ADHD: The mystery of the diagnosis, genetics, neurobiology & treatment

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Disclosures

- Disclosures: I am contracted as a speaker for Allergan, Otsuka, Genomind, Avanir, Neurocrine
- I am a member of Nurses Against Violence Unite, Slaying Dragons, Missouri Nurses Association, Sigma Theta Tau Iota, Phi Kappa Phi, Golden Key, Phi Beta Kappa, St. Louis Nurses in Advanced Practice, American Psychiatric Nurses Association, American Association of Nurse Practitioners, American Nurses Association

Objectives

- Introduce the state of the science for the diagnosis and treatment of Attention Deficit Hyperactivity Disorder (ADHD)
- Explore Neurobiology, neuropathology, genetics
- Explore Assessment
- Explore Treatment options

By the End of the Presentation the Learner Will:

- Understand how to identify symptoms of ADHD
- Be able to Assess ADHD
- Make evidence Based recommendations for treatment for ADHD

Definitions

Inattention

Manifests behaviorally in ADHD as wandering off task, lacking persistence, having difficulty sustaining focus, and being disorganized and is not due to defiance or lack of comprehension. .

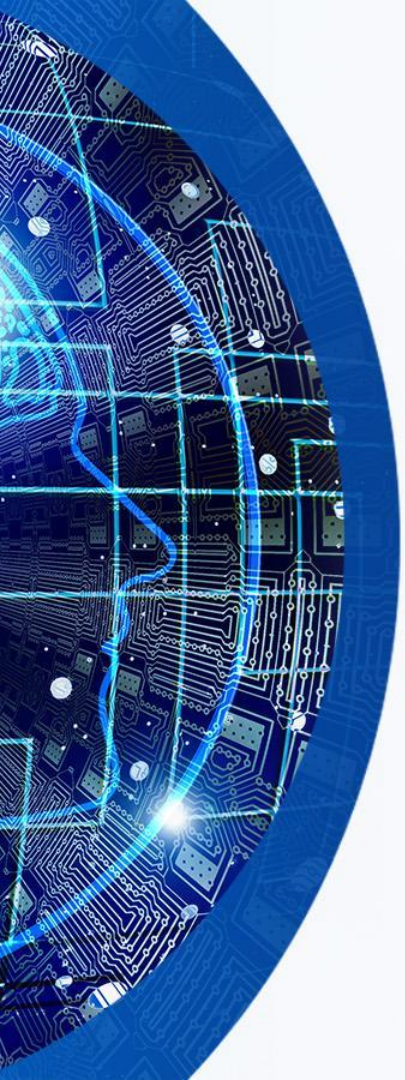
Hyperactivity

Refers to excessive motor activity (such as a child running about) when it is not appropriate, or excessive fidgeting, tapping, or talk ativeness.

In adults, hyperactivity may manifest as extreme restlessness or wearing others out with their activity.).

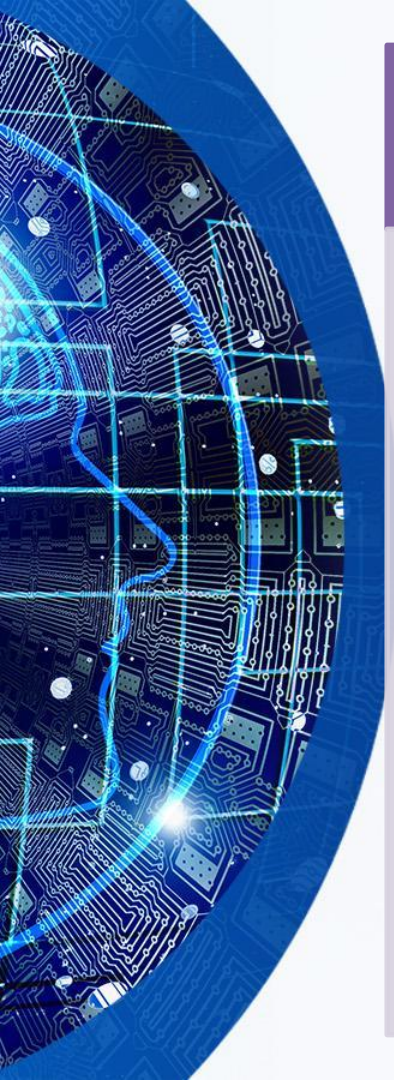
Impulsivity

may reflect a desire for immediate rewards or an in ability to delay gratification. Impulsive behaviors may manifest as social intrusiveness (e.g., interrupting others excessively) and/or as making important decisions without con sideration of long-term consequences (e.g., taking a job without adequate information).



Prominent Cognitive Models of ADHD

- Executive Dysfunction
- State Regulation
- Delay Aversion
- Dual Pathways Model
- Dynamic Developmental Theory
- Default Mode Network



Executive Dysfunction

- Deficits in higher order cognitive processes:
  - planning,
  - sequencing,
  - reasoning,
  - holding attention to a task,
  - working memory
  - inhibition
- Earlier sensory deficits precede motor inhibitory responses

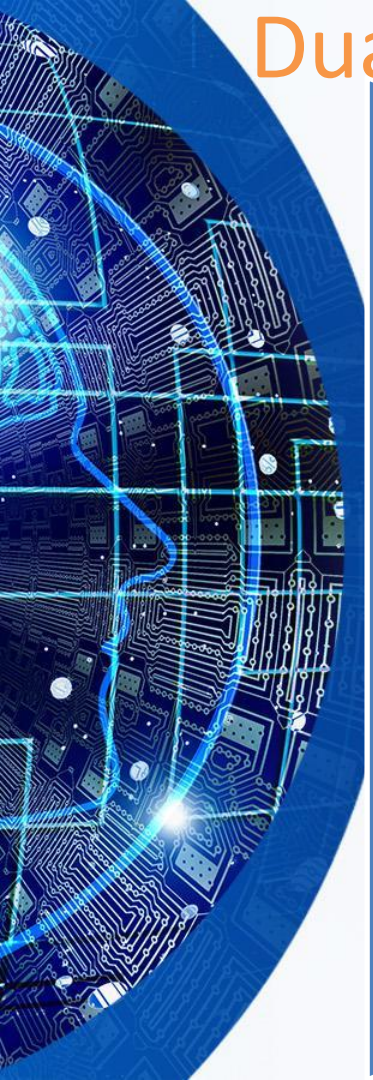
State Regulation

- Nonoptimal energetic state can explain performance deficits in ADHD.
- Performance efficiency is considered product of elementary cognitive stages and energy distribution.
- Availability of processes related to arousal & activation levels of individuals.
- Effort needed to meet task demands & compensate for suboptimal arousal or activation states

Delay Aversion

- Delay aversion = reason individuals with ADHD do not like to wait.
- Motivational account of ADHD vs. a cognitive explanations
- Inattentiveness & hyperactivity proposed to result from attempts to reduce subjective experience of delay in situations where delay cannot be avoided

Dual pathway models



1. The first dual pathway hypothesis proposed the existence of two distinct pathways to ADHD: delay aversion reflecting motivational factors, and inhibitory deficits reflecting poor cortical or executive control

2. Multivariate family and twin analyses identified two familial cognitive factors that account for most of the familial effects on ADHD: the first factor indexed by reaction time and reaction time variability, the second factor indexed by omission and commission errors. These measures are proposed to reflect state-regulation and executive function deficits, respectively

3. The identification of two key pathways in the multivariate family and twin studies is reflected in a developmental model proposed by Halperin that suggests that an early enduring primary neurodevelopmental abnormality leads to impairments that are modified as executive functions mature throughout development. It is proposed that the balance between these two processes leads to individual differences in persistence of ADHD during adolescence and early adulthood

Dynamic developmental theory

1: Altered reinforcement of novel behavior

Theory suggests 2 main behavioral mechanisms

underpinning symptoms of ADHD

Basis for theory lies in delay-of-reinforcement gradient between response to stimulus and reinforcement of response

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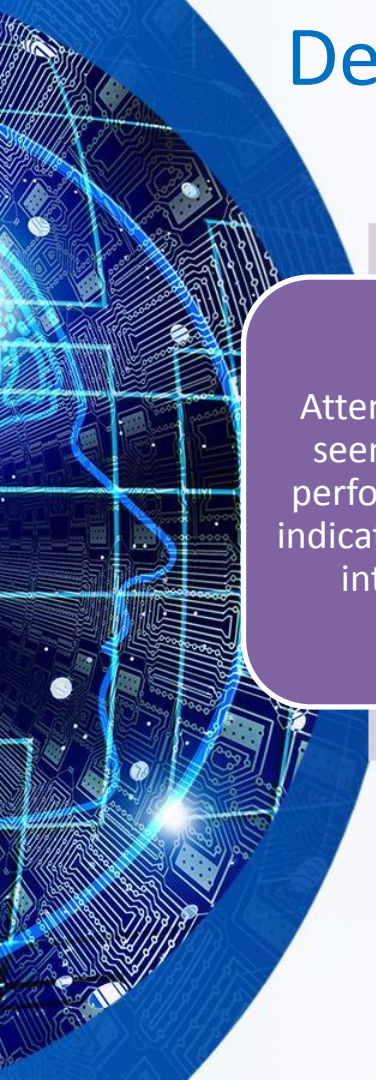
Proposed in ADHD-window of opportunity for reinforcement is smaller --- so socially desirable behaviors not reinforced fast enough, leading to symptoms associated with ADHD

2. Deficient extinction of inadequate behavior

Default mode network



Attentional lapses seen during task performance could indicate role of DMN interference.

The default DMN represents brain regions found to be activated during resting conditions. During normal task performance the DMN is attenuated.

In ADHD variable performance may arise because poor attenuation of activity of the DMN.

This may cause the DMN activity to intrude on task performance and thus cause periodic lapses of attention

Neurobiology Overview

Symptoms

Predominantly Inattentive

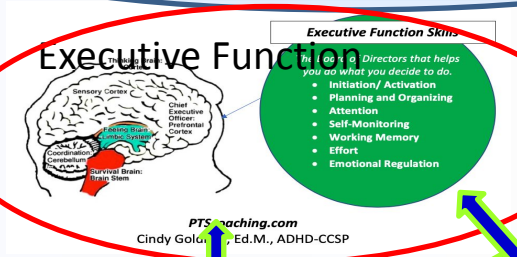
Combined

Predominantly Hyperactive

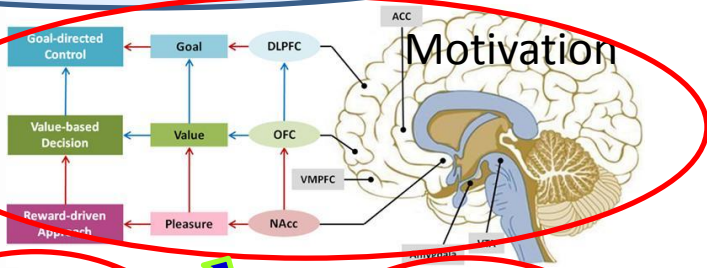
Basic Processes

Neural Mechanisms

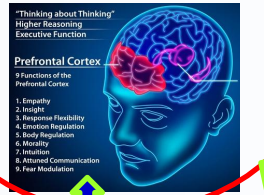
Executive Function



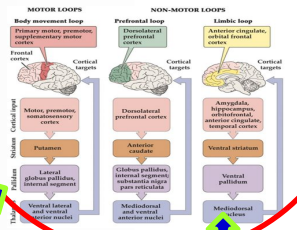
Motivation



Prefrontal Cortex



Basal Ganglia



Cerebellum

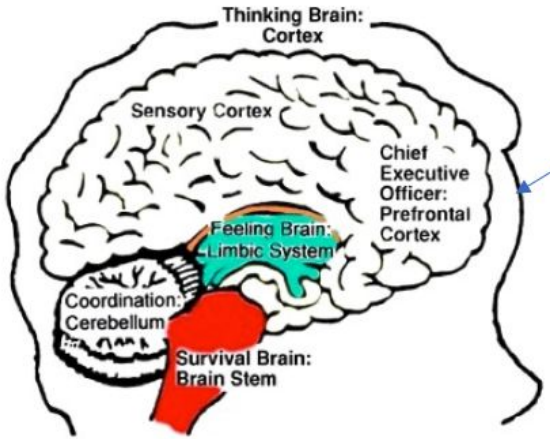
Noradrenaline

Dopamine

Serotonin

Neurobiology: Executive Function

"Difficulty with Problem Solving to Reach a Goal"



Executive Function Skills

The Board of Directors that helps you do what you decide to do.

- **Initiation/ Activation**
- **Planning and Organizing**
- **Attention**
- **Self-Monitoring**
- **Working Memory**
- **Effort**
- **Emotional Regulation**

PTScoaching.com

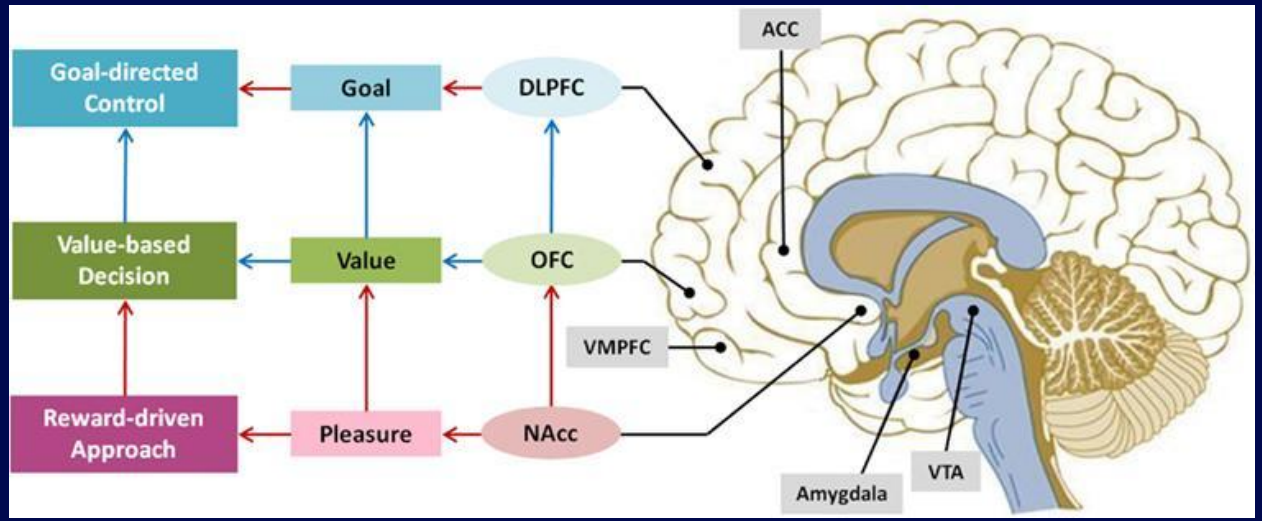
Cindy Goldrich, Ed.M., ADHD-CCSP

Most reliable and common ADHD deficits:

- Vigilance
- Inhibition
- Working memory
- Planning

(Tripp & Wickens, 2009)

Neurobiology: Motivation

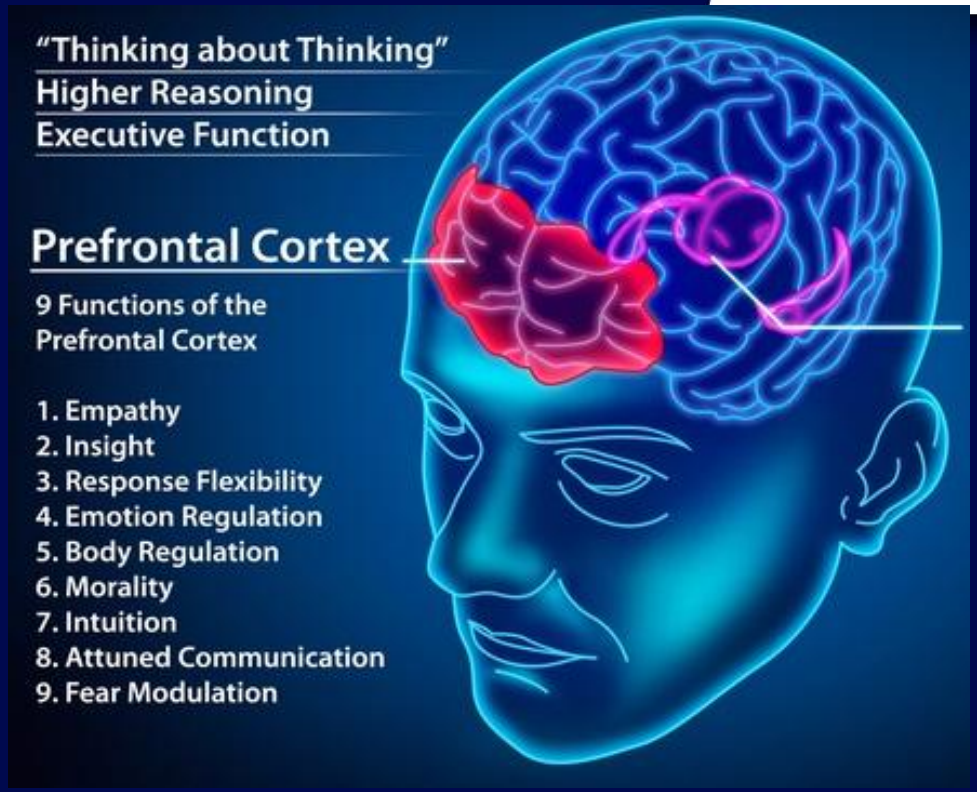


Most reliable and common ADHD deficits:

- Preference for immediate reward
- Needs consistent feedback and praise

(Tripp & Wickens, 2009)

Executive Function Dopamine Deficiency



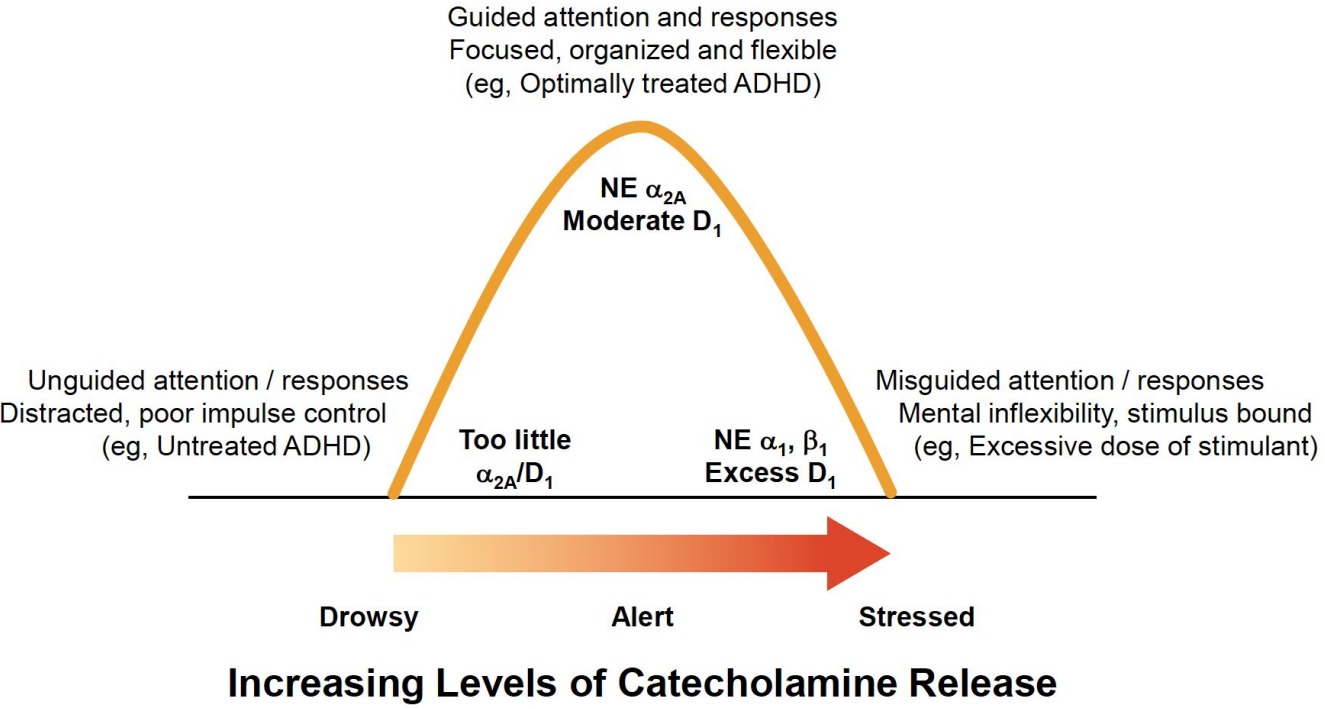
Dopamine / Norepinephrine Deficiency

- Emotional hypersensitivity
- Poor insight / Unaware
- Hyperflexibility / impulsivity

Body dysregulation – Arousal dysregulation

- Morality / Judgement impaired
- Poor Intuition/impulsive
- Poor Communication /Distracted
- Fear of Rejection

he Prefrontal Cortex Requires a Proper Level of Catecholamines for Optimal Function

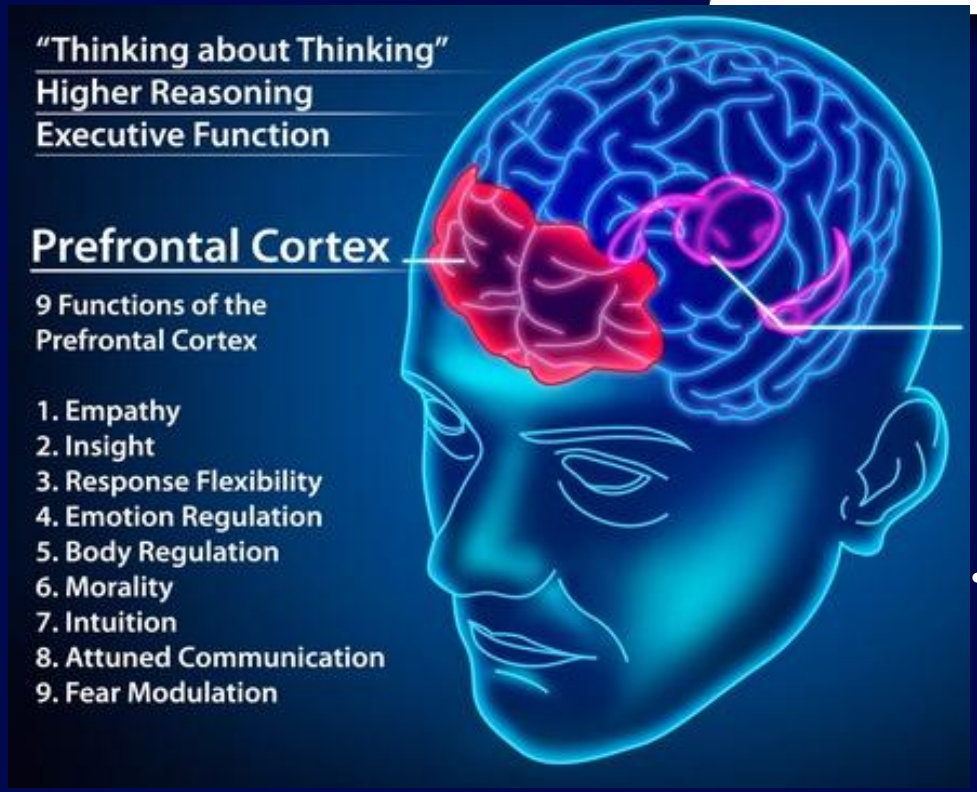


rnsten AF. *J Pediatr*. 2009;154(5):I-S43.

