivity reactions
- Persistent sleepiness
- Psychiatric Symptoms
- Cardiovascular events

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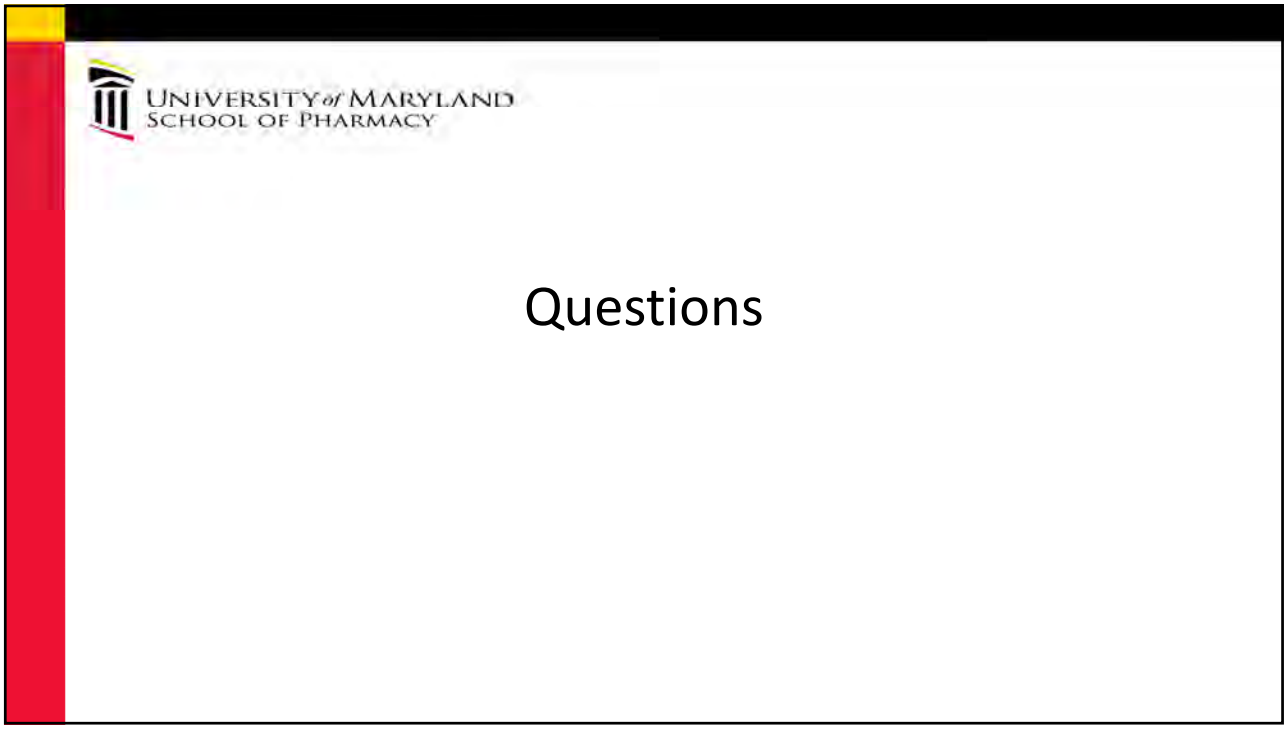
Adverse Effects

- Increased blood pressure in patients with HTN
- Headache
- Nausea/vomiting
- Anxiety
- Insomnia
- Dizziness

40



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Notes:

Inappropriate Use of Stimulants

Enrique Oviedo MD, FASAM
Board Certified Adult, Child & Adolescent, Addiction Psychiatrist
Medical Director for Substance Use Disorder Treatment, Catholic Charities
Medical Director, MATClinics

