

Symptoms and Circuits of ADHD

ADHD

- Inattentive symptoms
 - Selective
 - Dorsal anterior cingulate cortex
 - Sustained attention problem solving
 - DLPFC
- Impulsive symptoms
 - Orbitofrontal cortex
- hyperactive symptoms
 - prefrontal motor cortex

Hypotheses:

- Assessing sustained attention and problem solving
 - N-back test:
 - If the a number comes up and you have to remember the answer that many spaces back
 - Lights up dorsal lateral prefrontal cortex.
- Assessing selective attention
 - the Stroop test
 - see a word like Blue, but it is the color orange. You ask the color.
 - Brain scanner you light up the anterior singular cortex.
- Hyperactivity
 - You tune the brain my using medications to tune the neurotransmitters

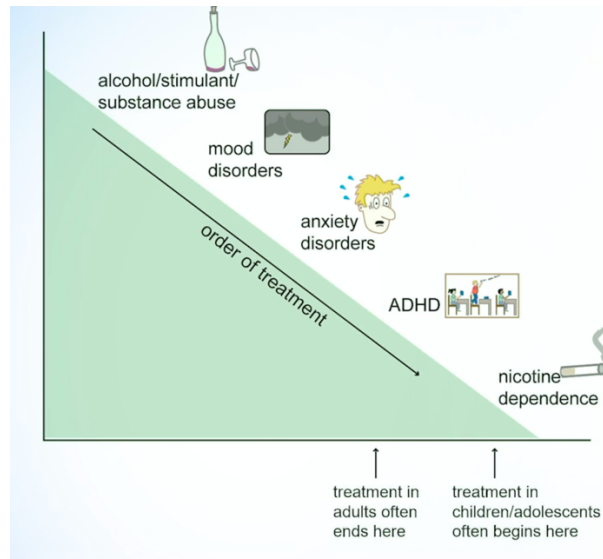
ADHD Core Symptoms: regional problems of the Prefrontal cortex tuning

- Orbital frontal cortex
 - Limbic
 - Interrupts blurt out or not wait turn impulsive
 - Motor
 - Fidgety climb hyperactive
- Dorsal lateral prefrontal cortex & Dorsal anterior cingulate cortex
 - Cognitive
 - Does not finish, disorganized, avoids sustained efforts,
 - Problems of sustain attention and problem solving
 - Does not listen is distracted, forgetful, careless
 - Problems of selective attention
- VNPFC
 - Limbic
 - Steal a car cruelty or pick a fight
 - Conduct disorder
 - Mood instability, mania, anxiety
 - Bipolar anxiety spectrum
 - Temper tantrums, argumentative, disobedient, and aggressive
 - Oppositional defiant disorder

Theory: ADHD is a deficient arousal

- Weak signals of NE and DA
- Inefficient cognitive dysfunction and inattention

How DA and NE hypothetically tune the pFC (prefrontal cortex)
 ADHD low DA and SE (reduces noise, and signal reduction)



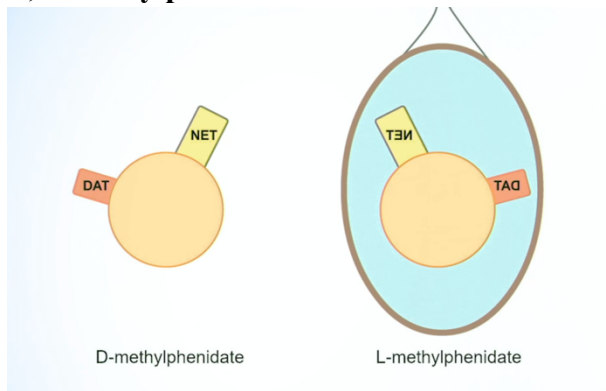
Importance of NE and DA levels in the PFC in ADHD

- Noise
 - Fidget and shift attention due to too much noise
- Signal
 - Sit in your seat and focus (not there in ADHD)
- ADHD
 - Low signals and/or too much noise
- Treatment
 - Increase NE and increase DA
 - Use a stimulant

Chronic stress

- Too much noise and not enough signals
- Due to too high of NE and DA
 - Which over time leads to depletion
 - Treatment increase NE and increase DA

D,L-Methylphenidate

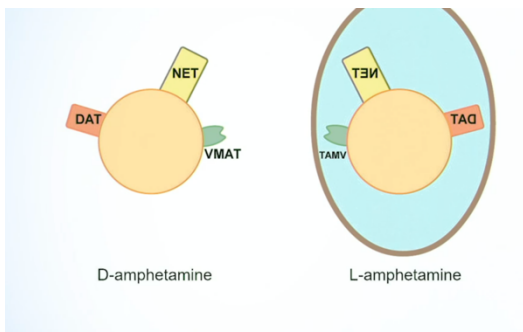


- Work by going onto the DAT by blocking the transport
- Slower onset, slowly absorbed.