"Higher doses of stimulant medications have been shown to impair prefrontal cortical cognitive functioning and to produce mental inflexibility, as is customarily observed in individuals who abuse high doses of central nervous system stimulant drugs, like cocaine and methamphetamine."

Excerpt From: Victor B. Stolberg. "ADHD Medications." Apple Books.

Executive Function – Dopamine Excess



- Emotional Insensitivity
- Smart / Astute
- Inflexible / Rigid / Stubborn

Body dysregulation – Arousal dysregulation

- Morality / Judgement impaired – high standards
- Paranoid/Compulsive

Poor Communication /Rumination /obsessive

- Less fear of rejection / higher self-esteem

Genetics

Adrenergic 2A – Receptor (ADRA2A)	•Improved MPH response with MspI G allele. & G allele linked to higher hyperactive-impulsive scores •link between C/C homozygosity and improved MPH response
Dopamine Receptor D2 (DRD2)	•Faster MPH response with C allele. Trend for rs2283265 T allele carriers to require a higher MPH dose. •Faster MPH response with C allele.
Dopamine Receptor D3 (DRD3)	•Improved MPH response with C/C homozygosity according to teacher but not parent ratings.
Catechol-O-Methyltransferase (COMT)	•link between Val/ Val homozygosity and an improved MPH respone
Latrophilin 3 / Adhesion G Proteincoupled Receptor L3 (LPHN3/ADGRL3)	• Improved MPH response on inattentive symptoms with rs6551665 G allele in both single marker and rs6551665, rs1947275, rs9683662 haplotype analysis. •Improved stimulant response linked to having rs6551665

Genetics

Brain-Derived Neurotrophic Factor (BDNF)	• Improved MPH response with Val/Val homozygosity.
Dopamine Beta Hydroxylase (DBH)	• Faster MPH response with C allele. Trend for rs2283265 T allele carriers to require a higher MPH dose.
N-methyl-D-aspartate (NMDA) Receptor Subunit 2B (GRIN2B).	• Improved MPH response with C/C genotype.
Metabotropic Glutamate Receptor Subtype 7 (mGluR7/GRM7)	• Improved MPH response with G/A genotype.
carboxylesterase 1 (CES 1)	• 143Glu allele required a lower MPH dose for symptom reduction compared to Gly/Gly homozygotes.

Limitations of PGx Testing

- Interpretation of ADHD PGx study results constrained by:
  - Heterogeneity
  - Limitations in study design
    - (open label)
    - Inability to account for placebo effects makes it difficult
- Make it difficult to identify true medication response and its association with genetic variability

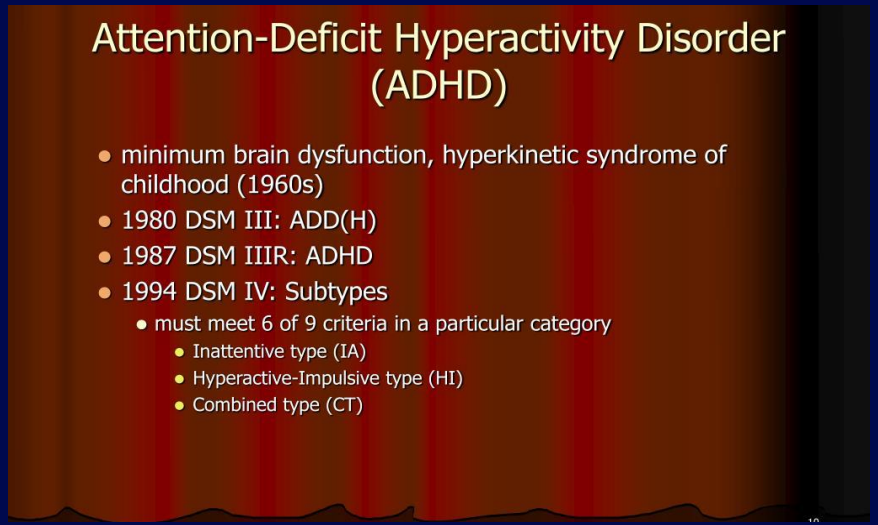
Attention-Deficit Hyperactivity Disorder Diagnostic Criteria

- Symptoms present prior to age 12 years.
- Present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
- Symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
- The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder)

Specify whether:
- **(F90.2) Combined presentation**
- **(F90.0) Predominantly inattentive presentation**
- **(F90.1) Predominantly hyperactive/impulsive presentation**

Specify if:
in partial remission
In full remission

Specify current severity:
Mild
Moderate
Severe



Diagnostic Features

- Persistent pattern of inattention and/or hyperactivity-impulsivity
- Interferes with functioning or development
- Several symptoms must be present before age 12
- Must be in more than one setting (home, work, school)
- In the uncommon cases where there is a known genetic cause (e.g., Fragile X syndrome, 22qll deletion syndrome), the ADHD presentation should still be diagnosed.

Inattention: Six (or more) of the following:

1. Often fails to give close attention to details or makes careless mistakes
2. Often has difficulty sustaining attention in tasks or play activities
3. Often does not seem to listen when spoken to
4. Often does not follow through on instructions
5. Often has difficulty organizing tasks and activities
6. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort
7. Often loses things necessary for tasks or activities
8. Is often easily distracted by extraneous
9. Is often forgetful in daily activities

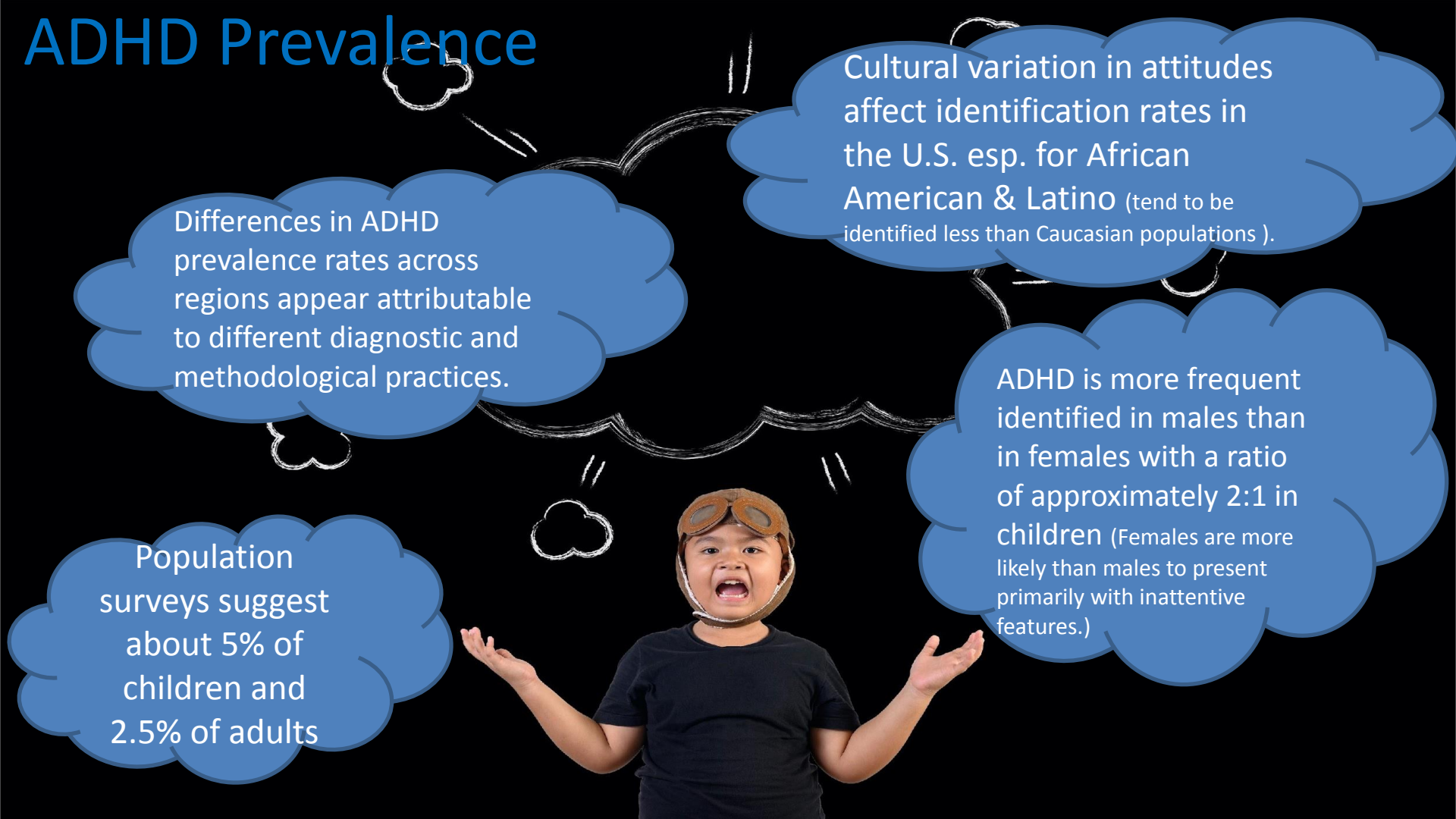
Hyperactivity and impulsivity: Six (or more) of the following symptom:

1. Often fidgets with or taps hands or feet or squirms in seat.
2. Often leaves seat in situations when remaining seated is expected
3. Often runs about or climbs in situations where it is inappropriate. **(Note:** In adolescents or adults, may be limited to feeling restless.)
4. Often unable to play or engage in leisure activities quietly.
5. Is often "on the go," acting as if "driven by a motor"
6. Often talks excessively.
7. Often blurts out an answer before a question has been completed
8. Often has difficulty waiting his or her turn
9. Often interrupts or intrudes on others

Attention-Deficit Hyperactivity Disorder Associated Features

- Mild delays in language
- Motor delays (not specific)
- Social development (not specific)
- Low frustration tolerance
- Irritability
- Mood lability
- Cognitive problems on tests of attention, executive function, or memory
- Increased risk of suicide attempt especially with substance use disorders (SUDs)
- Academic impairment / work impairment
- Increased slow wave EEGs
- Reduced total brain volume on MRI
- Delay in posterior to anterior cortical maturation
- Reduced behavioral inhibition, effortful control, or constraint; negative emotionality; and/or elevated novelty seeking behavior

ADHD Prevalence



Cultural variation in attitudes affect identification rates in the U.S. esp. for African American & Latino (tend to be identified less than Caucasian populations).

Differences in ADHD prevalence rates across regions appear attributable to different diagnostic and methodological practices.

ADHD is more frequent identified in males than in females with a ratio of approximately 2:1 in children (Females are more likely than males to present primarily with inattentive features.)

Population surveys suggest about 5% of children and 2.5% of adults

Development and Course

Toddler

- **Excessive motor activity**
- Symptoms are **difficult to distinguish** before age 4

Preschool

- Main manifestation **hyperactivity**

Elementary School

- Typical age identified
- Inattention be comes impairing

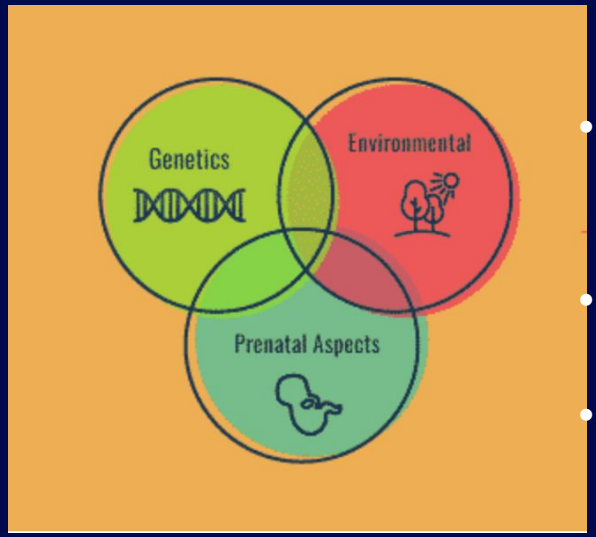
Adolescence

- The Disorder relatively stable
- Some antisocial behaviors
- Motoric hyperactivity less obvious
- **Restlessness, inattention, poor planning**, & impulsivity persist.

Adulthood

- **Inattention, restlessness,& impulsivity** remain problematic
- Hyperactivity diminishes
- Many remain impaired into adulthood.

Attention-Deficit Hyperactivity Disorder Diagnostic Criteria



Environmental.

- Very low birth weight (less than 1,500 grams) conveys a two- to three fold risk for ADHD (but most children with low birth weight do not develop ADHD)
- Although ADHD is correlated with smoking during pregnancy, some of this association reflects common genetic risk.
- A minority of cases may be related to reactions to aspects of diet.
- There may be a history of child abuse, neglect, multiple foster placements, neurotoxin exposure (e.g., lead), infections (e.g., encephalitis), or alcohol exposure in utero. (Exposure to environmental toxicants has been correlated with subsequent ADHD, but it is not known whether these associations are causal.)

Attention-Deficit Hyperactivity Disorder Diagnostic Criteria

Genetic and physiological.

- ADHD is elevated in the first-degree biological relatives of individuals with ADHD.
  - While specific genes have been correlated with ADHD, they are neither necessary nor sufficient causal factors.
- Visual and hearing impairments, metabolic abnormalities, sleep disorders, nutritional deficiencies, and epilepsy should be considered as possible influences on ADHD symptoms.
- ADHD is <u>not associated</u> with specific physical features
  - rates of minor physical anomalies (e.g., hypertelorism, highly arched palate, low-set ears) may be relatively elevated.
- Subtle motor delays and other neurological soft signs may occur.
  - (Note that marked co-occurring clumsiness and motor delays should be coded separately)

Functional Consequences ADHD

- Reduced school performance and academic attainment
- Social rejection
- Poorer occupational performance, attainment, attendance, and higher probability of unemployment
- Elevated interpersonal conflict.
- Higher rates of conduct disorder in adolescence and antisocial personality disorder in adulthood
- Higher raters of SUD and incarceration
- Higher rates of injury
- Higher rates of traffic accidents
- Elevated rates of obesity
- Others interpret frequently as lazy, irresponsible, or unable to cooperate
- Family relationships characterized by discord and negative interactions.
- Peer relationships *are* often disrupted
- Obtain less schooling, have poorer vocational achievement, and have reduced intellectual scores than their peers

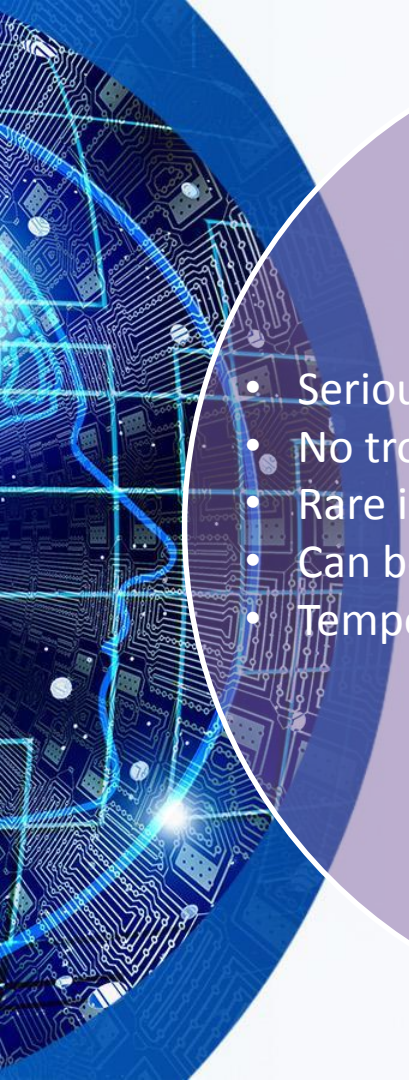
ODD co-occurs with ADHD half of children with combined presentation and a quarter with inattentive presentation.

ODD

- Resist conforming to demands
- Aggressive
- Purposefully annoys
- More difficult to manage
- Able to control activity level
- Manipulative
- Negative, hostile, defiant
- Stubborn / “Head strong
- Usually highly intelligent
- Temper tantrums & Tirades
- Spiteful & Vindictive
- Argues with authority figures
- Interrupts
- Usually listens when spoken to

ADHD

- Avoidant of demands needed sustained effort
- Forgetting instructions,
- May develop secondary oppositional attitudes toward tasks after trying to succeed and giving up.
- Impulsive
- Not purposeful
- Remorseful
- Interrupts r/t to lack of awareness others are talking
- Distracted when spoken to



IED

- Serious aggression
- No trouble sustaining attention
- Rare in childhood
- Can be comorbid with ADHD
- Temper tantrums & Tirades

Impulsive

ADHD

- Generally not aggressive
- Trouble sustaining attention
- Must be present in childhood
- Forgetting instructions
- Remorseful

Specific Learning Disorder

- Inattention not impaired outside of school-work
- May appear inattentive at school due to frustration, lack of ability, or lack of interest similar to ADHD – don't have this problem outside of school

Inattentive

ADHD

- Inattentive in all environments
- A diagnosis of ADHD in intellectual disability requires that inattention or hyperactivity be excessive for mental age.