1

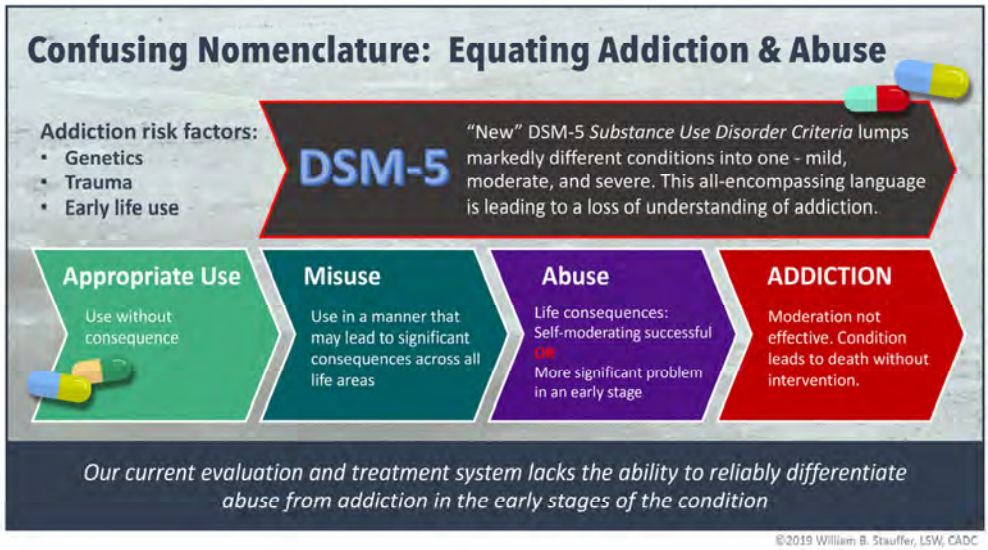
- Dr. Oviedo states that he does not have a relevant financial relationship with commercial interests and will not be discussing "Off-Label" uses of products or devices. This information is on file with Health Information Designs/KEPRO.

2

Objectives

- Discuss the epidemiology of stimulant misuse
- Talk about patterns of misuse in relation to other substances
- Review motivators/reasons for misuse
- Discuss short and long-term consequences of stimulant misuse
- Outline strategies to mitigate and prevent misuse and diversion
- Treatment of ADHD in the SUD population