D,L Methylphenidate Formulations	Brand Names	Duration	Dosing	Approval
Immediate-release tablet	Ritalin	Early peak 3–4-hr duration	Second dose at lunch	Ages 6 to 12 and adults
Immediate-release oral solution	Methylin	Early peak 3–4-hr duration	Second dose at lunch	Ages 6 to 12
Extended-release tablet	Ritalin SR, Methylin ER, Metadate ER	Early peak 3–8-hr duration	Lunch dosing may be needed	Ages 6 and older
Extended-release tablet	Concerta	Small early peak 12-hr duration	Once daily in the morning	Ages 6 and older
Extended-release chewable tablet	QuilliChew ER	Peak at 5-hr 8-hr duration	Once daily in the morning	Ages 6 and older
Extended-release capsule	Metadate CD	Strong early peak 8-hr duration	Once daily in the morning	Ages 6 to 17
Extended-release capsule	Ritalin LA	Strong early peak and again at 4 hr 6–8-hr duration	Once daily in the morning	Ages 6 to 12
Extended-release capsule	Aptensio XR	Up to 12-hr duration	Once daily in the morning	Ages 6 and older
Extended-release oral suspension	Quillivant XR	Peak at 5-hr 12-hr duration	Once daily in the morning	Ages 6 and older
Extended-release transdermal patch	Daytrana	Peak at 7–10-hr 12-hr duration	Once daily in the morning	Ages 6 to 17
Orally disintegrating tablet	Cotempla XR-ODT	12-hr duration	Once daily in the morning	Ages 6 to 17
Extended-release capsule	Jornay PM	Initial absorption delayed by 10 hrs Peak at 14 hr	Once daily in the evening	Ages 6 and older
Extended-release capsule	Adhansia XR	Two peaks (at 1.5- and 12-hrs)	Once daily in the morning	Ages 6 and older

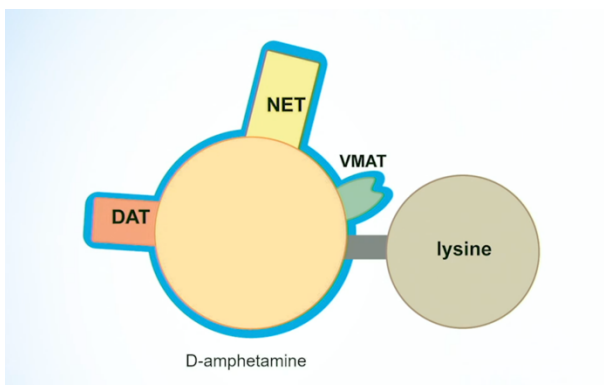
D-Methylphenidate Formulations	Brand Names	Duration	Dosing	Approval
Immediate-release tablet	Focalin	Early peak 4–6-hr duration	Second dose at lunch	Ages 6 to 17
Extended-release capsule	Focalin XR	Two peaks (after 1.5 and 6.5 hrs) 8–10-hr duration	Once daily in the morning	Ages 6 to 17 and adults

D,L-Amphetamines



- Stimulant
- VMAT: blocks the transporter on the vesicle

Lisdexamfetamine



- When you eat this, the stomach takes off the piece of lysine, and you can absorb it.

Mechanisms of actions of amphetamines

- Depends on route or dose levels
- Great drug at moderate dose, horrible drug at high dose
- Blocks the transporter and kicks the dopamine out
- Transported instead of dopamine
- Goes into the vesicles VMAT
- Then kicks dopamine out of vesicles
 - If too high it'll reverse the transporter kick dopamine out

D-Amphetamine Formulations	Brand Names	Duration	Dosing	Approval
Immediate-release tablet	Zenzedi	4–5-hr	Second dose at lunch	Ages 3 to 16
Immediate-release oral solution	ProCentra (previously Liquadd)	4–6-hr	Second dose at lunch	Ages 3 to 16
Extended-release capsule	Dexedrine	6–8-hr	Once daily in the morning	Ages 6 to 16
Lisdexamfetamine dimesylate capsule	Vyvanse	Peak at 3.5-hr Up to 12-hr duration	Once daily in the morning	Ages 6 to 17 and adults

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Slow dose stimulants amplify tonic NE and DA signals

- Give orally
- Do not give too high a dose
- D works better than L
- Improves tonic signals
 - Will sharpen signals and dampen your noise

Pulsatile stimulants amplify tonic and phasic NE and DA signals

- This is why we usually use extended release, less abuse steady dopamine release
- Immediate release leads to a quick firing of dopamine and crashing.

NDRI

- Used for ADHD atomoxetine, Bupropion used off label
- Works well in adults who have to tried anything before
- If they fail this may try a stimulant

Atomoxetine in ADHD with weak prefrontal NE and DA signals

- Get increase of NE and DA due to NDRI blocking NE transporter

Chronic stress with atomoxetine in ADHD with excessive prefrontal NE and DA signals

- Prefrontal cortex excessive NE and DA signals
 - Anxiety, ADHD, substance use,
- Treat with atomoxetine

Guanfacine

- Alpha 2 agonist
- Mechanism of action affect three alpha 2 receptors
- Better tolerated than clonidine

Clonidine

- Alpha 2 agonist
- Mechanism of action affect three alpha 2 receptors

Alpha 2A agonist in ADHD,

- Could not have something wrong with DA or NE but may have a problem with alpha 2
- Wont know until you try
- This sometimes gets added to stimulants
- Can also work with oppositional symptoms
 - Hypothetically very low signals in VMPFC
- In VMPFC
 - Noise high
 - Temper tantrums argumentative
 - Disobedient
 - Aggressive
 - Signal low
 - Behave cooperate

Viloxazine ER

- NET inhibitor
- 5HT2C antagonism
- 5HT2B possibly 5HT7C
- Raise serotonin