ASD

- Social disengagement / or severe difficulties with engagement
- Social isolation or difficulties social interactions (may not be as evident in females)
- Difficulties with facial, tonal, or non-verbal communication (may be less severe in females)
- Difficulty with change in environment and routine
- May tantrum from change routine
- Can both over or under talk

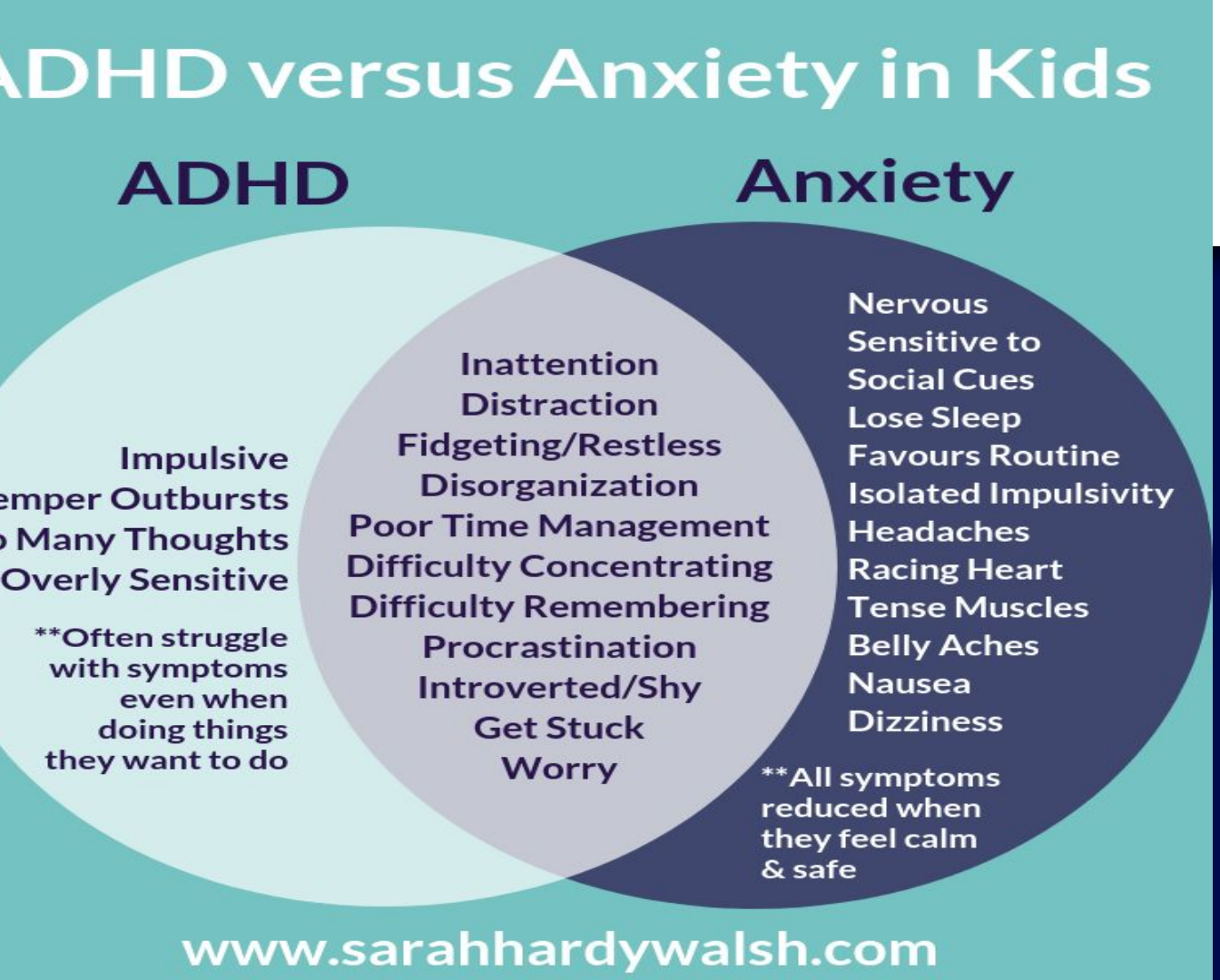
Inattentive

Social dys.

Diff. Behav.

ADHD

- Socially engaged/ may fear rejection
- Difficulties with interactions may arise from impulsivity
- Doesn't have difficulty with facial, tonal, or non-verbal communication
- Doesn't have difficulty with change in environment and routine
- May tantrum from impulsivity or poor self control
- Can both over or under talk



Reactive attachment disorder. Children with reactive attachment disorder may show social disinhibition, but not the full ADHD symptom cluster, and display other features such as a lack of enduring relationships that are not characteristic of ADHD.

Depression

- Not usually as active
- Marked change in mood
- Acute changes in concentration
- Acute changes in concentration after a stressful life event
- Changes in eating and sleeping habits
- Loss in pleasure of most activities

ADHD

- Still active
- No mood changes
- Not much variability in attention and focus deficits
- Appetite and sleeping are not acutely effected
- Desire to engage in activities not effected

Bipolar D/O

- Not generally forgetful
- Can usually complete tasks
- Decreased sleep (less than 6 hours in mania)
- May not have been present in childhood
- Mood disruption
- Usually elevated self esteem
- Can have psychosis
- Deliberate verbal aggression
- Deliberate destruction of property
- Can have SI

Inattention
Impulsivity
Hyperactivity
Distractibility
Rapid Speech

ADHD

- Forgetful
- Doesn't complete tasks
- Must be present in childhood
- Bedtime resistance
- No mood fluctuation except for with learning demands
- Usually low self esteem
- Never has psychosis
- Verbal aggression due to frustration
- Destrution of property due to inattention
- NO SI

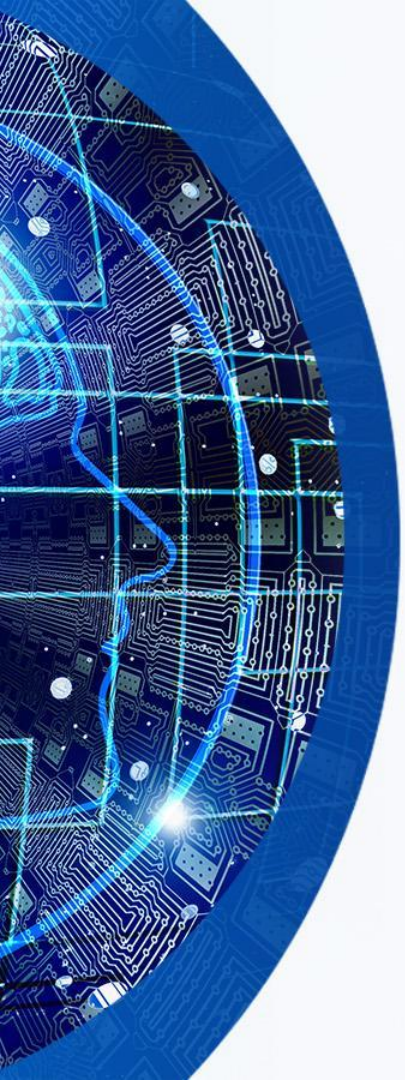
DMDD

- Depressive Disorder
- Mood expression abnormal
- Key symptoms: irritability, frustration & intolerance
- Not episodic
- Impacts all environments
- Associated with dangerous behavior
- Impulsiveness, disorganization, inattention not essential to the illness

Inattentive

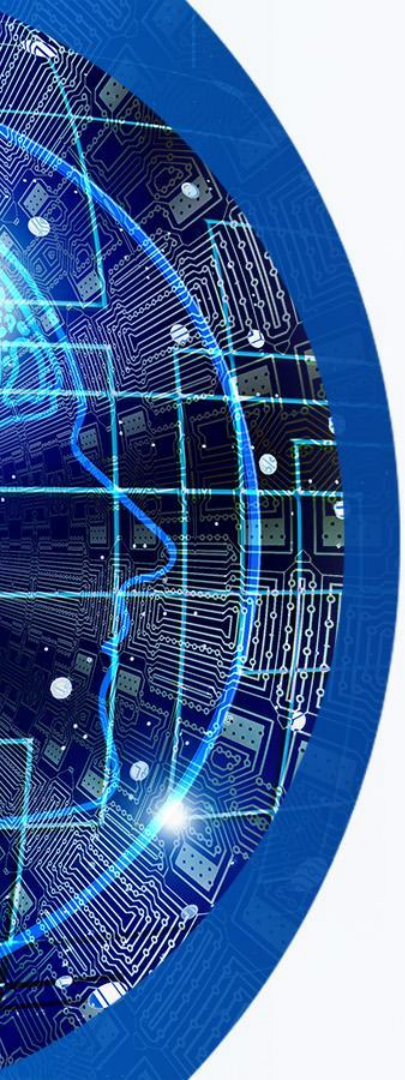
ADHD

- Inattentive in all environments
- Neurodevelopmental disorder
- No mood or anxiety criteria
- Impacts learning and structured environments most
- Impulsiveness, disorganization, inattention ARE essential to the illness



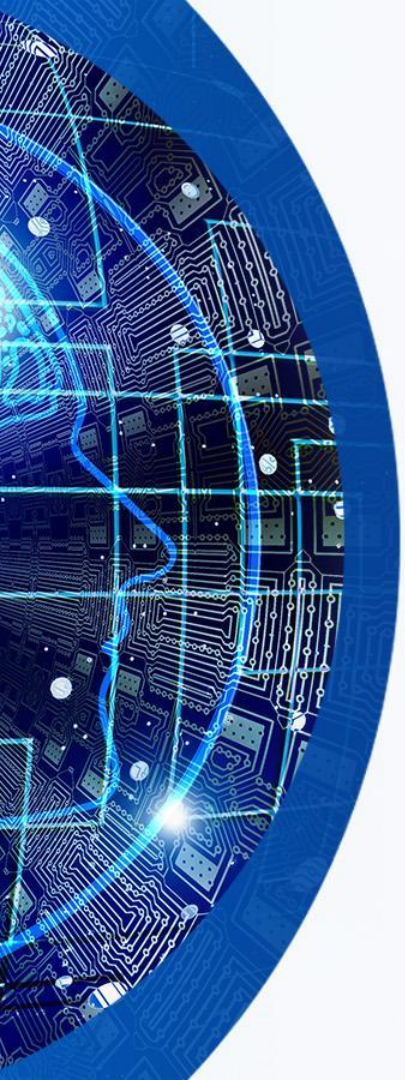
Differential Other Disorders

- **Medication-induced symptoms of ADHD.** Symptoms of inattention, hyperactivity, or impulsivity attributable to the use of medication are diagnosed as other specified or unspecified other (or unknown) substance-related disorders.
- **Neurocognitive disorders.** Early major neurocognitive disorder (dementia) and/or mild neurocognitive disorder are not known to be associated with ADHD but may present with similar clinical features.
- **Psychotic disorders.** ADHD is not diagnosed if the symptoms of inattention and hyperactivity occur exclusively during the course of a psychotic disorder.
- **Substance use disorders.** Differentiating ADHD from substance use disorders may be problematic; clear evidence of ADHD before substance misuse is essential for differential diagnosis.
- **Tic Disorders**: Motoric behavior generally fixed and repetitive (e.g., body rocking, self-biting). Frequent multiple tics can be mistaken for the generalized fidgetiness of ADHD.



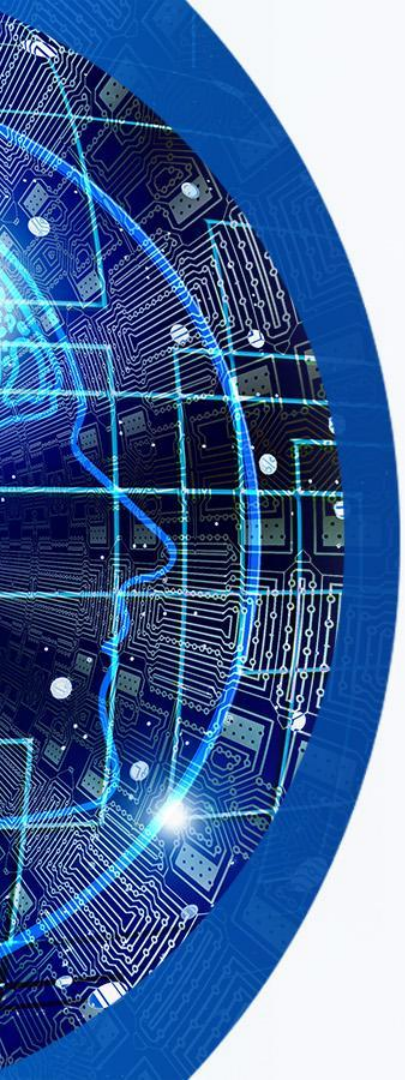
Differential Other Disorders

- **Personality disorders.** In adolescents and adults, it may be difficult to distinguish ADHD from borderline, narcissistic, and other personality disorders.
  - Share the features of disorganization, social intrusiveness, emotional dysregulation, and cognitive dysregulation.
  - ADHD not characterized by fear of abandonment, self-injury, extreme ambivalence, or other features of personality disorder.



ADHD Quick Check Question

- What is true regarding Bipolar Disorder vs. ADHD?
- A) Patients with Bipolar Disorder generally sleep more than patients with ADHD
- B) Patients with ADHD don’t have verbal aggression where patients with Bipolar Disorder do.
- C) ADHD does not have mood fluctuations where Bipolar Disorder does.
- D) Patients with Bipolar Disorder are more likely to complete tasks than patients with ADHD.



Answer:

- D: Patients with Bipolar disorder (without ADHD) are more likely to complete tasks than patients with ADHD who traditionally have trouble completing tasks that they begin.

Drugs

ntral Nervous System Stimulants

- Caffeine
- Amphetamine
- Methampehtamine
- lisdextroamphetamine
- Methylphenidate
- Dexfenfluramine
- ephedrine
- Fenfluramine
- Methcathinone
- Phenmetrazine
- phenylephrine
- Phenylpropanolamine
- pseudoephedrine

Non-Stimulants

- Amantadine
- TCAs
- Bupropion
- atomoxetine
- Antihypertensives
- Betablockers
- Antiobsessives
- Anticonvulsants
- MAOIs
- Eugeroics
- Antipsychotics
- cholinergic agents

Central Nervous System Stimulants

Actions

- To increase the release and inhibit the reuptake of dopamine, norepinephrine, and serotonin
- Mimic the effects of these three natural neurotransmitters
- Enhancing locomotor output, reinforcement processes, and rate dependency
- Enhances attention and stimulus control of behavior

Stimulants and Psychosis

- Therapeutic doses of stimulants are occasionally implicated in causing psychosis with no previous history.
- In the US, the FDA rates this side effect as ‘uncommon-rare.’
- High doses of amphetamines can produce psychotic symptoms indistinguishable from schizophrenia in predisposed patients.
- Risk of stimulant-induced psychosis in patients with a history of psychosis is greater.
- A systematic review showed 30% of patients with schizophrenia without active psychosis developed transient symptoms of an acute psychosis in response to stimulant use
- It is essential to screen for a past history of psychosis/psychotic illness and weigh up the risks and benefits of stimulant treatment.

Methylphenidate

Methylphendiate Products

- Ritalin, Ritalin LA, Ritalin SR
- Focalin, Focalin XR
- Concerta
- Metadate ER / CD
- Methylin ER
- Quillivant / Quillichew
- Journay
- Adhansia
- Daytrana Patch
- Aptesnio
- Cotempla XR ODT

Mechanism of Action:

1.) **B**locks the **norepinephrine transporters**

2.) **Blocks Dopamine transporters:** to a lesser degree (at therapeutic doses will be up to 60-70% of **striatal dopamine transporters**) which are abnormally low in individuals with ADHD

3.) significantly enhance activation in the **bilateral inferior frontal cortex**, which is a key area of cognitive control.

4.) Causes reduced activation in the right inferior frontal gyrus, the left anterior cingulate, and the bilateral posterior cingulate cortex

Methylphenidate

Mechanism of Action

- Methylphenidate is a dopamine and noradrenaline reuptake inhibitor.
- It acts on both the prefrontal cortex and the subcortical striatum
- Modulates catecholaminergic tone.
- Main action is through enhancement of dopamine signaling by blockade of the dopamine transporter increases in extracellular dopamine and norepinephrine
- Enhances the direct release of dopamine.
- May have actions on histamine and serotonine

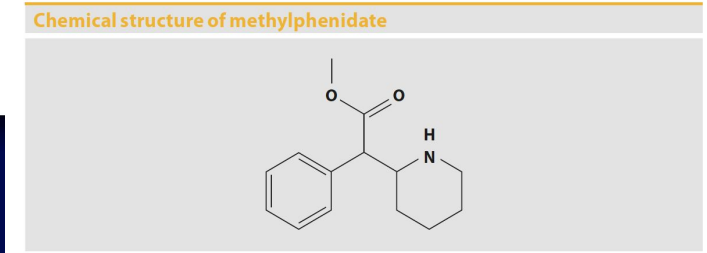
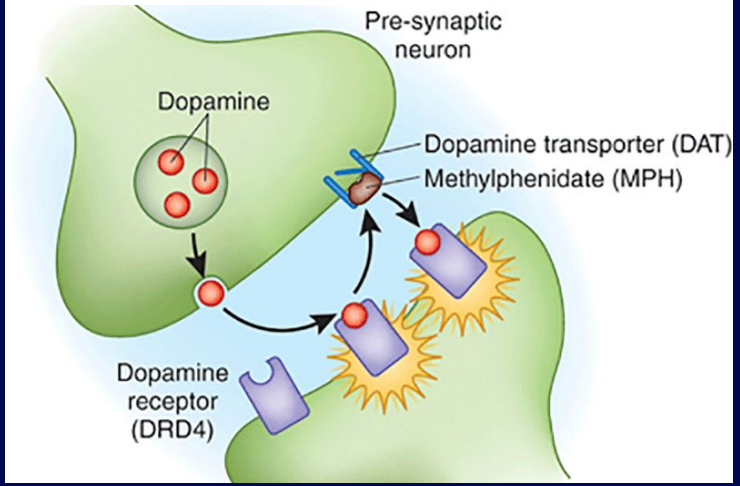


Figure 7.2 Chemical structure of methylphenidate.



Methylphenidate

ABSORPTION

- Methylphenidate is easily absorbed orally, particularly if taken with food.

BIOAVAILABILITY:

- In the gut, and only 30% of the oral dose is bioavailable.

PEAK PLASMA CONCENTRATION:

- Peak plasma concentrations are reached 1 or 2 hours after oral administration,though this may vary according to whether it is an IR or ER preparation.

PHARMACOKINETICS:

- Methylphenidate does not have any significant P450 interactions.
- It undergoes an important first-pass metabolism by de-esterification

ELIMINATION:

- Eliminated by the kidneys as piperidine acetic acid, an inactive metabolite.

CONTRAINDICATIONS AND CAUTIONS

- Susceptibility to angle-closure glaucoma is a caution in the use of methylphenidate.
- Avoided in patients with current drug or alcohol dependence; active psychosis; severe depression; anxiety or agitation; suicidal ideation; or anorexia nervosa. It is contraindicated in the presence of cardiovascular disease, including structural cardiac abnormalities, cerebrovascular disease, vasculitis, hyperthyroidism, or pheochromocytoma.
- Methylphenidate may rarely produce tics or exacerbate existing tic disorders (such as Tourette's syndrome), and both the British National
- Formulary [12] and the FDA [13] advise caution in individuals with tic disorders. However, studies do not seem to support a worsening of tics in most children with ADHD and a comorbid tic disorder
- Methylphenidate should be used with caution in patients using monoamineoxidase inhibitors, dopaminergic drugs, and central alpha-adrenergic agonists. Methylphenidate inhibits the metabolism of tricyclic antidepressants therefore downward dosage adjustment of these drugs may be required when given concomitantly with methylphenidate.
- Carbamazepine induces the metabolism of methylphenidate, decreasing its therapeutic effect.

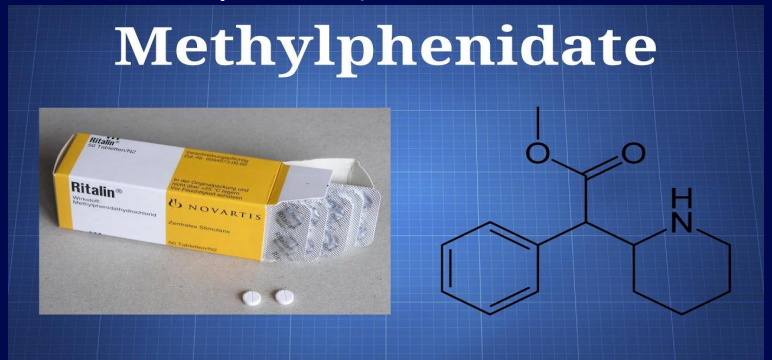
Methylphenidate

CONSIDERATIONS

- Potential for abuse
- Theoretically has street value
- Tolerance, addiction and psychological dependency may occur .
- Methylphenidate is reported to be much less pleasurable than ‘street’ stimulant such as amphetamines and cocaine, which are known to produce a rapid feeling of euphoria.
- (Concerta XL) lower abuse potential because the methylphenidate cannot be easily extracted for intravenous injection.
- IR formulations are not recommended in patients at risk of abuse

Side Effects and Precautions

- Appetite loss, insomnia, headache, irritability, and tachycardia.
- Some side effects may disappear after 1 or 2 weeks of treatment (eg, headache, irritability), while insomnia and appetite loss may persist and may require dose reduction. Table 7.3 lists associated side effects (those with an asterisk affect more than 1 in 10 patients).



Amphetamines

Chemical structure of an amphetamine

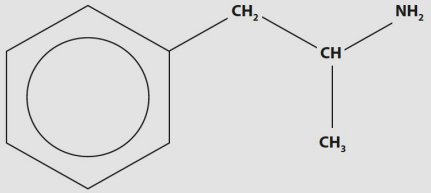


Figure 7.3 Chemical structure of an amphetamine.