3



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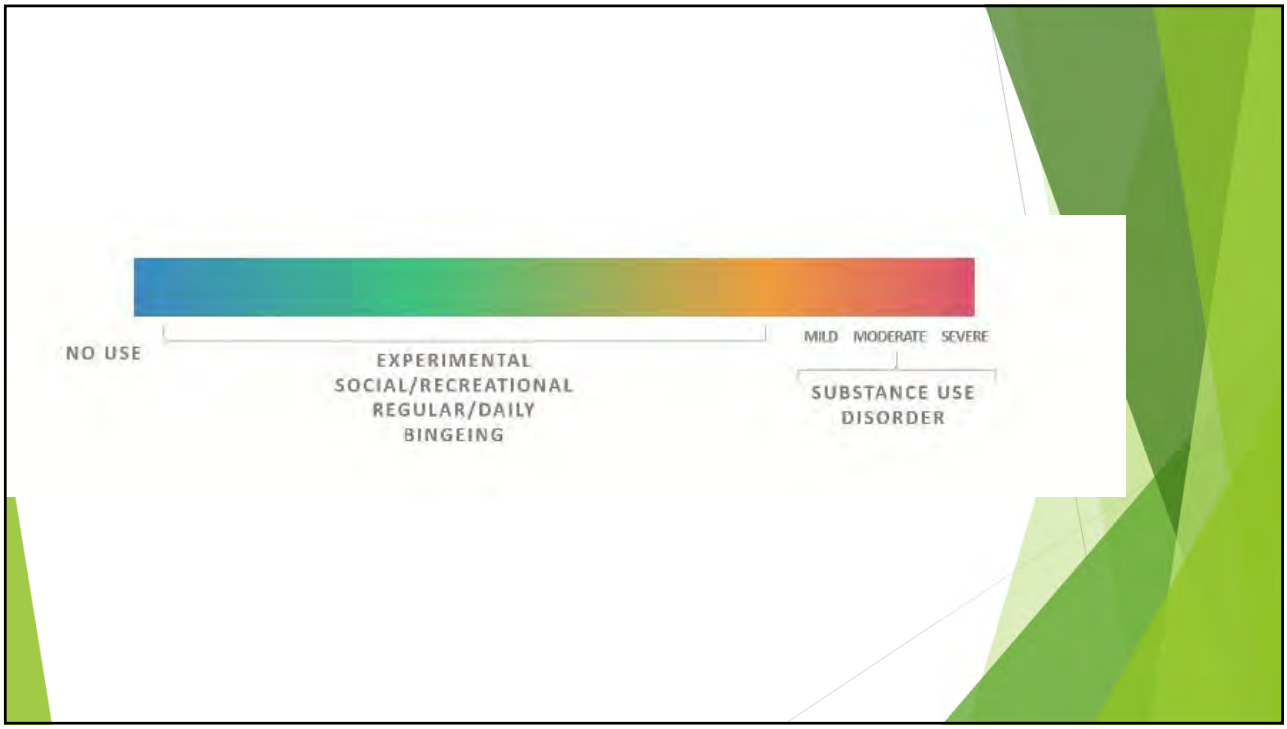
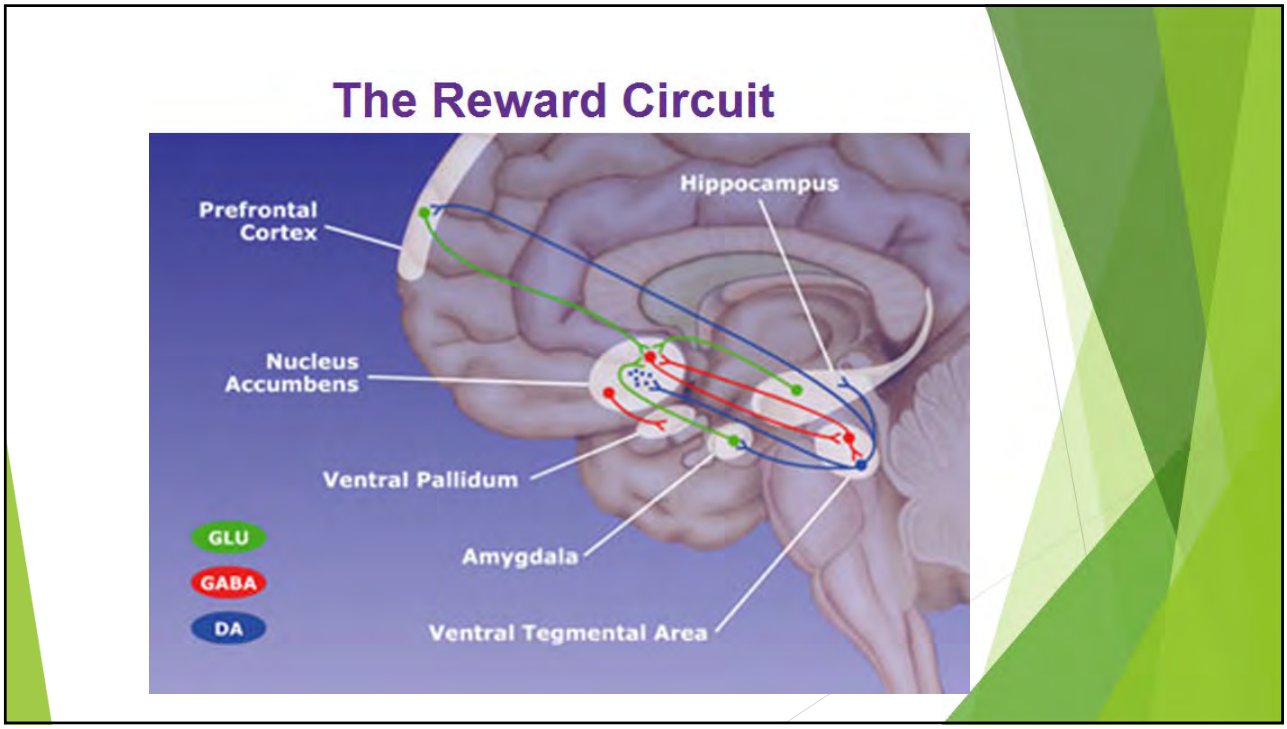

NO USE
EXPERIMENTAL
SOCIAL/RECREATIONAL
REGULAR/DAILY
BINGEING
MILD MODERATE SEVERE
SUBSTANCE USE
DISORDER

5


The Reward Circuit
Prefrontal Cortex
Hippocampus
Nucleus Accumbens
Ventral Pallidum
Amygdala
Ventral Tegmental Area
GLU
GABA
DA

6

Methylphenidate (MPH) in ADHD

Medication	Starting Dose	Maximum Dose*	Duration
Ritalin IR®	5 mg QD/BID	2 mg/kg/day	4 hr /BID
Focalin®	2.5 mg QD/BID	1 mg/kg/day	4–5 hr / BID–TID
Focalin XR®	5 mg QD	1 mg/kg/day	10–12 hr QD
Daytrana®	10 mg		6–16 hr
Concerta®	18 mg QD	2 mg/kg/day	12 hr / once
Metadate CD®	20 mg QD		8 hr / once
Ritalin LA®	20 mg QD		8 hr /once
Quillivant®	<10 mg QD		12 hr /once
Quillichew™	<10 mg QD		8 hr /once
Aptensio XR	10 mg QD		12 hr/once
Contempla XR (disintegrating tab)	8.6 mg QD	51.8 mg	12 hr/once
Jornay®	20 mg QD	100 mg	12 hr/once
Adhansia XR	25 mg QD	100 mg (adult)	to 16 hours/once

- *May exceed FDA approved dose.
- *May exceed FDA approved dose; Wilens TE, et al. *Postgrad Med*. 2010;122(5):97-109. www.drugs.com.

7

Amphetamine (AMPH) in ADHD:

Medication	Starting Dose	Maximum Dose*	Duration
Adderall®	2.5–5 mg QD	1.5 mg/kg/day	6 hr / BID
Adderall XR®	2.5–5 mg QD		12 hr / QD
Vyvanse®	30 mg QD		12–14 hr / QD
Mydayis®	12.5 mg QD	50/25 mg (adults/adol)	To 16 hr/QD
Dexedrine Tablets®	2.5–5 mg BID	1.5 mg/kg/day	3–5 hr / BID–QID
Evekeo®	2.5–5 mg BID		3–5 hr / BID–QID
Dexedrine Spansule®	5 mg QD		6 hr / QD–BID
Dyanavel XR™ (suspension)	2.5–5 mg QD	1.5 mg/kg/day	12 hr / QD
Adzenys XR™ (disintegrating tab)	6.3–12.5 mg QD	12.5 mg (adolescents)	12 hr / QD

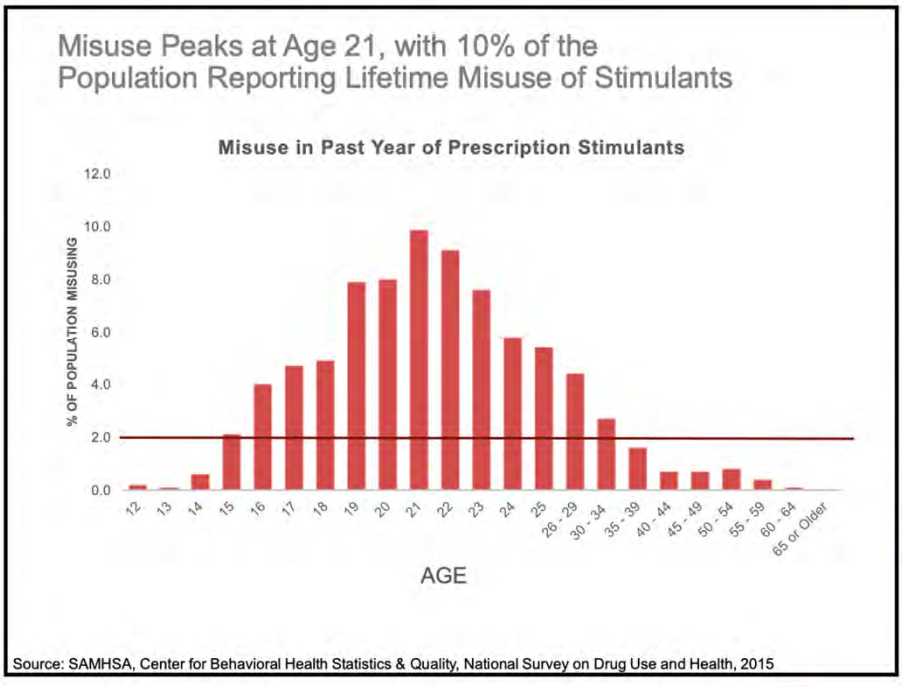
- *May exceed FDA approved dose (eg, > 20 to 30 mg/day).
- Wilens TE, et al. *Postgrad Med*. 2010;122(5):97-109.www.drugs.com.