Mechanism of Action

- Cause a release of catecholamines, mainly dopamine and norepinephrine, from the vesicles in the presynaptic terminals of neurons of the brain
- Inhibit the activity of the enzyme monoamine oxidase
- Through competitive inhibition of the transporters (dopamine active transporter [DAT] and norepinephrine transporter [NAT]) help block the reuptake norepinephrine and dopamine
- Competitive inhibition of the intraneuronal vesicular monoamine transporter (VMAT) promoting release of dopamine and noradrenaline- at high doses causes serotonergic effect
- Activate the trace amine receptors and increase biogenic amine and excitatory neurotransmitter activity levels in the human brain
  - improving cognitive control,
  - generate feelings of euphoria, and
  - promote wakefulness.
  - Methamphetamine has more pronounced effects in the brain but less in the rest of the body than amphetamine; thus methamphetamine causes less increase in heart rate, blood pressure.. Amphetamines also cause dilation of the pupils and closure of the bladder sphincter, which makes urination more difficult. They also cause the lungs “to expand, which is why they were once used to treat asthma and related conditions.”

Dextroamphetamine (Dexadrine, Dexadrine Spanules, Dextrostat, Liguadd

Mechanism of Action

- Non-catecholamine, dextrorotary stereoisomer of the amphetamine molecule
- lipophilic, sympathomimetic amine and a slightly polar, weak base
- prevent the direct reuptake of dopamine
- blocks MAOI

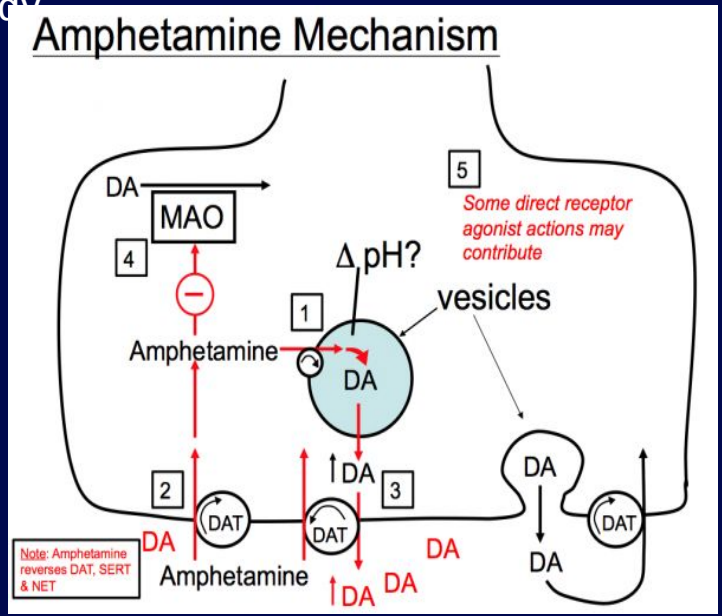
Dextroamphetamine

Indications

- On label:
  - ADHD
  - Narcolepsy
- Off label:
  - Anxiety
  - Depression
  - Euphoriant
  - Aphrodisiac
  - Military and Sports performance enhancement

Pharmacokinetics

- Dexamphetamine absorbed by the small intestine and rapidly distributed to body tissues.
- About 30% eliminated unchanged by renal system
- Remainder metabolized in the liver primarily by P450 2D6 enzyme.



Lisdextroamphetamine (Vyvanse)

Mechanism of Action

- Stimulates release norepinephrine from vesicles in nerve terminals and from central adrenergic receptors
- Has longer duration of action and less abusable
- Causes release of dopamine from mesocorticolimbic system and nigrostriatal dopamine systems.
- Lisdexamphetamine is a prodrug (ie, it is inactive).
  - After absorption by small intestine, l-lysine portion of molecule is cleaved off, leaving active substance dexamphetamine.
  - The conversion facilitated by enzymes in heme element of red blood cells

Side Effects

- Can affect the circulatory system
  - increasing heart rate
  - less common increase in blood pressure; poor circulation in the fingers or in the toes, or the skin turning blue.
- Can alter functioning digestive system
  - Substantial loss of appetite
  - Anorexia reported
- Reproductionn
  - passed through breast milk
  - prolonged erections

Methamphetamine (Desoxyn)

Mechanism of Action

- Prevents the direct reuptake of dopamine
- Stimulates the release of norepinephrine from the vesicles in nerve terminals and from the central adrenergic receptors
- Initiates a cascade of release of norepinephrine, dopamine, and serotonin.
- Inhibits dopaminergic and adrenergic reuptake
- At high doses inhibits MAO

Considerations

- Closely related to amphetamine and ephedrine
- Treats ADHD and weight loss
- Decreases appetite
- Can elevate blood pressure.

Combination Amphetamines (Evekeo, Adderall, Adderall XR, Mydayis, Evekeo ODT)

Mechanism of Action

- Cause the release of dopamine from the mesocorticolimbic system and nigrostriatal dopamine systems
- Act as direct agonists of the central serotonin receptors
- Inhibit the enzyme MAO

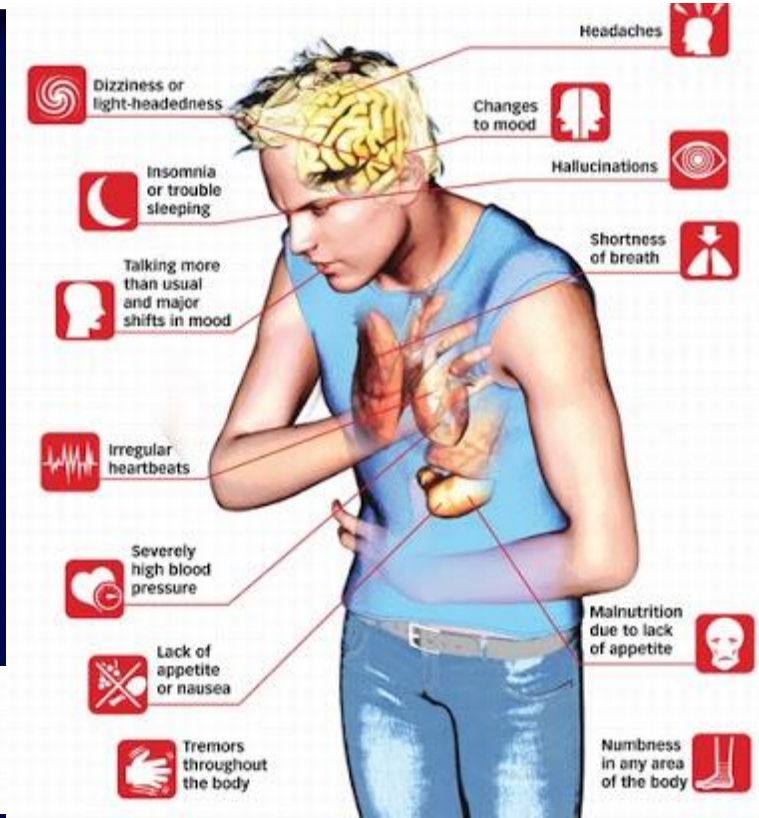
- **Adderall:** 25 percent amphetamine sulfate, 25 percent dextroamphetamine sulfate, 25 percent dextroamphetamine saccharate, and 25 percent amphetamine aspartate monohydrate.
- **Evekeo:** 1:1 ratio of levoamphetamine and dextroamphetamine."

Mixed salts of a single-entity amphetamine product (dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate)	Adderall® Adderall XR®	Ages 6 and older	Advanced arteriosclerosis; symptomatic cardiovascular disease; moderate-to-severe hypertension; hyperthyroidism; known hypersensitivity or idiosyncrasy to the sympathomimetic amines; glaucoma; history of drug abuse; MAOIs	Sudden death (avoid in patients with serious cardiac conditions); hypertension and other cardiovascular conditions; psychosis; depression; seizures; visual disturbance; drug abuse or dependence

Amphetamine Side Effects

Side Effects

- Insomnia
- Restlessness
- Associated with tolerance and addiction when taken in high doses (particularly when snorted or injected
- Lisdexamphetamine negligible risk of abuse even when injected, –
  - when it is injected intravenously, the active compound is released slowly from the inactive component – meaning there is no rapid peak in plasma concentration and brain entry. Consequently, it does not produce the fast euphoric reaction associated with IR dexamphetamine.



Amphetamines

Drug Interactions

- Alkalinization or acidification of the urine: agents that acidify the urine tend to increase the rate of renal excretion.
- Amphetamine compounds are substrates of the enzyme system CYP2D6. Drugs that inhibit this system (eg, fluoxetine, paroxetine, tricyclic antidepressants, cocaine) may **increase** levels of dexamphetamine.
- Drugs that induce the CYP2D6 system (eg, carbamazepine) will **DECREASE PLASMA** levels of dexamphetamine.
- As amphetamines have several potential metabolic pathways available CYP2D6 inhibitors and inducers usually have only a moderate effect on the bioavailability of the drug, unless other relevant CYP enzymes are simultaneously affected.

Contraindications

- Cardiovascular disease (eg, moderate-to-severe hypertension, cardiomyopathy, arrhythmia, family history of sudden death), hyperexcitability or agitated states, hyperthyroidism, and glaucoma.
- Potential for abuse or diversion
- Amphetamines linked to reports of sudden death in children. the temporary suspension of the license for mixed amphetamine salts in Canada in 2004.
- The FDA maintained a general recommendation of monitoring pulse and blood pressure with stimulant medication, but no further monitoring tests are required.

Summary of interactions of amphetamines

Selective serotonin re-uptake inhibitors (SSRIs)	Possible increase in plasma levels of amphetamines and hypertensive crisis
Tricyclic antidepressants (TCAs)	Possible increase in plasma levels of amphetamines and hypertensive crisis
Monoamine oxidase inhibitors (MAO) inhibitors	Possible increase in plasma levels of amphetamines and hypertensive crisis
Carbamazepine	Possible decrease in plasma levels of amphetamines
Typical antipsychotics (haloperidol+phenothiazines – eg, chloropromazine trifluoperazine)	Due to reduction in dopamine levels, may diminish effect of amphetamines
Propranolol	As propanolol works by blocking adrenaline, its effects may be diminished when using amphetamines causing hypertension
Dopaminergic agents	Additive effect – potential caution
Noradrenergic agents	Additive effect – potential caution
Gastric acidifying agents (eg, ascorbic acid)	Decreased absorption of amphetamines
Gastric alkalizing agents (eg, acetazolamide)	Increased absorption of amphetamines
Urinary acidifying agents (eg, ascorbic acid)	Increased excretion of amphetamines
Urinary alkalizing agents (eg, sodium citrate)	Decreased excretion of amphetamines

Stimulants and Cardiac

- Stimulants and cardiovascular risk
- Both methylphenidate and dexamphetamine are contraindicated in severe cardiovascular disease.
- NICE recommends that before treatment with stimulants is started, there is an evaluation of cardiovascular symptoms/ disease in the individual (particularly hypertrophic obstructive cardiomyopathy), and a history taken of cardiovascular disease in family members (particularly a familial history of sudden death) [

- Examination should include
  - pulse rate and blood pressure
  - height, weight, and body mass index
  - Cardiovascular investigations (eg, electrocardiogram, echocardiogram) are only indicated where there is a personal or family history of cardiovascular disease or cardiovascular abnormalities on examination.
- Stimulants can be given to patients who have controlled hypertension.
- Sudden death is no more common in patients taking stimulants than in the general population,
  - exception patients with **hypertrophic obstructive cardiomyopathy** where the **risk is significant**

Cardiac Screening for Stimulants

General Recommendations

- Current FDA stipulates sudden death can occur at usual doses in patients with a pre-existing structural cardiac abnormality or other serious heart problem
- Careful history of heart-related problems must be obtained and documented before stimulant
- Maximize cardiac med and address risk factors; patients with ADHD may find it difficult to make necessary lifestyle changes
- Introduce ADHD meds at low dose and titrate up slowly
- Monitor symptoms, BP/HR regularly
- Longer term effects of ADHD medications on CV status unclear

Screening

Important screening questions:

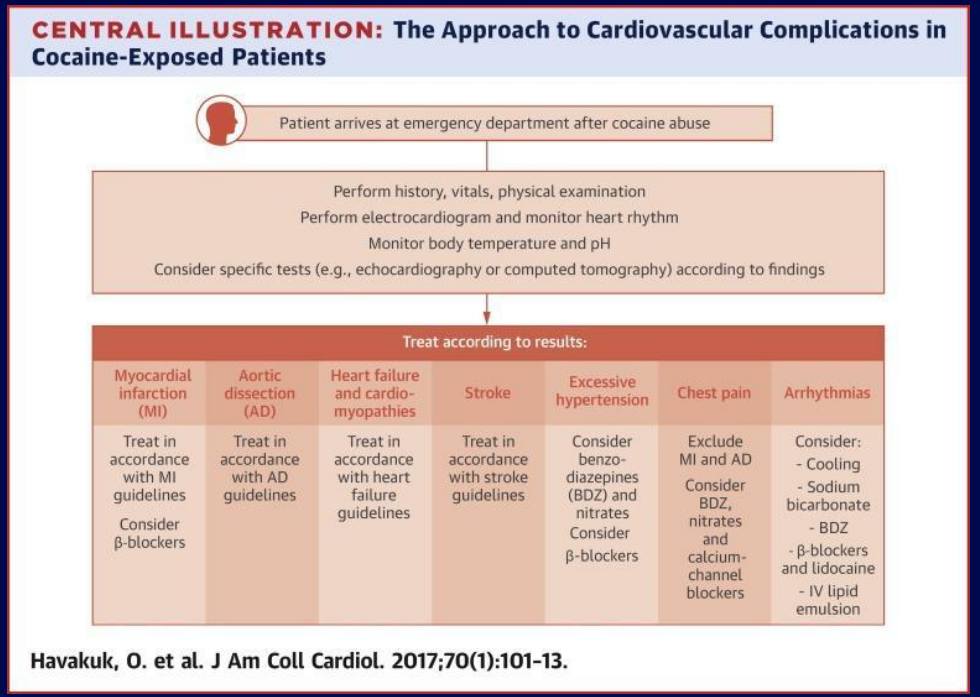
- Patient-related factors:
  - history of murmur,
  - syncope,
  - CVD illness
- Family-related factors:
  - history of early or sudden cardiac death
- Other health considerations that increase CVD risk
- Smoking history, caffeine use, over-the-counter sympathomimetic medications

If cardiac screening is negative, EKG is NOT required prior to initiating treatment

Clinical Assessment of Cardiac Risk

CONSIDER EKG FOR:

- Exercise-induced syncope
- Exercise-induced chest pain
- Sudden death in family member under age 30
- History of cardiac abnormalities (structural or electrical) in self or family members
- History of palpitations or arrhythmia
- Recent myocardial infarction
- Syncopal episodes, dizziness
- Multiple risk factors, such as smoking, high body mass index, hypertension, metabolic syndrome



Havakuk, O. et al. J Am Coll Cardiol. 2017;70(1):101-13.

Treating ADHD Patients with Heart Disease

ECGs NOT needing Referral

- Sinus bradycardia, arrhythmia, or tachycardia
- Right ventricular conduction delay or incomplete right bundle branch block without right ventricular hypertrophy or right axis deviation
- Isolated intraventricular conduction delay
- Right axis deviation in patients 8 years or younger
- Early repolarization
- Nonspecific ST-T wave changes
- Juvenile T-wave pattern
- QTc ≥ 0.45 seconds by computer, but normal by hand calculation

LOW RISK REFERRAL

- Isolated atrial enlargement, especially right atrial enlargement; this usually will not need further evaluation
- Biventricular hypertrophy with only mild midprecordial voltages of 45 or 50 mm; this may need further evaluation
- Ectopic atrial rhythms; right atrial, left atrial, wandering atrial pacemaker at normal rates
  - Low right atrial rhythms are common, usually are normal variants, and will rarely need further evaluation; other ectopic atrial rhythms are less common and may need further evaluation

Treating ADHD Patients with Heart Disease

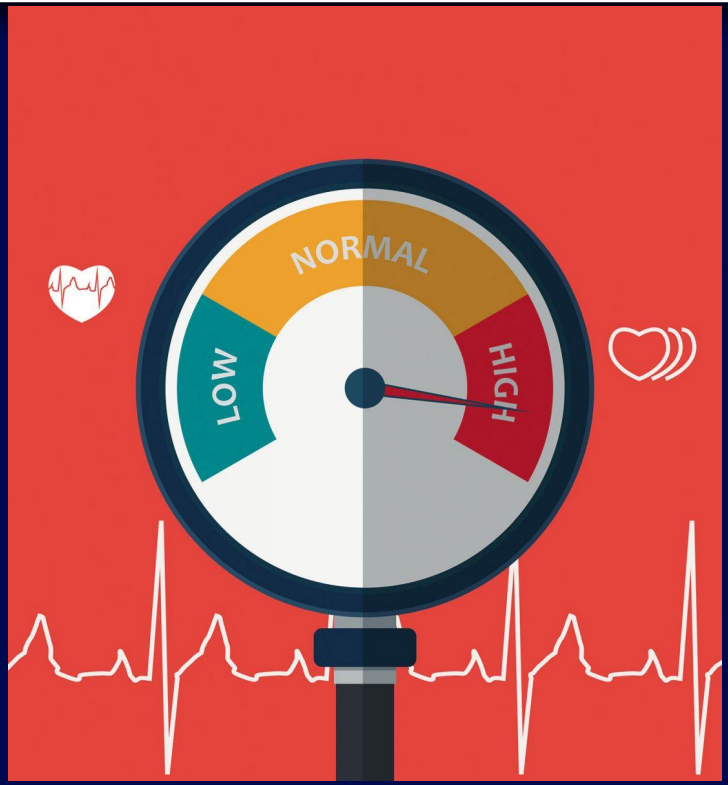
HIGH RISK REFERRAL

- Left or right ventricular hypertrophy
- Wolff-Parkinson-White Syndrome
- Left Axis Deviation
- Right Axis Deviation, especially in patients older than 8 years
- Right ventricular conduction delay and right axis deviation
- Second- and third-degree atrioventricular block
- Right bundle branch block, left bundle branch block, intra-ventricular conduction delay > 0.12 seconds in patients older than 12 years (> 1.10 seconds in patients younger than 8 years)
- Prolonged QTc > 0.46 seconds
- Abnormal T waves with inversion V_5, V_6; bizarre T-wave morphology, especially notched or biphasic, or flat and/or ST-segment depression suggesting ischemia or inflammation
- Atrial, junctional, or ventricular tachyarrhythmias, including frequent premature atrial contractions or premature ventricular contractions

Treating ADHD Patients with Hypertension

CURRENT RECOMMENDATIONS

- Evaluate blood pressure/pulse prior to initiating ADHD treatment
- Address hypertension before treating ADHD
- Once hypertension is controlled, treat ADHD and monitor blood pressure
- Stimulants have a clinically insignificant effect on blood pressure in treated, normotensive adults



ADHD Quick Check Question

True or False

- Amphetamines can cause sudden death in children?

Answer:

- True

Amphetamines can cause sudden death in children and were actually pulled for a short while from the market in Canada related to this risk.

Amantadine (Symmetrel)

Mechanism of Action

- Acts on the presynaptic membranes of neurons
- Enhances the release of the neurotransmitter dopamine
- In high doses Inhibits dopamine reuptake
- Induces hypersensitivity of the postsynaptic dopamine receptors transiently P
- Potentiates the effects of dopamine

Treatment Response

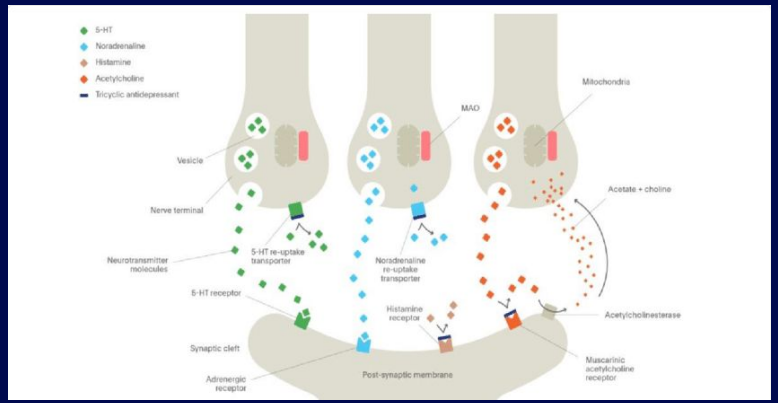
- Helps increase central dopaminergic tone and therefore is helpful in controlling impulsive behaviors

TCAs

Amitriptyline (Elavil) + Nortriptyline (Pamelor). + desipramine (Norpramin) + amoxapine (Asendid) +. clomipramine (Anafranil) + doxepin (Sinequan) imipramine (Tofranil) + protriptyline (Vivactil) + trimipramine (Surmontil)

Mechanism of Action

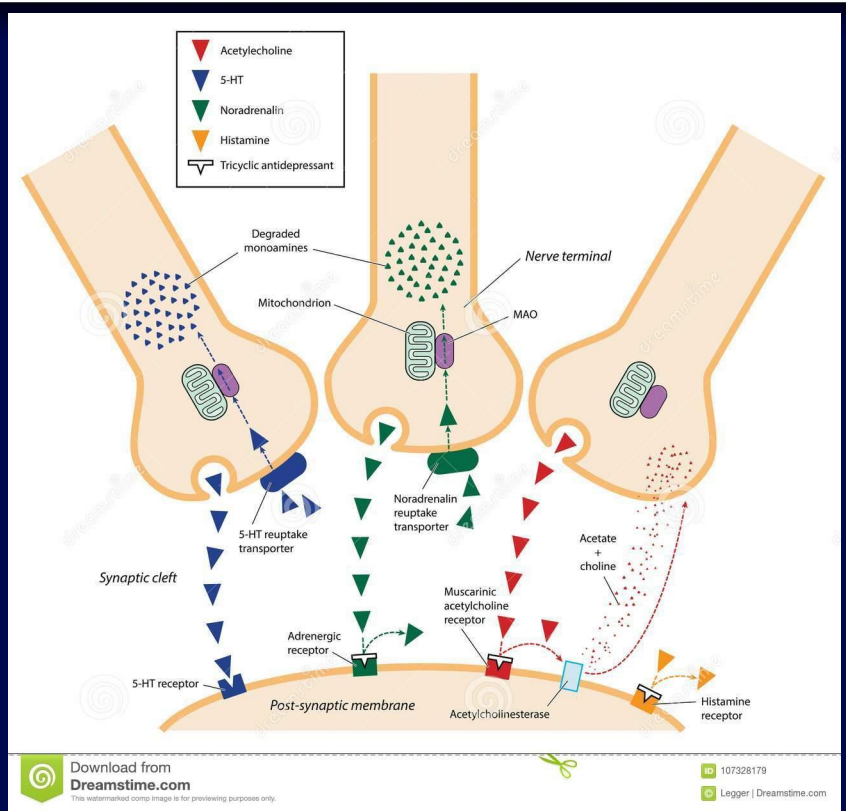
- All have three-ring nucleus structure and some essentially mimic NE
- Down regulate beta adrenergic receptor sites in the cerebral cortex
- Sensitize postsynaptic neurotransmission of 5HT
- Some TCAs actually enhance the action of NE
- constipation, and urinary retention
- Block some of the histamine receptor sites, which largely accounts for sedative effects
- Block alpha adrenergic receptor sites, which accounts for hypotensive effects
- Block muscarinic acetylcholine receptor sites, which specifically accounts for their anticholinergic effects, such as dry mouth,



TCAs

Treatment Modality

- TCAs have generally been found to effectively decrease hyperactivity
- Enhance mood and self-esteem
- They also tend to have a longer lasting therapeutic effect than the stimulant ADHD meds
- Less of the rebound effects frequently reported with psychostimulant meds
- Efficacy in ADHD has been described both with desipramine and nortryptiline,
  - mostly in combination with stimulant medications
- These substances may be useful to control some specific symptoms
  - ADHD-like stimulant-induced insomnia and
  - weight loss. c
- Limited addictive potential but possible toxicity
- Cardiovascular risk associated with TCAs



Amitriptyline

Mechanism of Action

- Inhibit the reuptake of mainly serotonin
- Inhibits somewhat less so NE in presynaptic neuron terminals
- Decreases membrane pump reuptake by inhibiting sodium dependent serotonin transporter and, to a lesser degree, the sodium dependent norepinephrine transporter.

Treatment Modalities

- Amitriptyline hydrochloride is a dibenzocycloheptene derivative
- Consists of two benzenes connected by a cycloheptene ring
- Usually prescribed to treat symptoms of depression as well as for treating eating disorders, postherpetic neuralgia, and for preventing migraine headaches; it is also used off label for treating ADHD
- Is a tertiary amine TCA with sedative effects

Desipramine (Norpramin, desmethylimipramine)

Mechanism of Action

- Inhibits the reuptake of norepinephrine and to a lesser extent that of serotonin

Treatment Modalities

- “Desipramine hydrochloride (Norpramin), also called desmethylimipramine, is an active metabolite of imipramine.
- Desipramine is a dibenzazepine derivative TCA,
- Contains a tricyclic ring system with an alkylamine substituted on the central ring.
- Generally prescribed to treat symptoms of depression; common off-label uses of desipramine include for treating neuropathic pain, insomnia, and, of course, ADHD
- Is a secondary amine TCA”

Nortriptyline (Pamelor)

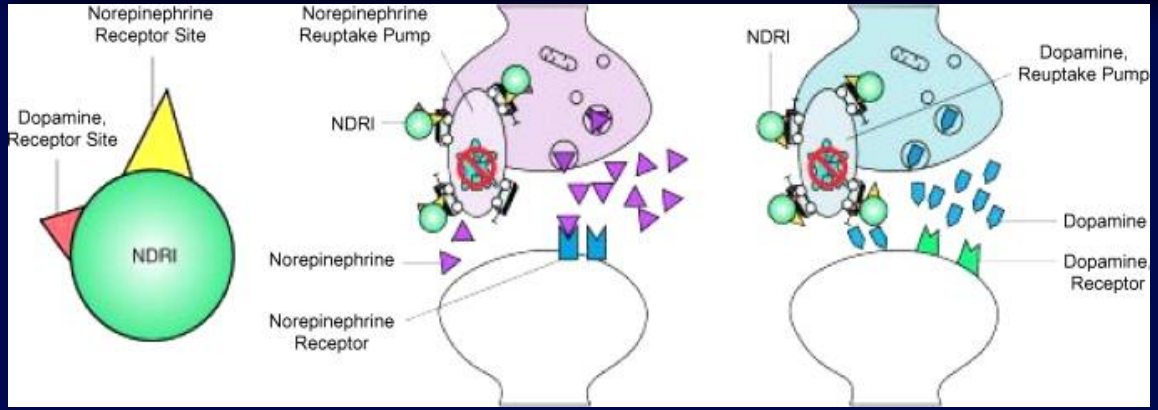
Mechanism of Action

- Increases the pressor effect of norepinephrine
- Interferes with the transport, release, and storage of the catecholamines,
- Inhibits the activity of acetylcholine, histamine, and 5-hydroxytryptamine
- Is the N-demethylated active metabolite of amitriptyline
- Accordingly, nortriptyline is a more potent inhibitor of NE reuptake than amitriptyline or doxepine;
- Potent inhibitor of the reuptake of 5HT at the neuronal membrane

Treatment Modalities

- Usually treats symptoms of depression as well as for treating panic disorders, postherpetic neuralgia, and as a smoking cessation aid; it is also used off label for treating ADHD.
- Nortriptyline hydrochloride is the N-demethylated active metabolite of amitriptyline.
- Nortriptyline hydrochloride is a dibenzocycloheptene derivative TCA,
- Contains a tricyclic ring system with an alkyl amine substituted on the central ring
- Is a secondary amine TCA;

Buproprion (Wellbutrin, Aplenzin)



Mechanism of Action

- Not sedating,
- No anticholinergic or antihistamine properties
- Functions as both a weak norepinephrine and a dopamine reuptake inhibitor
- Also a nicotinic acetylcholine antagonist

Buproprion (Wellbutrin, Wellbutrin SR, Wellbutrin XL, Aplenzin)

Mechanism of Action

- Bupropion is a noradrenaline and dopamine reuptake inhibitor (NDRI)
- Bupropion belongs chemically to the aminoketones and
- Structure similar to that of stimulants like amfepramone and cathinone
- IS a unicyclic, aminoketone antidepressant medicine, which has an acetophenone chemical structure.
- Works by mimicking norepinephrine and dopamine.
- Nicotinic antagonist, with moderate anticholinergic effects.
- Selectively inhibits systems controlled by dopamine more than the TCAs, causes less blockage of the reuptake of norepinephrine and serotonin at neuronal membranes than the TCAs
- May enhance noradrenergic functional activity by promoting increased excretion of the hydroxyl metabolite of melatonin
- Facilitates a compensatory decrease in norepinephrine turnover
- Stimulates presynaptic release of norepinephrine and dopamine

Treatment Modalities

- It is only approved in the UK for use as a smoking cessation agent (eg, Zyban®).
- In the US, it is also licensed for the treatment of ADHD and depression (eg, Wellbutrin®, Zyban®, Voxra®, Budeprion®, or Aplenzin®).
- Sometimes used (off-label) as a third-line drug in ADHD when stimulants and atomoxetine have failed to improve symptoms or they have not been tolerated. Useful consideration when the ADHD is relatively mild with less profound effects or if the patient is also keen to give up smoking.
- Atypical antidepressant medicine
- Has demonstrated clinical efficacy in off-label treatment of individuals with ADHD comorbid with either aggression or substance abuse

Buproprion

PHARMACOKINETICS

- Bupropion is rapidly absorbed by the digestive system and its concentration
- Peaks in the plasma within 2 hours of oral ingestion.
- It has a half-life of 14 hours. ER formulations prolong the half-life further

CONTRAINDICATIONS

- Bupropion is contraindicated in patients with a previous history of bipolar disorder, an eating disorder, or seizures (or conditions that reduce the seizure threshold such as alcohol or benzodiazepine withdrawal).
- It should be used with caution in liver or renal impairment and severe hypertension. It also should not be used in combination with, or within 2 weeks of using, monoamine oxidase inhibitors.
- Is a dopaminergic agent, bupropion should be used with caution with levodopa and other substances that increase dopamine availability.

DRUG INTERACTIONS

- Bupropion is metabolized by the CYP2B6 enzyme
- CYP2B6 inhibitors (eg, paroxetine, fluoxetine, fluvoxamine, and clopidogrel) may increase its plasma levels. CYP2B6 inducers (eg, efavirenz, modafinil, and rifampicin) have the reverse effect.
- Bupropion is itself a moderately strong inhibitor of CYP2D6, which metabolizes atomoxetine and venlafaxine (and to a lesser extent, amphetamine). Combinations of these drugs are not recommended as they can potentially increase side effects.
- As bupropion lowers the seizure threshold, it should not be used with other medications that also lower the seizure threshold. Caution should be exercised when using bupropion with alcohol, as it may reduce alcohol tolerance.

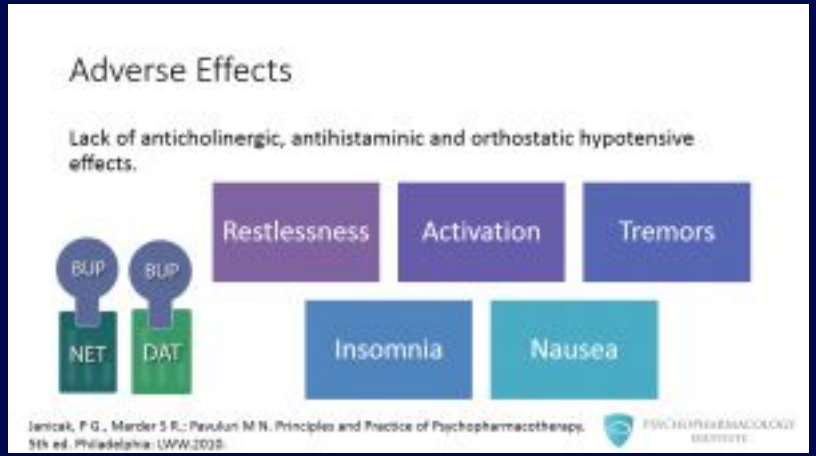
- Potential for abuse Anecdotal reports of bupropion as a recreational drug exist but it is not a controlled drug and can be prescribed to patients with a history of drug abuse.

Buproprion

Side Effects

SIDE EFFECTS

- Rarely, serious side effects can occur, including seizures (bupropion
- reduces the seizure threshold and caution is required when using other
- drugs that do this), anaphylaxis, psychosis, mania, and suicidal ideation.
- Cardiovascular side effects can also occur.
- Bupropion also has mild anorexiant effects, which may help in weight loss.



Atomoxetine (Strattera)

Mechanism of Action

- Potent and highly selective presynaptic norepinephrine transporter inhibitor
- Low affinity to several other receptor classes commonly associated with adverse side effects: acetylcholine receptors, the alpha and beta noradrenergic receptors, the dopaminergic receptors, the histaminergic receptors, and the serotonin receptors.
- Found to increase NE available to receptors, while having minimal effect upon other neurotransmitter receptors and transporters.
- First nonstimulant medicine approved for ADHD
- Belongs to the phenylpropylamine class of organic compounds, which means that it consists of a phenyl group that has a propan-1-amine substituted at the third carbon
- Increases synaptic dopamine in the prefrontal cortex (as dopamine is normally taken up by the noradrenaline transporter in this region).

Treatment Modalities

- Can be prescribed for individuals with concerns about addiction to stimulant medications or with some SE typically associated with stimulants.
- Effective in treating adults and children with ADHD
- Highly unlikely to be an abused drug
- Rapidly and completely absorbed within 1 hour and it offers 24-hour coverage of ADHD symptoms in children and adults,
- Can be safely and effectively administered once per day
- Less abuse potential than the CNS stimulant ADHD medications and, is not scheduled as a controlled substance
- Helps increase attention span, wakefulness, decreases their hyperactivity, and decreases impulsive behaviors
- Can be more helpful with Predominantly inattentive variant of ADHD

Atomoxetine (Strattera)

Pharmacokinetics

- Well absorbed from digestive tract after oral administration, reaching peak plasma concentrations 1 or 2 hours after dosing
- Almost completely bound to plasma proteins, primarily albumin.
- Metabolized in the liver (with only modest first-pass metabolism) and the metabolites are excreted renally in the urine.
- Metabolized by the CYP2D6 enzymatic pathway.
- 7% of the Caucasian population and 2% of the Asian population have mutations or deletions in genes that codify CYP2D6 considered **'poor metabolizers**,' having a several-fold higher exposure to plasma concentration of atomoxetine
- Atomoxetine itself does not cause significant inhibition or induction of cytochrome P450 enzymes.

Contraindications

- Atomoxetine is contraindicated in narrow-angle glaucoma.
- It also should not be used in combination with, or within 2 weeks of, monoamine oxidase inhibitors.

Atomoxetine (Strattera)

Side Effects

- Common SE include gastrointestinal symptoms (eg, nausea, vomiting, reduced appetite, abdominal pain, and constipation), insomnia, dry mouth, dizziness, and headache. Reduced libido and other sexual side effects are commonly reported Some people report tachycardia, palpitations, hot flushes, and urinary symptoms.
- Disappear in the first weeks of treatment
- Avoided by gradual up-titration of dose.
- Modest increase in pulse (mean <10 beats/minute and/or increase in blood pressure (mean <5 mmHg)
- Caution is advised where there is: pre-existing hypertension, tachycardia, cardiovascular, or cerebrovascular disease.
- Pulse and blood pressure measure periodically
- Increased incidence of suicidal thoughts

Rare Side Effects

- Rare case reports of acute liver disease
  - symptoms of liver failure: (abdominal pain, jaundice, unexplained nausea), elevated hepatic enzymes or bilirubin should prompt immediate medical review and discontinuation of the medication.
- Both seizures and treatment-emergent psychotic or manic symptoms
- NICE guidelines recommend monitoring of weight, heart rate, and blood pressure before and after every dose change .
- Weight should be measured every 6 months
- Heart rate and blood pressure should ideally be recorded every 3 months.

Atomoxetine (Strattera)

INHIBITORS CYP2D6

Inhibitors of the CYP2D6 complex	
Strong inhibitors	Fluoxetine
	Norfluoxetine
	Paroxetine
Moderate and weak inhibitors	Bupropion
	Modafinil
	Duloxetine
	Escitalopram
	Haloperidol
	Chlorpromazine
	Clomipramine
	Amiodarone
	Chloroquine
	Cimetidine
	Cocaine

Table 7.14 Inhibitors of the CYP2D6 complex. Adapted from Bazire et al [18].

Drug Interactions

- Drugs that affect noradrenaline (eg, antidepressants such as imipramine, venlafaxine,Mirtazapine, or decongestants such as pseudoephedrine and phenylephrine) have additive effect.
- An increased risk of ventricular arrhythmias with drugs that prolong the QT interval (eg, antipsychotics, methadone, tricyclic antidepressants, lithium)
- Drugs that lower the seizure threshold (eg, some antipsychotics, buproprion, tricyclic antidepressants) may increase the risk of seizures
- Use caution when using salbutamol (high-dose nebulized or systemically administered intravenously or orally) together with atomoxetine, as the effect of salbutamol on the cardiovascular system can be potentiated
- Should not be used with MAOIs
- Potent inhibitors of CYP2D6 increase
- atomoxetine concentrations in plasma similar to those observed in CYP2D6 poor metabolizer patients. Paroxetine is a strong inhibitor of CYP2D6, and fluoxetine, is a relatively strong inhibitor of the cytochrome.

Alpha 2 agonists (Clonidine, Kapvay, Tenex, Guanfacine, Intuniv, Catapres)

Mechanism of Action

- Enhanced noradrenergic input from the locus coeruleus and to direct postsynaptic stimulation of the alpha 2A receptors, where they help to reduce cell firing
- Presynaptic alpha 2A receptors in the CNS inhibit the release of NE, thus serve in negative feedback control of the noradrenergic system.
- The alpha 2B subtype less common in the brain, concentrated primarily in the thalamus, & accounts for sedating effect.
- Stimulating postsynaptic alpha 2A receptors on dendrites of prefrontal cortical pyramidal cells results in increased functional connectivity of the prefrontal cortex neural networks

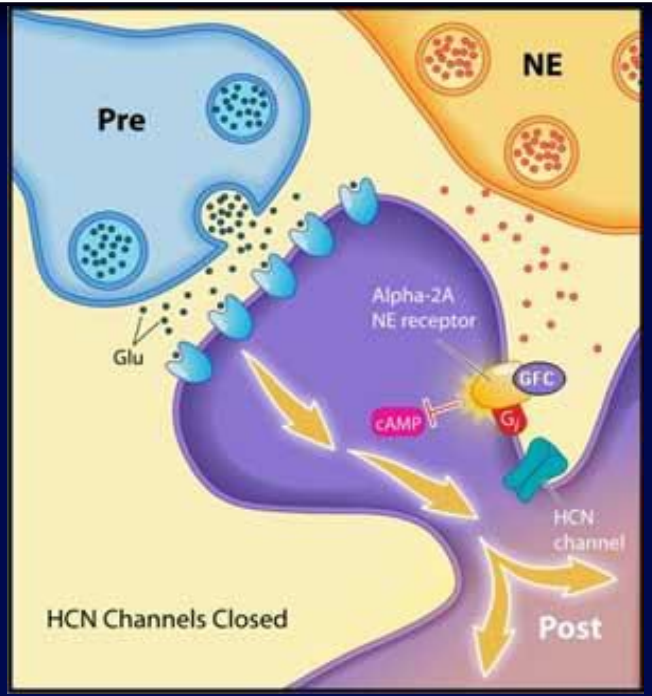
Treatment Modalities

- Lessen peripheral resistance, heart rate, and, with respect to their primary use, also effectively lower blood pressure
- Selective alpha 2 adrenergic receptor agonists act directly on the prefrontal cortex to improve executive function.

Alpha 2 Agonists

Other information

- Clonidine and guanfacine are alpha-2 adrenergic agonists that are approved for the treatment of hypertension, now rarely used for this indication
- In 2010, the FDA approved the use of clonidine as a monotherapy or as an adjunct to traditional stimulant treatment for ADHD. It can be particularly useful in patients with comorbid Tourette's syndrome.
- The FDA has also approved an ER formulation of guanfacine (Intuniv®) for children and adolescents. Neither clonidine nor guanfacine are approved in the UK for this use but may have a place in patients with ADHD who have hypertension and therefore may have problems with stimulants and atomoxetine. Treatment with these medications should be guided by ADHD specialists.



α2 Adrenergic Agonists(Clonidine, Guanfacine)

Mechanism of Action

- Guanfacine phenylacetamide class of organic compounds, = amide derivative of phenylacetic acid.
- Mechanism of action: partial agonist of NE
- Decreases erratic activity of locus coeruleus & Strengthens connectivity DLPFC microcircuits
- Increases neurotransmission prefrontal cortex & Increases pyramidal excitability
- Inhibits cAMP production closes nearby HCN channels
- Restricted to activation of postsynaptic alpha 2A receptors in the prefrontal cortex of the brain- improve the delay-related firing of prefrontal cortex neurons
- Selectively inhibit striatal activity, causes reduced sympathetic outflow, as well as decrease vasomotor tone and heart rate, lowered diastolic and systolic blood pressure by means of activation of the central nervous system alpha 2 adrenoreceptors.
- Guanfacine more selective alpha 2A agonist at low doses improves prefrontal cortical cognitive functioning without adverse side effects associated with nonselective alpha 2A agonists clonidine.