8

Background

- Stimulant misuse highest in Transitional Age Youth (TAY) group (18yo-25yo)
- 2017 National Survey on Drug Use and Health found 7.4% of TAY reported past-year stimulant misuse

9



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Background

- 4-8% of college students have ADHD
- Stimulants are increasingly being diverted to those without a diagnosis of ADHD
- Nonmedical use (use without a prescription or not following clinical guidelines) is rising
- Rate is higher in college students compared to same-aged peers not attending college

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Background

- Most people acquire stimulants from friends or family
- Far fewer people acquire stimulants fraudulently from physicians
- Academic / pro-cognitive reasons are the top reason people misuse stimulants
- Far fewer use them to “get high”

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The American Journal on Addictions, 26: 379–387, 2017

ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1111/ajad.12551

Neuropsychological Functioning in College Students Who Misuse Prescription Stimulants

Timothy E. Wilens, MD,[1,2] Nicholas W. Carrellas, BA,[1] MaryKate Martelon, MPH,[1] Amy M. Yule, MD,[1,2] Ronna Fried, EdD,[1] Rayce Anselmo, PsyD,[2] Sean Esteban McCabe, PhD[3]

[1]Pediatric Psychopharmacology Program, Division of Child Psychiatry, Massachusetts General Hospital, Boston, Massachusetts
[2]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
[3]Institute for Research on Women and Gender, University of Michigan, Ann Arbor, Michigan

Background and Objectives: Relatively little is known about the neuropsychological profiles of college students who misuse prescription stimulant medications.
Methods: Data presented are from college students aged 18–28 years who misused prescription stimulants prescribed for attention-deficit/hyperactivity disorder and controls (no prescription stimulant misuse). Students were assessed neuropsychologically using the self-report Behavioral Rating Inventory of Executive Functioning (BRIEF-A), the Cambridge Automated Neuropsychological Test and Battery (CANTAB), and other tests of cognitive functioning. The analyses included 198 controls (age 20.7 ± 2.6 years) and 100 prescription stimulant misusers (age 20.7 ± 1.7 years).
Results: On the BRIEF-A, misusers were more likely than controls to

INTRODUCTION

Stimulant medications continue to be among the first line agents for attention-deficit/hyperactivity disorder (ADHD) in older adolescents, and young adults.[1] Many of the 4% to 5% of college students with ADHD[2] receive stimulants,[3] and stimulants are increasingly being diverted to those without a diagnosis of ADHD or a prescription.[4,5] Nonmedical use of prescription stimulants (eg, use without a prescription) has risen accordingly, and has become a public health concern.[6,7]

Several studies have shed light on the context of prescription stimulant misuse. For instance, data from

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Which college students are misusing stimulants?

- Misusers more likely to subjectively endorse executive dysfunction symptoms, and performed worse on objective tests of neuropsychological functioning.
- More likely to be white, male, attending competitive colleges

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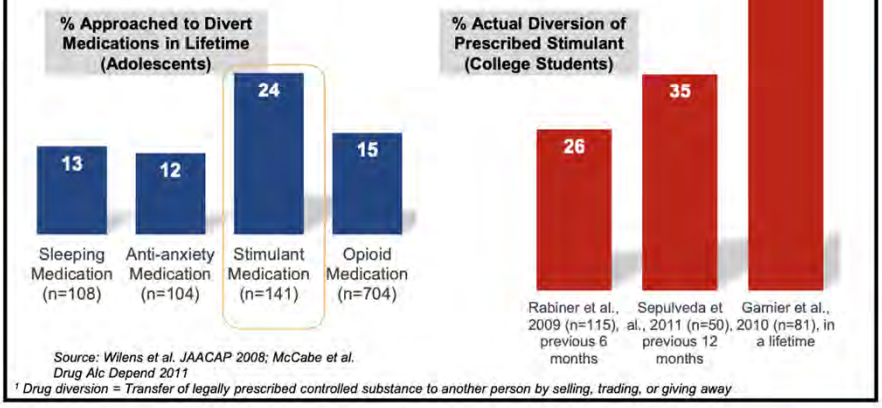
Stimulants are Frequently Diverted