Treatment Modalities

- First introduced as anti-hypertensive agents
- Helpful for highly aroused, impulsive, emotionally labile, irritable and explosive
- Reduces anxiety, defiance, and aggression
- Useful in controlling tics
- Reduces distractibility and improves working memory in monkeys and humans
- Two other medications to consider are methyldopa (Aldomet) and tizanidine (Zanaflex).
- Absorption characteristics of immediate release clonidine and guanfacine lead to rapid peak blood plasma concentrations that then decline precipitously.

Clonidine (Kapvay, Catapres)

Mechanism of Action

- Partial alpha adrenergic agonist and a partial antagonist.
- Acts as an agonist in the anterior hypothalamus, inhibition of excitatory cardiovascular neurons; antagonist in posterior hypothalamus, decreases the stimulation of excitatory cardiovascular neurons, antagonist and in the medulla inhibiting the stimulation of the sympathetic nervous system. The net result is decreased arterial blood pressure.
- Stimulation of presynaptic alpha 2 receptor sites in the brain stem, decreases presynaptic calcium levels decreased release of norepinephrine at central and peripheral terminals; to peripheral vascular resistance lowers blood pressure.
- Diminishes afferent pain transmission.
- Binding to the postsynaptic adrenergic receptor sites, increasing adrenergic tone in the prefrontal cortex, and it also increases noradrenergic input in the locus coeruleus = helpful for ADHD.

Treatment Modalities

- Alone, clonidine minimal effect on inattention; in combination with stimulant, helps extremely high levels of aggression, hyperactivity, and impulsivity, comorbid secondary conditions such as conduct disorders or oppositional defiant disorder.”
- “clonidine hydrochloride (Kapvay) = general affinity for alpha 2- A, B, and C receptors, imidazoline receptors, elevates histamine levels hypothalamus;
- guanfacine hydrochloride (Intuniv) preferentially binds to the alpha 2 A receptors, increases attentiveness, causes less sedation, and improves executive functioning, including enhancing working memory.

Formulation and Delivery Mechanism	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect	Duration of Effect	Comments	References
Amphetamine								
Short 	Amphetamine mixed salts	Adderall	Children ≥3	1–3	1.5 h	4-6 h	Elimination half-life 9.77-11 h for the D-isomer and 11.5-13.8 h for the L-isomer	13–15
Intermediate  	Racemic amphetamine sulfate	Evekeo	Children ≥3 (tablet) Children 6-17 (ODT)	1–2	45 min	9.25 h	Elimination half-life 10.0-11.7 h	16–18
Long 	Amphetamine mixed salts	Adderall XR	Children ≥6, adults	1	1.5 h	10.5–12 h	May be sprinkled on applesauce	19, 20
Long 	Amphetamine	Adzenys ER	Children ≥6, adults	1	1.5 h[a]	10–12 h[a]	Do not add to food or other liquids	21
Long 	Amphetamine	Adzenys XR-ODT	Children ≥6, adults	1	1.5 h[a]	10–12 h[a]	Allow tablet to disintegrate in saliva before swallowing	22
Long 	Amphetamine	Dyanavel XR	Children ≥6	1	1 h	12 h		23

Formulation and Delivery Mechanism	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect	Duration of Effect	Comments	References
Long 	Amphetamine mixed salts	Mydayis	Children ≥13, adults	1	2 h	14 h	May be sprinkled in applesauce	24, 25
Long, prodrug  	Lisdexamfetamine dimesylate	Vyvanse	Children ≥6, adults	1	1.5–2 h	12–14 h	Capsule: may be sprinkled in water, orange juice, or yogurt Chewable tablet: chew thoroughly before swallowing	26, 27
Dextroamphetamine								
Short 	Dextroamphetamine sulfate	Dexedrine	Children 3-16	1–2	NA	4–6 h		14, 28
Short 	Dextroamphetamine sulfate	Zenzedi	Children 3-16	1–3	NA	4–6 h		29
Short 	Dextroamphetamine sulfate	ProCentra	Children 3-16	1–3	NA	4–6 h		30
Intermediate 	Dextroamphetamine sulfate	Dexedrine Spansule	Children 6-16	1–2	NA	6–10 h	Plasma half-life of approximately 12 h	14, 28

Formulation and Delivery Mechanism	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect	Duration of Effect	Comments	References
Methamphetamine								
Short 	Methamphetamine HCL	Desoxyn	Children ≥6	1–2	NA	NA	Not readily available	31

Note:  , tablet;  , capsule;  , liquid;  , chewable tablet;  , orally disintegrating tablet.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FDA, U.S. Food and Drug Administration; HCL, hydrochloride; NA, not available; ODT, orally disintegrating tablet.
[a]Adzenys XR-ODT and Adzenys ER are bioequivalent to extended-release mixed amphetamine salts (ie, Adderall XR),[32, 33] but have not been tested independently in a classroom study.

Methylphenidate[a]								
Short 	Methylphenidate HCL	Ritalin	Children ≥6, adults	2–3	1–2 h	4 h		66, 67
Short  	Methylphenidate HCL	Methylin	Children ≥6, adults	2-3	1 h[b]	4 h[b]	Chewable tablet: take with 8 oz of water 30-45 min before meals Oral solution: take 30-45 min before meals Last dose before 6 PM	68, 69
Intermediate 	Methylphenidate HCL	Methylin ER	Children ≥6, adults	1	NA	NA		70
Intermediate 	Methylphenidate HCL	Ritalin-SR	Children ≥6, adults	1	1.5 h	8 h	Take after meals for maximum duration of effect	66, 71

Formulation and Delivery Mechanism	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect	Duration of Effect	Comments	References
Intermediate 	Methylphenidate HCL	Metadate ER	Children ≥6, adults	1	NA	8 h		72
Intermediate 	Methylphenidate HCL	Metadate CD	Children 6-15	1	1.5 h	8-9 h	May be sprinkled on applesauce	73, 74
Long 	Methylphenidate HCL	QuilliChew ER	Children ≥6, adults	1	45 min	8 h		75, 76
Long 	Methylphenidate HCL	Ritalin LA	Children 6-12	1	30 min–1 h	12 h	May be sprinkled on applesauce	71, 74, 77
Long 	Methylphenidate HCL	Concerta	Children ≥6, adults	1	1–2 h	10–12 h		74, 78
Long 	Methylphenidate HCL	Quillivant XR	Children ≥6, adults	1	45 min	12 h	Shake bottle vigorously for 10 s before dispensing	76, 204
Long 	Methylphenidate HCL	Aptensio XR	Children ≥6, adults	1	1 h	12 h	May be sprinkled on applesauce	76, 89

Formulation and Delivery Mechanism	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect	Duration of Effect	Comments	References
Long 	Methylphenidate	Cotempla XR-ODT	Children ≥6	1	1 h	12 h	No crushing or chewing Allow to disintegrate in saliva before swallowing	76, 91
Long 	Methylphenidate	Daytrana	Children ≥6	1	2 h	12 h	Wear for ≤9 h	74, 79
Long 	Methylphenidate HCL	Jornay PM	Children ≥6, adults	1	8-10 h	12+ h	Take in the evening between 6:30 and 9:30 PM to provide early morning symptom control May be sprinkled on applesauce	80, 81
Long 	Methylphenidate HCL	Adhansia XR	Children ≥6, adults	1	1 h	13-16 h	May be sprinkled on applesauce or yogurt and consumed within 10 min	82
Dexmethylphenidate								
Short 	Dexmethylphenidate HCL	Focalin	Children ≥6	2	NA	6 h	At least 4 h between doses	71, 83
Long 	Dexmethylphenidate HCL	Focalin XR	Children ≥6, adults	1	30 min	12 h	May be sprinkled on applesauce	74, 84

Note:  , tablet;  , capsule;  , liquid;  , chewable tablet;  , orally disintegrating tablet;  , transdermal patch.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FDA, U.S. Food and Drug Administration; HCL, hydrochloride; NA, not available; ODT, orally disintegrating tablet.

[a]AAP recommends utilizing methylphenidate as a first choice for preschool aged children.[12]

[b]Methylin is bioequivalent to Ritalin,[69] but it has not been tested independently in a classroom study.

Table 3. FDA-Approved Nonstimulant Medications for ADHD

Formulation and Delivery Mechanism	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect[a]	Duration of Effect	Comments	References
Norepinephrine transporter reuptake inhibitor								
Long 	Atomoxetine	Strattera	Children ≥6, adults	1-2	3-4 wk	NA[b]	Dosed by body weight	34, 35
$Alpha_2$-adrenergic receptor agonist								
Long 	Clonidine HCL	Kapvay	Children ≥6	2	2 wk	NA	An antihypertensive agent May be prescribed in addition to a stimulant Discontinuation must be gradual	36, 37
$Alpha_{2A}$-adrenergic receptor agonist								
Long 	Guanfacine	Intuniv	Children ≥6	1	3 wk	Up to 24 h per dose	An antihypertensive agent Dosed by body weight May be prescribed in addition to a stimulant	38, 39

Note:  , tablet;  , capsule.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FDA, U.S. Food and Drug Administration; HCL, hydrochloride; NA, not available.
[a]Time to onset of the full effect of nonstimulant medications is extended compared to stimulant medications due to long titration periods.[34, 36, 38]
[b]The duration of effect of atomoxetine has not been formally measured as in studies of stimulant medications. Evidence from clinical studies suggests that once-daily dosing of atomoxetine is associated with efficacy into the evening.[40]

FDA-APPROVED DRUGS TO TREAT ADHD

Generic Name	Brand Name	Indications/ Approvals	Contraindications	Precautions
Bupropion	Wellbutrin® Wellbutrin SR® Wellbutrin XR®	Ages 12 and older	Hypersensitivity to bupropion or any component; MAOI use within 14 days; abrupt alcohol, benzodiazepine, sedative, or antiepileptic discontinuation; seizure disorder	Suicidal ideation; arteriovenous malformation; drug or alcohol abuse; lowered seizure threshold; renal or haptic impairment; older adults
Clonidine HCl	Kapvay®	Ages 6 to 17	Hypersensitivity to clonidine or to any component of the product	Dry mouth; orthostatic hypotension; syncope; somnolence; fatigue; dizziness; headache; risk of rebound hypertension with abrupt withdrawal; risk of decreased blood pressure and decreased heart rate in patients with history of cardiovascular disease, bradycardia, heart block, or hypotension
Dexmethylphenidate	Focalin® Focalin XR®	Ages 6 and older	Hypersensitivity to methylphenidate; glaucoma; tics or family or personal history of Tourette's syndrome; history of drug abuse; MAOIs	Sudden death (avoid in patients with serious cardiac conditions); hypertension and other cardiovascular conditions; psychosis; depression; seizures; visual disturbance; drug abuse or dependence; priapism (in men)
Dextroamphetamine sulfate	Dexedrine®	Ages 3 to 16	Advanced arteriosclerosis; symptomatic cardiovascular disease; moderate-to-severe hypertension; hyperthyroidism; known hypersensitivity or idiosyncrasy to sympathomimetic amines; glaucoma; history of drug abuse; MAOIs	Sudden death (avoid in patients with serious cardiac conditions); hypertension and other cardiovascular conditions; psychosis; depression; seizures; visual disturbance; drug abuse or dependence

Pharmacologic Treatments Approved for ADHD

Amphetamine-based Formulations	Duration of Effect	Peds/Adult
Adderall® (mixed amphetamine salts)	4-6 hours	-/-
Adderall XR® (mixed amphetamine salts XR)	~12 hours	+/+
Dexedrine® Spansule (dextroamphetamine)	6-8 hours	+/-
Vyvanse™ (lisdexamfetamine)	~12 hours	+/+
Methylphenidate-based Formulations		
Concerta® (MPH)	~12 hours	+/+
Daytrana® (MPH patch)	~12 hours (worn for 9)	+/-
Focalin® (dexMPH capsule)	~5 hours	+/-
Focalin® XR (dexMPH XR capsule)	10-12 hours	+/+
Metadate® CD (MPH controlled-release capsule)	8-10 hours	+/-
Ritalin® (MPH)	~4 hours	+/-
Ritalin® LA (MPH XR capsule)	8-10 hours	+/-
Quillivant XR™ (MPH XR liquid)	~12 hours	+/-
Nonstimulants		
Strattera® (atomoxetine)	8-24 hours	+/+
Intuniv® (guanfacine XR)	~12 hours	+/-
Kapvay® (clonidine XR)	~12 hours	+/-

Wilens TE, et al. *Postgrad Med.* 2010;122(5):97-109. Stevens JR, et al. In: Adler LA, et al (Eds). *Attention-Deficit Disorder in Adults and Children.* Cambridge University Press: Cambridge, UK; 2015:245-258.

Non-stimulants in Development

- Dasotraline-*DNRI*
- •Mazindol CR -*TRI + Orexin*
- •FasoracetamNFC1 -*mGluRactivator**
- •Centanafadine-*TRI*
- •Viloxazine –*NRI*
- **gene mutation predicts response*

Beta Blockers

Mechanism of Action

- Antagonist effect blocking norepinephrine binding
- Most of these effects occur in the heart not in the brain.. Compete with epinephrine at the beta receptors sites & interfere with epinephrine.
- prevent the functioning of part of the sympathetic half of the autonomic nervous system.
- have little to no effect upon the alpha receptors.
- Ttend to lower blood pressure, decrease blood circulation, slow the pulse, and partially constrict the airways in the lungs.
- They are thus often used to treat hypertension, atrial fibrillation, migraine headaches, and congestive heart failure,
- Able to reduce symptoms of anxiety and tremor, ADHD; in particular, these antihypertensive medications are helpful for settling down symptoms of aggressiveness and/or hyperactivity.

Treatment Modalities

- Atenolol treats abnormally fast heart rhythms.
- Atenolol, nadolol, and propranol, treat angina, arrhythmias, hypertension, and myocardial infarctions,
- Metoprolol also CHF
- Nonselective: Like nadolol (Corgard) and propranolol (Inderal), inhibit both beta 1 and beta 2 receptor sites”
- Selective: “selective beta 1 blockers include acebutolol (Sectral), betaxolol (Kerlone), bisoprolol (Zebeta), esmolol (Brevibloc), levobunolol (Betagan, Liquifilm), metipranolol (Optipranolol), and metoprolol (Lopressor, Toprol-XL)”
- “The beta blocker ADHD medications, such as atenolol (Tenorim), nadolol (Corgard), and propranolol (Inderal), reduce HR and cardiac output; Reduce SBP and DBP inhibit tachycardia. ”
- Nadolol (Corgard) has low lipophilicity difficulty crossing the blood-brain barrier have limited effects CNS, including the brain.

Atenolol (Tenorim, Tenoretic)

Mechanism of Action

- “Selective beta 1 receptor site antagonist that competes with sympathomimetic neurotransmitters, as such it is an effective adrenergic blocking agent that inhibits responses to adrenergic stimuli by blocking beta adrenergic receptor sites within heart muscle; atenolol, accordingly, thereby decreases heart rate by about 25 percent to 35 percent slowing atrioventricular (AV) nodal conduction and it also, indirectly, reduces blood pressure, without the bronchoconstriction that is sometimes experienced by users of propranolol.

Nadolol (Corgard)

Treatment Modalities

- Nadolol (Corgard) is a nonselective beta blocker, similar but noted for its very long duration of action.”

Propranolol (Dociton, Inderal)

- Propranolol (Dociton, Inderal) prototypical beta blocker as it binds to beta receptor sites, particularly those located at adrenergic junctions prevents activation, while also having no detectable partial agonist action at beta receptors as well as having negligible effects at alpha and muscarinic receptor sites.
- Simply put, propranolol essentially blocks the action of norepinephrine

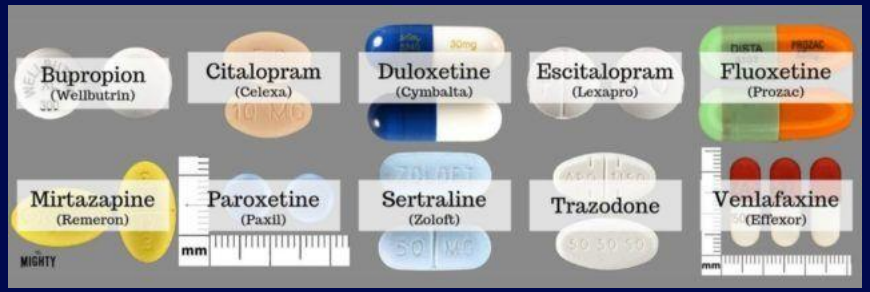
Antiobsessives

Mechanism of Action

- Fluoxetine = phenylpropylamine class of organic compounds, which means that it contains a phenyl group that is substituted by a propan-1-amine at the third carbon.
- to fluoxetine, include fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), and sertraline (Zoloft). Fluvoxamine = benzene class of organic compounds one monocyclic ring system that consists of a benzene
- Nefazodone hydrochloride (Serzone) = phenylpipeazine class of organic compounds consists of a piperazine bound to a phenyl group.
- Paroxetine = phenylpiperdine class of organic compounds consists of a phenyl group with a piperdine bound to it, = phenylpiperdine skeleton; paroxetine is available formulated in two forms, a ” “phenyl or as a phenylmesylate.

Treatment Modalities

- Regarded as antiobsessive medications.



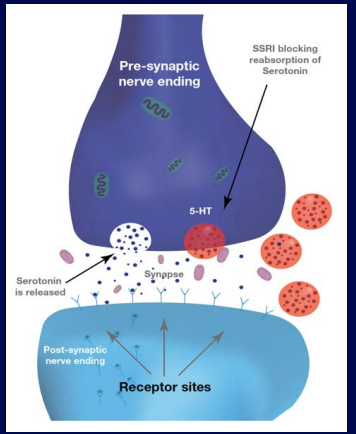
Antiobsessives

Treatment Modalities Cont

- Sertaline hydrochloride (Zoloft = tametraline class of organic compounds, = consists of a tetrahydronaphthalene linked to a phenyl group.
- Citalopram = phenylbutylamine class of organic compounds, it contains a phenyl group with a butan-1-amine substituted at the fourth carbon
- Venlafaxine = phenylpropylamine class of organic compound which means that it consists of a phenyl group substituted at the third carbon by a propan-1-amine.
- Clomipramine (Anafranil) is a 3-chloro = analog of imipramine and = dibenzazepine derivative. Clomipramine belongs to the dibenzazepine class of organic compounds, which means that it consists of two benzene rings connected by a azepine ring; the latter being an unsaturated seven member heterocycle with a carbon atom replaced by a nitrogen atom
- The antiobsessive medications are sometimes referred to as “antistuck” medications.
- “

Side Effectis

- Most SSRIs, such as fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft), cause sexual dysfunction and decrease sexual arousal
- Small percentage of individuals on fluoxetine more depressed or more irritable, not generally true of all antidepressant medications.



Sertraline (Zoloft)

- (Zoloft), block the serotonin transporter from reuptaking the neurotransmitter serotonin.

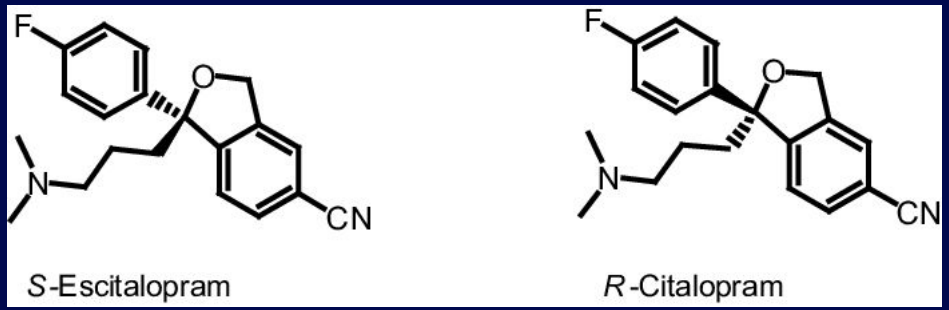
Fluoxetine (Prozac)

- Fluoxetine and the other SSRIs seem to be most useful when used as supplemental medications, particularly when administered in combination with a stimulant ADHD medicine for treating those individuals with the most severe symptoms.
- Prototypical SSRI treats major depressive disorder and ADHD fluoxetine is used to treat OCD, premenstrual dysphoric disorder, moderate to severe bulimia nervosa, panic disorder with or without agoraphobia, and along with coadministration of olanzapine for treatment resistant bipolar depression.

Paxil (Paroxetine)

- Paroxetine has more evidence indicating its use for anxiety-related disorders than any of the other SSRIs; it is used to treat generalized anxiety disorder, major depressive disorder, OCD, panic disorder with or without agoraphobia, PTSD, premenstrual dysphoric disorder, and social anxiety disorder as well as off-label use for ADHD.