- 65-85% of stimulants are diverted[1] from "friends"
  - Majority *not* "scamming" local docs
  - Not seen as potentially dangerous
- May occur in substance (ab)users during academic decline



Source: Wilens et al. JAACAP 2008; McCabe et al. Drug Alc Depend 2011

[1] Drug diversion = Transfer of legally prescribed controlled substance to another person by selling, trading, or giving away

15

Reasons for Misusing Stimulants

- To improve concentration/focus
- To stay awake
- To reduce distraction
- To get more energy
- To experiment - to see what it's like
- To have a good time with friends
- To feel good / get high

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Stimulant use in non-ADHD groups

- Mixed findings in the literature
- Large placebo affect?

Table 1
Representative studies of recent controlled studies of the cognitive enhancement effects of prescription stimulants

Study	Study Design	N	Age Range (y)	Stimulant	Dose	Cognitive Enhancement	Comments
Weyandt et al,[46] 2018	Double-blind, PBO-controlled, crossover	13	18–24	AMP	30 mg	Minimally improved attention performance (d = 0.17 – 0.73) and impaired working memory performance (d = 0.08–0.23)	Substantial effects on autonomic activity (d = 0.86–1.25; *P*<.001), subjective drug experience (d = 1.04–1.26; *P*<.01), and activated positive emotion (d = 0.71; *P*<.05)
MacQueen et al,[44] 2018	Double-blind, PBO-controlled, parallel	71	18–35	d-AMP	10 mg or 20 mg	Increased 5-choice continuous performance test for both doses in signal detection (d = 0.821, 0.758; *P*<.05) and response accuracy (d = 1.115 and 1.076; *P*<.001)	
Cropsey et al,[48] 2017	PBO-controlled, crossover	39	19–30	AMP	10 mg	None	Expecting medication was associated with cognitive enhancement and expecting placebo was associated with worse cognitive performance.
Agay et al,[45] 2014	PBO-controlled, crossover	39	20–40	MPH	0.3 mg/kg	Improved sustained attention (*P*<.05) and working memory (*P*<.01); no effects in decision making	Healthy individuals with lower baseline performance showed most improvement.
Linssen et al,[42] 2012	Double-blind, PBO-controlled, crossover	19	18–40	MPH	10 mg, 20 mg, or 40 mg	Dose-dependent improvement in memory consolidation (*P*<.05), set shifting (*P*<.01), and stopped signal performance (*P*<.01); no effects on spatial working memory or planning	
Looby & Earleywine,[47] 2011	Controlled, parallel (no active stimulant)	96	18–25	None	N/A	None	Expecting medication (blinded PBO) was associated with improved subjective mood (*P*<.01) vs no intervention.

All studies presented were randomized.
Abbreviations: AMP, mixed-salts amphetamine; d-AMP, dextroamphetamine; PBO, placebo.

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Route of use

- Most NMU is by oral administration
- Some will use intranasally (which shifts the pharmacokinetics and enhances abuse liability). Also used via inhalation (smoked) and IV injection.

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Consistent finding

- Stimulants are often misused in the context of alcohol, marijuana, and other drug use.

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Problems associated with non-medical use of stimulants

- Substance Use Disorders
- Academic decline
- ADHD
- Neuropsychological dysfunction
- Other psychopathology

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RED Flags for Misuse or Diversion

- Symptoms of intoxication or symptoms associated with heavier use (agitation, agitation, psychosis, SOB, palpitations)
- Demands for a particular, usually fast acting, medication (amphetamine IR)
  - "Extended-release doesn't work for me"
- Repeated lost prescriptions
- Discordant pill count (escalation of doses)
- Excessive preoccupation with securing medication supply
- Multiple prescribers