Citalopram (Celexa)
Escitalopram (Lexapro)



- Escitalopram has equivalent dose ½ of citalopram
- Citalopram and escitalopram most selective of the SSRIs and low likelihood of inhibiting the CYP 450 enzymes no significant drug to drug interactions;
- NO significant affinity for dopaminergic, muscarinic, or norepinephrine receptors
- citalopram = mild histamine antagonist
- escitalopram does not block histamine receptors

Nefazodone (Serzone)

Mechanism of Action

- Inhibits the reuptake of serotonin and norepinephrine
- Serves as agonist of selected serotonin receptors

Treament Modalities

- Nefazodone hydrochloride (Serzone) is another SSRI that is an atypical antidepressant

Venlafaxine (Effexor)

Mechanism of Action

- that blocks the reuptake of both norepinephrine and “serotonin
- It appears that some symptoms associated with ADHD, in some individuals at least, are more likely related to a dysfunction of specific brain circuits, particularly those of the frontal cortex, rather than to an actual dysfunction of the serotonin system. Thus, modulation of these circuits by serotonergic neurons may underlie the specific mechanism of action of most antiobsessive medications. Although higher SSRI doses, at about 50 mg of fluoxetine or 250 mg of imipramine, appear to be more effective, this slight benefit is offset somewhat by reduced tolerability.”

Treatment Modalities

- Antiobsessive & ADHD medicine
- Associated with less adverse side effects for most individuals than the TCAs
- Result in improvements with both impulsivity and hyperactivity. These medications, accordingly, increase the amount of serotonin present in the neural synapses, which causes repeated activation of serotonin receptors.

Venlafaxine (Effexor)

Mechanism of Action

- Selective serotonin reuptake inhibitors and serotonin and
- noradrenaline reuptake inhibitors
- Selective serotonin reuptake inhibitors have not been found beneficial in the management of ADHD in the absence of any depressive symptoms.
- One small RCT in adults and several in children have reported positive effects of venlafaxine in ADHD [42,43]. However, further research is necessary to estimate the real effect size of treatment with serotonin/ noradrenaline reuptake inhibitors in the absence of depression. There is currently no trial evidence for other licensed serotonin/noradrenaline reuptake inhibitors such as duloxetine.

Anticonvulsants

Mechanism of Action

- The anticonvulsant ADHD medications, such as carbamazepine (Tegretol) and valporic acid (Depakote), are both GABA receptor agonists, which explains their efficacy

Agent	Epilepsy Seizure Type	Other
phenobarbital 	partial & generalized	
phenytoin 	partial & generalized	
valproic acid 	absence & partial	manic episodes, migraine
carbamazepine 	partial & generalized	bipolar I, pain (neuralgia)
oxcarbazepine 	partial	
lamotrigine 	partial & generalized	bipolar I
gabapentin 	partial	pain (neuralgia)

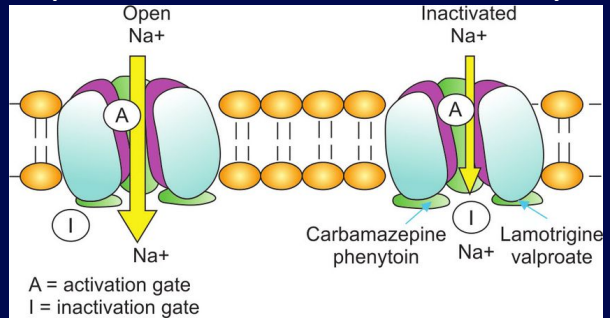
Treamtent Modalities

- Reduce reducing abnormal electrical activity in the brain.
- Used as sedating “agents for anxiety and as mood stabilizers for bipolar depressive disorder, also to control agitation in dementia, as well as for ADHD.

Carbamazepine (Tegretol, Carbatrol, Equetro)

Mechanism of Action

- Carbamazepine = tricyclic compound structurally similar to imipramine and related antidepressant medications.
- Carbamazepine belongs to the dibenzazepine class of organic compounds, which means that it has two benzene rings that are connected by an azepine ring.
- “Carbamazepine (Tegretol, Carbatrol, Epitol, Equetro) increases levels of GABA. Carbamazepine stabilizes hyperexcited neuron membranes, inhibits repetitive discharges of sodium dependent action potentials, and reduces synaptic transmission of excitatory impulses.



Treatment Modalities

- Carbamazepine used for partial seizures and for generalized tonic clonic seizures.
- Addressing neuropathic pain; carbamazepine also has anticholinergic, antirrhythmic, and muscle relaxant properties.”
- Carbamazepine anticonvulsant medicine seizures in individuals with epilepsy but also to treat diabetic neuropathy and trigeminal neuralgia, as well as for episodes of mania and bipolar depression
- Off-label use for treating ADHD. Carbamazepine is sometimes also used to treat PTSD, restless legs syndrome, alcohol and drug withdrawal, diabetes insipidus, and chorea.

Depakote (Valproic Acid)

Mechanism of Action

- Valporic acid (Depakote, Depakene) is a carboxylic acid derivative, which influences the activity of the GABA signaling systems, a pathway that serves to regulate the movement of “chloride ions into and out of cells. More specifically, it functions as a GABA transaminase inhibitor, blocks sodium and calcium channels, is an inhibitor of the histonedeacetylase enzyme, thus indirectly increases GABA levels.”
- Valporic acid is a free acid
- At normal body pH, valporic acid is fully ionized, thus whether the free acid or one of its salts is used, the active drug with therapeutic efficacy is in either case the valproate ion.
- Valporic acid belongs to the methyl branched fatty acids, which means that it consists of an acyl chain that has a methyl branch.

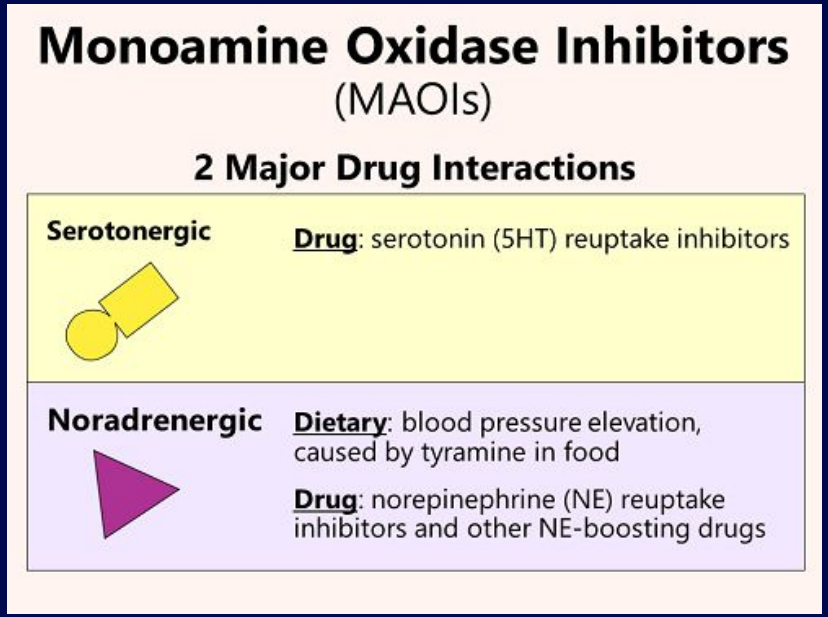
Treatment Modalities

- “Valproic acid = potent anticonvulsant treating generalized seizures and effective mood stabilize
- Known teratogen.
- It is important that individuals taking these anticonvulsant medications, also known as anti-seizure medications, have their white blood cell counts and their liver functions monitored regularly.
- The anticonvulsant medications are particularly helpful in treating individuals with ADHD who have explosive, violent outbursts and for those who may have had some head trauma

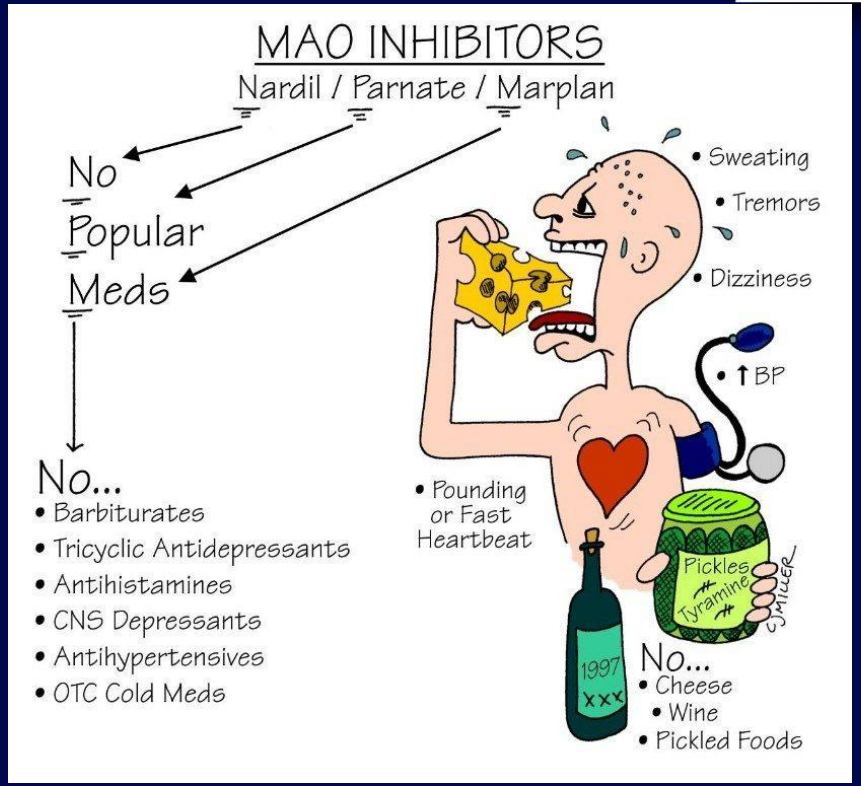
MAOIs

Mechanism of Action

- MAOIs inhibit one or both forms MAO enzyme.
- Mimic the effects of norepinephrine, dopamine, and serotonin.
- Present in the central and peripheral nervous system as well as in the gastrointestinal tract, liver, blood platelets, and mitrochondrial membranes.
- The MAO-A degrades norepinephrine and serotonin as well as epinephrine and melatonin;
- MAO-B enzyme subtype B degrades phenylclhylene and certain other trace amines,
- Subtype A and subtype B degrade dopamine. Since MAO subtype B inhibitors help to block the degradation of dopamine in the brain, their use makes more dopamine available and also reduces some of the excessive locomotor activity.
- The MAOIs can interact with certain foods, such as those containing tyramine (like some cheeses, meats, or beans), many pain or cold medications.
- Accordingly, individuals using MAOIs are typically placed on restricted diets. However, two of the newer MAOIs, selegiline (Emsam) and rasagiline (Azilect), have been FDA approved without dietary restrictions.



MAOIs



Treatment Modalities

- The irreversible MAOIs rapidly absorbed and quickly eliminated.
- Physiological effects do not end when the medicine clears pharmacodynamic half-life of irreversible MAOIs is considerably longer than their pharmacokinetic half-life.
- Nonselective MAOIs that are presently available in the United States include isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate); all three of these MAOIs are irreversible inhibitors of MAO enzyme activity.

MAOIs

Mechanism of Action

- “The MAOIs, such as moclobemide (Amira) and rasagiline (Azilect), are associated with dry mouth and digestive problems, like loss of appetite, weight loss, nausea, and constipation.
- Conflicting evidence as to whether the MAOIs alter cortisol levels and increase growth hormone levels
- The mechanism of action of moclobemide (Amira), is selective, in that it inhibits the activity of the subtype A MAO enzyme; and, it is reversible such that it can detach from the MAO enzyme and thereby resume facilitating the normal catabolism of the respective substrate neurotransmitter substances.
- Selective and reversible MAOIs, such as moclobemide, which is not yet available in the United States, are safer and require fewer dietary restrictions than the traditional MAOIs.

Treatment Modalities

- Phenalzine = sedation and greater weight gain than those taking other MAOIs.
- Tranylcypromine inhibits the MAO enzyme; this enzymatic inactivation of neurotransmitter substances, particularly as focused at the adrenergic
- Rasagiline and selegeline are selective MAOIs that only inhibit the activity of the subtype B MAO enzyme; however, rasagiline is reversible, while selegeline is irreversible.
- Selegiline is used mainly for treating individuals with newly diagnosed Parkinson’s disease. Selegiline belongs to the amphetamines and derivatives class of organic compounds.

Eugeroics

Mechanism of Action

- Eugeroics literally means “good arousal,”
- Represented by modafinil (Provigil) and armodafinil (Nuvigil).”
- The eugeroic ADHD medications, such as modafinil (Provigil) and armodafinil (Nuvigil), produce loss of appetite and consequent weight loss.
- The cholinergic agent nicotine (Nicorette) elevates blood pressure and heart rate and constricts pupils.”
- Modafinil functions essentially as an atypical dopamine transporter inhibitor and, interestingly, appears to promote wakeful “B enzyme.

Treatment Modalities

- Modafinil (Provigil), adrafinil (Olmifons), and armodafinil (Nuvigil) are eugeroics of wakefulness-promoting
- Treat conditions like narcolepsy, excessive daytime sleepiness associated with obstructive sleep apnea, and shift work–related sleep disorders,
- Used off label for helping to treat individuals with fatigue associated with many other conditions including that for chronic fatigue syndrome, depression, fibromyalgia, myotonic dystrophy, neurological fatigue as associated with multiple sclerosis, opioid induced sleepiness, Parkinson’s disease, SAD, spastic cerebral palsy, and, of course, also for ADHD.

Modafanil

Mechanism of Action

- Competitively binds to the cell membrane of the dopamine transporter, □ blocks the activity of the transporter, □ inhibits the reuptake of dopamine □ elevated levels of dopamine, particularly in the nucleus accumbens and in other associated regions of the brain, and the striatum more generally
- Modafinil also acts as a weak, but highly selective, partial agonist at the dopamine receptor site.
- Increase in dopamine levels □ increases locomotor activity and elevates extracellular levels of □ improved mood, wakefulness, and enhanced cognition.
- Modafinil has been shown to increase levels of norepinephrine in the hypothalamus and ventrolateral preoptic nucleus; serotonin in the amygdala and in the frontal cortex; and histamines in the hypothalamus
- Increased levels of norepinephrine □ stimulation sympathetic nervous system□ increasing heart rate and blood pressure and resulting in enhanced energy levels
- The increased norepinephrine □ increased memory, learning, and attention as well as greater cerebral plasticity.
- Modafinil, further, inhibits the release of GABA by acting on the 5-HTP serotonin receptors and activates Orexin.

Modafanil

Mechanism of Action

- Increase levels of dopamine in the striatum, & nucleus accumbens; norepinephrine in the hypothalamus and ventrolateral preoptic nucleus; serotonin in the amygdala and in the frontal cortex; and histamines in the hypothalamus
- Modafinil selective agonist of the alpha 1 adrenergic postsynaptic receptor sites
- Direct agonist effect on the alpha 1 adrenergic receptor sites facilitates inhibition of norepinephrine uptake promoting wakefulness.

- Analeptic drug, = a medicine that stimulates the respiratory system of the brain.
- Blocks methamphetamine hydrochloride (Desoxyn) induced dopamine release
- Modafinil, as well as related eugeroic medications like armodafinil (Nuvigil) produce wakefulness without the need for compensatory sleep; they also enhance electronic coupling, which increases the efficiency of neural communication
- Modafinil, as well as related eugeroic medications like armodafinil (Nuvigil), thus produce wakefulness without the need for compensatory sleep; they also enhance electronic coupling, which increases the efficiency of neural communication.”

Modafanil

Mechanism of Action

- Increase in dopamine levels increases locomotor activity and elevates extracellular levels of dopamine in the human brain, improved mood, wakefulness, and enhanced cognition.
- Functions essentially as an atypical dopamine transporter inhibitor promote wakefulness without the apparent need for compensatory sleep.
- Low potential for substance abuse.
- Modafinil is the active metabolite of adrafinil, which “of Olmifons until September 2011 when marketing permission was withdrawn.

Modafanil (Provigil)

Treatment Modalities

- Modafinil is a ‘wakefulness-promoting substance’ used in narcolepsy
- Modafinil is not a controlled drug in the UK. Use in ADHD is exclusively off-label.
- In ADHD, reduction of symptoms summarized as being clinically meaningful but statistically modest and far less than accomplished with classic stimulants
- Use with caution as a third-line agent in patients not responded to any other stimulant or atomoxetine, but prescribers should be specialists (or guided by specialists in ADHD
- Been used off label by astronauts and by the militaries of many countries while engaged in situations of sleep deprivation.

Adverse Effects

- Modafinil should not be used in moderate-to-severe hypertension or in severe cardiovascular disease.
- Addictive potential has been described in animals
- Modafinil may reduce the effectiveness of oral contraceptives.
- Potential serious adverse reactions include severe rashes, Stevens-Johnson syndrome, and toxic epidermal necrolysis
- Psychiatric side effects can include anxiety, irritability, hallucinations, and psychoses. Other side effects include gastrointestinal disturbance, tachycardia, sleep disruption, drowsiness, and visual symptoms.

Armodafanil (Nuvigil)

Mechanism of Action

- Armodafinil appears to inhibit the reuptake of dopamine by binding to the dopamine transporter; this results in increased levels of extracellular dopamine.
- Armodafinil appears less selective alpha 1 adrenergic drug than modafinil, thus higher doses of armodafinil are typically required to achieve comparable therapeutic results compared to those of the more potent modafinil.

Treatment Modalities

- Armodafinil is prescribed for treating narcolepsy, obstructive sleep apnea, and shift work sleep disorder
- Common off-label uses of armodafinil include Parkinson's disease, mytonic muscular dystrophy, excessive daytime sleepiness, and, of course, ADHD.
- Further, the greater adverse side effects profile typically associated with use of armodafinil limits its widespread applicability as a eugeroic
- Armodafinil is the enantiomer or single R isomer of the racemic modafinil.
- Armodafinil greater delayed period of time needed to achieve peak concentration compared to modafinil.

Antipsychotics

Treatment Modalities

- Used off label to treat individuals with ADHD
- The antipsychotics generally used for treating schizophrenia and related disorders,
- Increasingly used to treat ADHD and disruptive behaviors in children and adolescents
- Most commonly used off label antipsychotic medications in this regard are haloperidol (Haldol), pimozide (Orap), and thioridazine.
- Haloperidol (Haldol) = phenyl-piperidinyl-butyrophenone medicine treats schizophrenia and other psychoses, delusions, Tourette's syndrome, and adjunctive therapy for cognitive impairment and, ADHD.

Treatment Modalities

- The atypical antipsychotics used most frequently for offlabel ADHD are clozapine (Clozaril), olanzapine (Zyprexa), quetiapine fumarate (Seroquel), and risperidone (Risperdal).

Antipsychotic Medications

Conventional Antipsychotics	Atypical Antipsychotics
Chlorpromazine	Aripiprazole
Fluphenazine	Clozapine
Haloperidol	Olanzapine
Loxapine	Paliperidone
Molindone	Quetiapine
Perphenazine	Risperidone
Pimozide	Ziprasidone
Prochlorperazine	
Thiothixene	
Thioridazine	
Trifluoperazine	

Antipsychotics Pimozide (Orap)

Treatment Modalities

- Pimozide (Orap) is an antipsychotic medicine that is used as an alternative to haloperidol and to suppress the motor and vocal tics associated with Tourette's syndrome as well as for off-label use to treat ADHD.
- Pimozide belongs to the diphenylmethane class of organic compounds, which means that it consists of a methane with two phenyl groups that replace two hydrogen atoms.

Treatment Modalities

- Pimozide = diphenylmethane class of organic compounds =consists of a methane with two phenyl groups that replace two hydrogen atoms.
- Pimozide (Orap) blocks dopaminergic activity by binding to and inhibiting the dopamine 2 receptors
- Pimozide (Orap) instead of haloperidol suppress the motor and vocal tics Tourette's syndrome and off-label use to treat ADHD.

Antipsychotics
Clozapine (Clozaril)

Treatment Modalities

- Clozapine (Clozaril) = tricyclic dibenzodiazepine atypical antipsychotic medicine that is mainly used for treating schizophrenia.
- Clozapine = dibenzodiazepine class of organic compounds consists of two benzenes connected by a diazepine ring.
- Clozapine (Clozaril) has lower dopamine affinity than haloperidol (Haldol) but, in addition, clozapine blocks serotonin receptors in the frontal cortex.”

- Clozapine (Clozaril) is a tricyclic dibenzodiazepine atypical antipsychotic medicine that is mainly used for treating schizophrenia. Clozapine belongs to the dibenzodiazepine class of organic compounds, which means that it consists of two benzenes connected by a diazepine ring.

Antipsychotics
Olanzapine (Zyprexa)

Treatment Modalities

- Olanzapine = benzodiazepine class of organic compounds = consists of a benzene ring fused to a diazepine isomer.
- Olanzapine (Zyprexa), similarly, acts as an antagonist on the dopamine 3 receptors in the mesolimbic pathway and also in the serotonin receptors of the frontal cortex
- Olanzapine pamoate (Zyprexa) is an atypical antipsychotic medicine that is a synthetic derivative of thienobenzodiazepine that is used primarily for treating schizophrenia and bipolar disorder and that also has antinausea and antiemetic activities.