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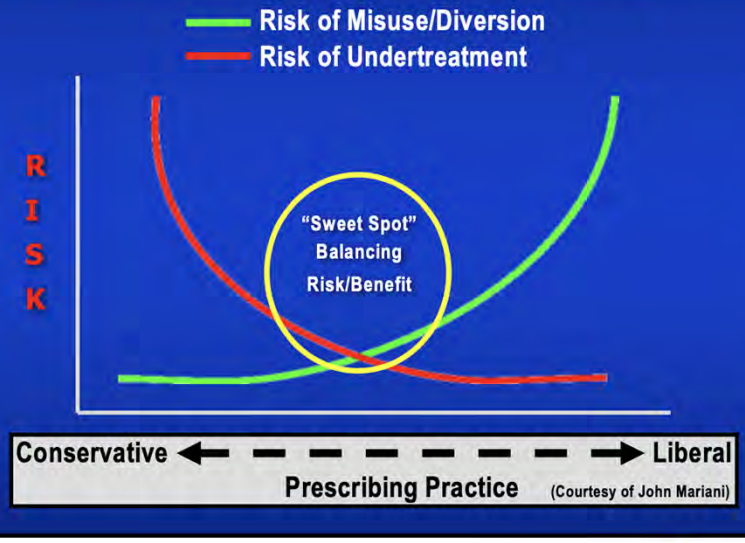
Competing Risks of Controlled Medication RX: Overall Clinical Stability and Optimal Functioning is the Therapeutic Goals



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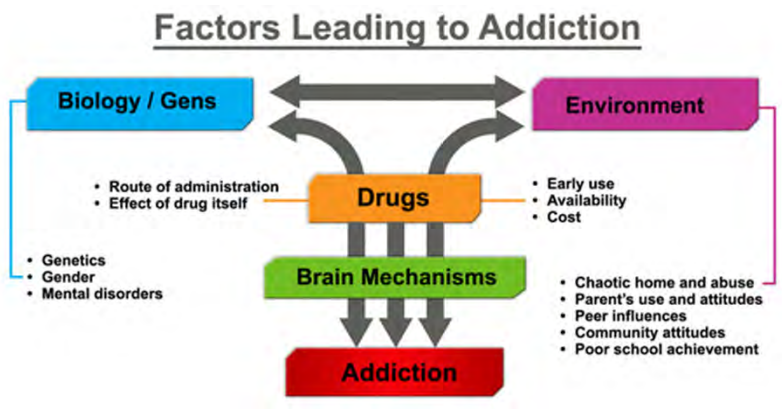
Side effects of stimulants

- Decreased appetite, insomnia, irritability, headaches, stomachaches
- Increase heart rate and blood pressure which can lead to adverse cardiovascular events in individuals with underlying cardiac conditions
- Diversion can be fatal
- May cause decompensation in people who have Bipolar Disorder
- Intoxication: symptoms include: agitation, psychosis, shortness or breath, palpitations.

23



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Patient education!

- Discuss diversion and safe storage
- Discuss legal issues of diverting stimulants (Schedule II substance) - Felony
- Prescribe the right amount! (excess supply is a driver of diversion)
- Dispel mythology of the normality of misuse – "Everyone is doing it" is simply not true.

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Other strategies

- Prescribe agents with lower abuse liability (eg non-stimulants, extended-release stimulants).
  - Atomoxetine, bupropion, Alpha-agonsists
- Reduce the use of immediate-release stimulants
- Consider use of pro-drugs (eg lisdexamfetamine)
- Check state PDMP
- More research needed to develop delivery systems which prevent non-oral use.

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More strategies

- Emphasize to patients to take medications regularly, not on a prn basis
- Limit setting: compassionate, yet boundaried
- If problems emerge, take a nonjudgmental approach
- Consider ordering neuropsychological functioning testing in college students who misuse stimulants

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Take home points

- 1) Non-medical use (NMU) of stimulants is rising
- 2) Persistent misusers of stimulants may be self-medication attentional difficulties, executive dysfunction, and academic impairment.
- 3) NMU can be prevented by optimizing patient education and using mitigation strategies to minimize diversion.

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Resources for Written Material

- Chadd.org/for-parents/medication-abuse-and-diversion/
- Coalition to Prevent ADHD Medication Misuse (CPAMM)
  - Cpamm.org/about-us/

29

Sources

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DEPARTMENT OF HEALTH

201 W. Preston Street, Baltimore, MD 21201
Toll Free: 1-800-492-5231 TTY: 1-800-735-2258
https://mmcp.health.maryland.gov/pap/pages/paphome.aspx