Treatment Modalities

- Olanzapine pamoate (Zyprexa) = atypical antipsychotic medicine = synthetic derivative of thienobenzodiazepine □ primarily for treating schizophrenia and bipolar disorder and has antinausea and antiemetic activities.
- Olanzapine (Zyprexa) has been approved for use with adolescents with schizophrenia or with bipolar disorder with mixed or manic episodes
- Olanzapine belongs to the benzodiazepine class of organic com”

Antipsychotics
Quetiapine (Seroquel)

Treatment Modalities

- Quetiapine fumarate = dibenzothiazepine class of organic compounds contains two benzenes connected by a thiazepine ring.
- Quetiapine fumarate functions as a norepinephrine, dopamine, and serotonin antagonist, as well as a potent antihistamine with little to no anticholinergic effects.
- Quietiapine strongly binds to serotonin receptor sites and can also act as a partial serotonin agonist. Further, since it can antagonize norepinephrine and “serve as autoreceptors, their blockage helps to stimulate the release of these neurotransmitter substances.”

Treatment Modalities

- Quetiapine off label for sleep aid and ADHD.
- Quetiapine fumarate (Seroquel) = atypical antipsychotic medicine treating schizophrenia, acute episodes of mania associated with bipolar I disorder, and along with an antidepressant medicine to treat unipolar depression.
- The FDA, approved use of quetiapine fumarate (Seroquel) for children with bipolar disorder with manic episodes and for adolescents with schizophrenia

Antipsychotics

Treatment Modalities

- Risperidone = pyridopyrimidine class of organic compounds = consists of a pyridine fused to a pyrimidine.
- Risperdone = affinity for dopamine 2 receptors in limbic system, antagonist to serotonin 2A receptors in the mesocortical tract excess of available dopamine increase in dopaminergic transmission
- Risperidone (Risperdal) is an atypical antipsychotic medicine that is a benzisoxasole derivative
- Risperidone belongs to the pyridopyrimidine class of organic compounds, which means that it consists of a pyridine fused to a pyrimidine.

Treatment Modalities

- Risperidone (Risperdal) = atypical antipsychotic medicine = benzisoxasole derivative that is prescribed mainly for treating schizophrenia and bipolar disorder and to alleviate irritability in individuals with autism.
- Risperidone (Risperdal) has been approved for use with adolescents with schizophrenia, for treating irritability associated with autism, and for bipolar disorder with mixed or manic episodes.

Antipsychotics
Thioridazine (Mellaril)

- Thioridazine hydrochloride is a phenothiazine antipsychotic generic medicine that is used for treating schizophrenia and other psychoses, as well as for controlling severely agitated or disturbed behaviors, like those associated with ADHD.
- Thioridazine belongs to the phenylthiazine class of organic compounds, which means that it has a linear tricyclic system that “consists of two benzene rings joined with a parathiazine ring.

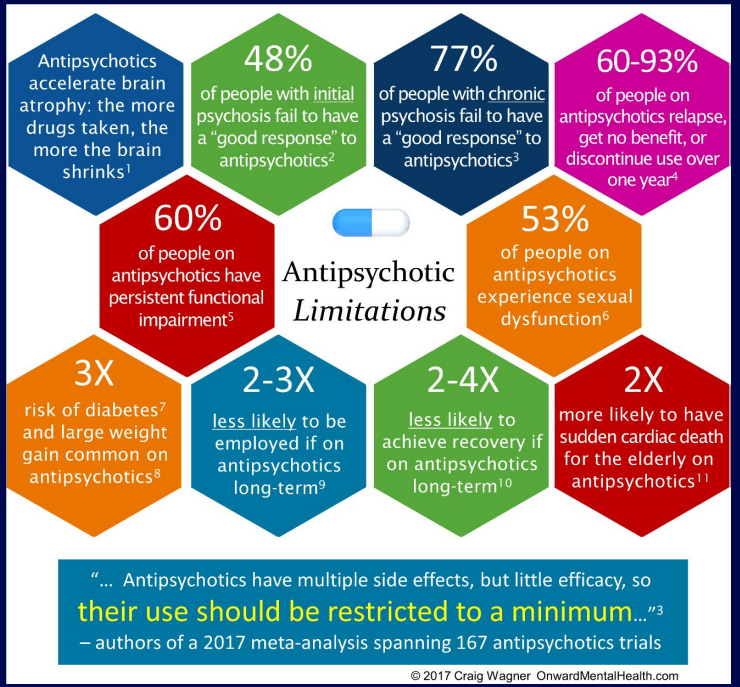
Treatment Modalities

- Thioridazine hydrochloride (Mellaril) blocks postsynaptic dopamine 1 and dopamine 2 receptors in the mesolimbic pathway of the human brain
- Blocks alpha adrenergic effects & depressing release of hypothalamic hormones suppresses the reticular activating system
- Thioridazine hydrochloride = phenothiazine antipsychotic = generic medicine that is used for treating schizophrenia and other psychoses, severely agitated or disturbed behaviors, and ADHD.

Antipsychotics

Adverse Side Effects

- The antipsychotic ADHD medications, such as clozapione (Clozaril), haloperidol (Haldol), olanzapine (Zyprexa), pimozide (Orap), and risperidone (Risperdal), tend to produce muscle stiffness, flattened facial expressions, lowered seizure threshold, sedation, and sexual dysfunction."



Cholinergic Agents

Mechanism of Action

- "Cholinergic agents =cholinomimetic agents: mimic the effects of acetylcholine.
- 2 types of cholinergic agents,
  - the cholinoceptor stimulants act primarily on muscarinic or nicotinic receptor sites
  - the cholinesterase inhibiting drugs act indirectly by inhibiting the hydrolysis of acetylcholine.

Cholinergic Receptors

M1	**Secretory glands**	salivation, stomach acid, sweating, lacrimation
M2	**Heart**	Decreases heart rate → bradycardia
M3	**Smooth muscle (GI/GU/Resp)**	Contraction of smooth muscles (some) → diarrhea, bronchospasm, urination
M3	**Pupil and ciliary muscle**	Contracts → Miosis Increased flow of aqueous humor
Nm	**Skeletal muscle end plate**	Contraction of skeletal muscle
Nn	**Autonomic ganglia, Adrenal Medulla**	Secretion of Epinephrine Controls ANS

Nicotine

Mechanism of Action

- Nicotine stimulates neurons but overall blocks synaptic transmission= selective agonist of the nicotinic acetylcholine receptor activated by acetylcholine.
- Nicotine binds selectively nicotinic receptors, esp. sites at nicotinic cholinergic junctions, like autonomic ganglion and neuromuscular end plates, opens up ion channels in postsynaptic membranes.
- Mimics acetylcholine high propensity abused substance.
- Nicotine activates the dopaminergic pathway that projects from the ventral tegmental area to the cerebral cortex and limbic system.
- Nicotine primary cholinergic considered for use in ADHD

Mechanism of Action

- Nicotine = highly toxic tertiary natural cholinomimetic alkaloid
  - as a liquid is sufficiently lipid soluble to be absorbed directly across the skin.
- Prolonged exposure /agonist occupancy, of the nicotinic receptor abolishes the effector response, postganglionic neurons stop firing and skeletal muscle cells relax & prevents electrical recovery postsynaptic membrane depolarizing blockade.
- Low dose: nicotine creates mild alerting action stimulating the brain stem and cortex good for ADHD
- High doses: nicotine causes tremor, emesis, and respiratory stimulation; and, higher dosage: nicotine causes convulsions, which can be lethal

Quick Check Questions

- 1) What is the best off label treatment for a patient with ADHD with explosive anger, mood lability, and hx of brain trauma?

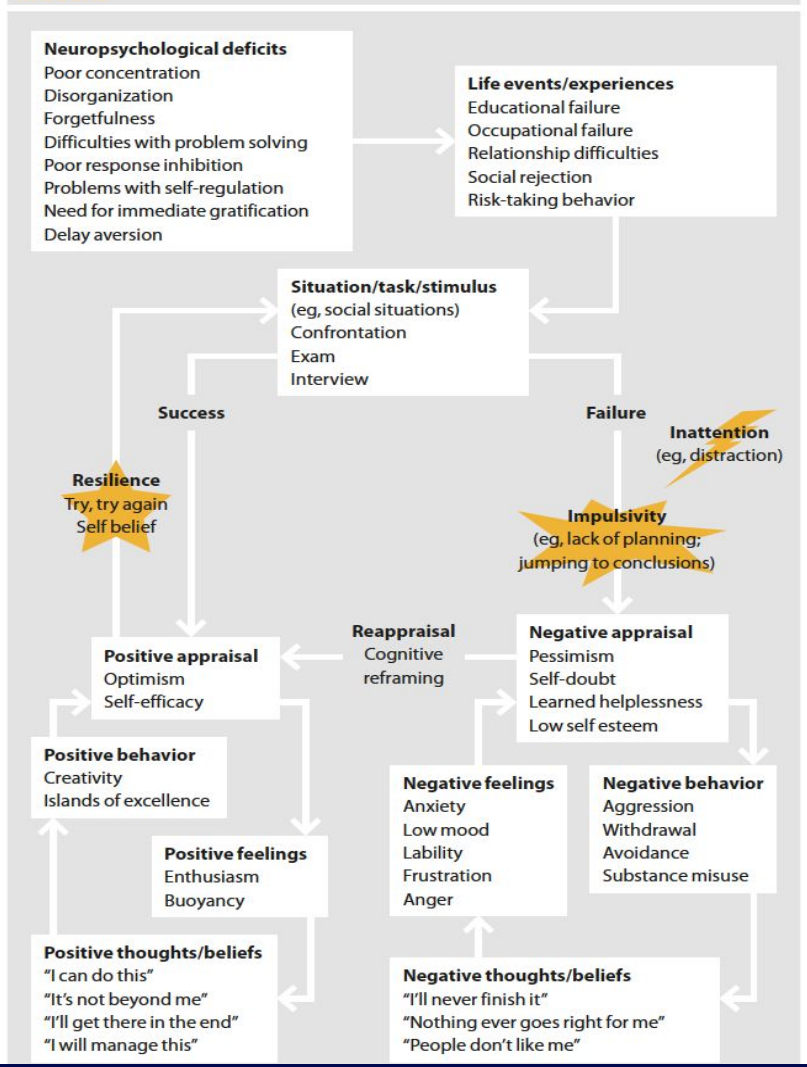
- A. Antipsychotics
- B. Mood Stabilizers
- C. Methylphenidate
- D. Modafanil
- E. Alpha 2 Antagonists

Answer:

- ANTICONVULSANTS

are the best off-label treatment for a patient with ADHD with explosive anger, mood lability, and hx of brain trauma

CBT


Neuropsychological deficits
Poor concentration
Disorganization
Forgetfulness
Difficulties with problem solving
Poor response inhibition
Problems with self-regulation
Need for immediate gratification
Delay aversion
Life events/experiences
Educational failure
Occupational failure
Relationship difficulties
Social rejection
Risk-taking behavior
Situation/task/stimulus
(eg, social situations)
Confrontation
Exam
Interview
Success
Failure
Inattention
(eg, distraction)
Resilience
Try, try again
Self belief
Impulsivity
(eg, lack of planning; jumping to conclusions)
Reappraisal
Cognitive reframing
Positive appraisal
Optimism
Self-efficacy
Negative appraisal
Pessimism
Self-doubt
Learned helplessness
Low self esteem
Positive behavior
Creativity
Islands of excellence
Positive feelings
Enthusiasm
Buoyancy
Negative feelings
Anxiety
Low mood
Lability
Frustration
Anger
Negative behavior
Aggression
Withdrawal
Avoidance
Substance misuse
Positive thoughts/beliefs
"I can do this"
"It's not beyond me"
"I'll get there in the end"
"I will manage this"
Negative thoughts/beliefs
"I'll never finish it"
"Nothing ever goes right for me"
"People don't like me"

CBT

- NICE identified CBT to be the most appropriate intervention because = person-centered and highly structured.
- Flexibility and adaptability.
- May be minimal or limited to one specific technique, such as coping self-talk with the predominant emphasis being on behavioral techniques.
- Alternatively, the therapist may shift the emphasis to include more cognitive interventions that aim to reduce psychological distress and maladaptive behavior by altering cognitive processes.

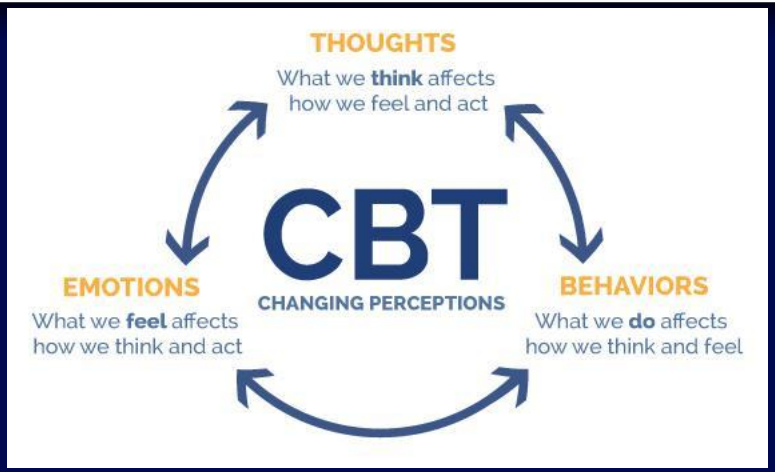
- Cognitive behavioral therapy for attention deficit hyperactivity disorder symptoms
- Clinical trials suggest that impulsivity and hyperactivity tend to diminish but that attentional problems persist into adulthood [5,6], and adult symptoms are often experienced as difficulty with time management and organization.
- For people whose symptoms are not recognized until adolescence or later and are diagnosed de novo, psychological treatments will help them to accept their diagnosis and reframe their past experiences.

CBT

- The treatment of core symptoms will involve the provision and rehearsal of coping strategies and skills development techniques, including:
  - cognitive remediation strategies to address core deficits in attention, impulsivity, and emotional regulation;
  - cognitive restructuring strategies that aim to change negative thought patterns;
  - cognitive reframing techniques to challenge past beliefs and assumptions;
  - problem-solving techniques and consequential thinking; • setting behavioral experiments to test new skills;
  - the rehearsal of adaptive behaviors. The aim is to work with patients to generate a repertoire of practical strategies that they can successfully apply to:
  - improve their attention and memory (eg, using self-instructional training and memory aids);
  - develop better impulse-control skills (eg, using ‘stop and think techniques’); and
  - improve time-management, organizational, prioritization and planning skills (eg, by using diaries and time schedules).

CBT

- Cognitive behavioral therapy for comorbid and associated problems
- Most adults with ADHD have experienced a host of negative life events, including:
  - academic underachievement,
  - occupational difficulties and unemployment,
  - interpersonal relationship problems, and divorce
- Comorbid and psychosocial problems are the rule rather than exception, & include:
  - mood and anxiety disorders, emotional lability,
  - frustration, irritability, sleep disturbances,
  - problems with alcohol and substance misuse,



  - personality disorders (primarily cluster B), antisocial behavior, social skills deficits, poor interpersonal
  - relationships, and a sense of failure and low self esteem.

CBT

- Some generic interventions that will be helpful in treating these problems include strategies to help the patient to learn and develop protocols for:
  - problem-solving,
  - social communication skills,
  - self-monitoring skills,
  - social-perspective taking,
  - emotional control,
  - management of lability,
  - and assertiveness training.
- The treatment of comorbid and psychosocial problems does not differ greatly from treatment that would be given to non-ADHD patients other than in their delivery.

- Interventions need to be adapted for patients with ADHD by:
  - delivery of individual treatment on a 'little and often' basis, for patients who struggle to focus in a 1-hour treatment session;
  - appointment reminders (by telephone, text or email)
  - supplementation psychoeducation, specific treatment strategies, and 'learning points' with written materials;
  - inclusion of feedback and reinforcement mechanisms provided on a frequent basis;
  - introduction of reward systems (both immediate and delayed) to motivate adherence and reward achievement

DBT

- Dialectical behavioral therapy (DBT) developed from CBT
- Initially adapted to suit the specific needs of people with borderline personality disorder
- Aims to meet the needs of people with emotional problems by encouraging them to dialectically balance acceptance with change,
- CBT techniques to change behavior are supplemented with ‘acceptance strategies’ that focus on validation

- A RCT evaluating DBT in comparison to an unstructured discussion group (all patients being on ADHD medication)
  - reported a medium post-treatment effect for improvement in ADHD symptoms
  - no statistically significant differences in measures of anxiety, depression, sleep, and stress

Coaching

- Coaching is supportive intervention applies a brief, solution-focused paradigm.
- Coaching does not draw on any clear methodology
- Coaches are not required to have any specific qualifications.
- May improve completion rates reflecting that individual coaching sessions support participants to transfer skills learned in the process of treatment and apply them into their daily lives.

- Coaching has been utilized in two key ways:
  - to support group CBT treatments with the aim of improving completion rates and the transference of skills from a therapeutic ‘theoretical’ setting to an existential setting;
  - to facilitate individual performance. These aims are achieved by the coach adopting a tutoring or instructional approach within a collaborative partnership that aims to provide structure, support, and feedback.

Coaching

- The intervention draws on patients' personal strengths helps them to better manage their lives through mentoring and supporting them to set and achieve goals in their daily activities.
- Development of functioning problem solving skills and coping strategies.
- The work most commonly negotiated on an individual basis between coach and client focuses on the client's goals and needs.
- No standard methodology, the process of the intervention varies considerably; may include:
  - face-to-face contact,
  - brief regular telephone conversations,
  - text messaging,
  - and email contact

Homeopathic

Hyoscyamus niger (black henbane)

- Recommended by homeopaths for treating some individuals who experience poor impulse control

Type	Chemical	Plant species	Common plant name
Cholinesterase inhibitors	Physostigmine	Physotigma venenosa	Calabar bean
	Galanthamine	*Galanthus nivalis*	Snowdrop
		Narcissus pseudonarcissus	Daffodil
	Huperzine	*Huperzia serrata*	Fern
Muscarinic agonists	Arecoline	*Areca catechu*	Betel nut
	Pilocarpine	*Pilocarpus jaborandi*	
	Muscarine	*Amanita muscaria*	Fly agaric
Muscarinic antagonists	Atropine	*Atropa belladona*	Deadly nightshade
	Hyoscamine	*Hyoscamus niger*	Henbane
	Scopolamine (or hyoscine)	*Mandragora officinarum*	Mandrake
		Datura (numerous species)	e.g. thorn apple
		Scopalia carniolica	

Listol

- Listol is a formulation of natural substances, which was developed and marketed by Progressive Health, and that is used to mana symptoms of ADHD in children and adults.
- Active ingredients in Listol are mostly minera and amino acids, including calcium carbonat copper gluconate, iron citrate, magnesium oxide, zinc oxide, and GABA powder;
- most ingredients have no proven clinical effects for treating ADHD and some can have toxic effects if taken in large doses

Homeopathic

Addasil

- Addasil is a liquid nutritional supplement marketed as stimulating attention and concentration as well as for promoting focus in children and adults with ADHD.
- Contains phospholipids (which helps promote the structural integrity of neurons and contribute to neurotransmitter synthesis), essential fatty acids, assorted minerals, like calcium gluconate and magnesium gluconate, and several vitamins, including thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), cyanocolilamin (B12), and vitamin C

Synaptol

- Synaptol, developed and marketed by Hello Life
- liquid homeopathic formulation
- Consists of herbal extracts and ingredients marketed as improving attention span and enhancing mental focus and concentration;
- Ingredients include extracts of Aconitum ferox (Indian aconite), Aesculus hippocastanum (hosre cherstnut), Apis mellifica (Western honey bee), Argentum nitricum, (silver nitrate), Avena sativa (green oats), Baptisia tinctoria (wild indigo), Cochlearia armoracia (hosreradish), Scleranthus annuus (German knotweed), Scutellaria lateriflora (blue skullcap), and Viola odorata (wood violet).”

Homeopathic

Pemoline Magnesium (Cylert)

- Marketed under the trade name of Cylert, is a product that had been available and was, previously, prescribed for treating individuals diagnosed with ADHD.
- Pemoline had been approved for use with individuals who were six years of age and older.
- Is a central nervous system stimulant drug that had severe adverse side effects associated with its use.
- Pemoline belongs to the benzene class of organic compounds, which means that it is an aromatic compound that contains a monocyclic benzene ring system.
- It was a medicine that patients were advised that they would have to have regular liver function tests to monitor its usage
- Recognized that about 2 percent to 3 percent individuals taking pemoline might develop hepatitis.
- In 2005, the FDA removed approval of magnesium pemoline and in March of 2005, Abbott Laboratories discontinued its production.”

Homeopathic

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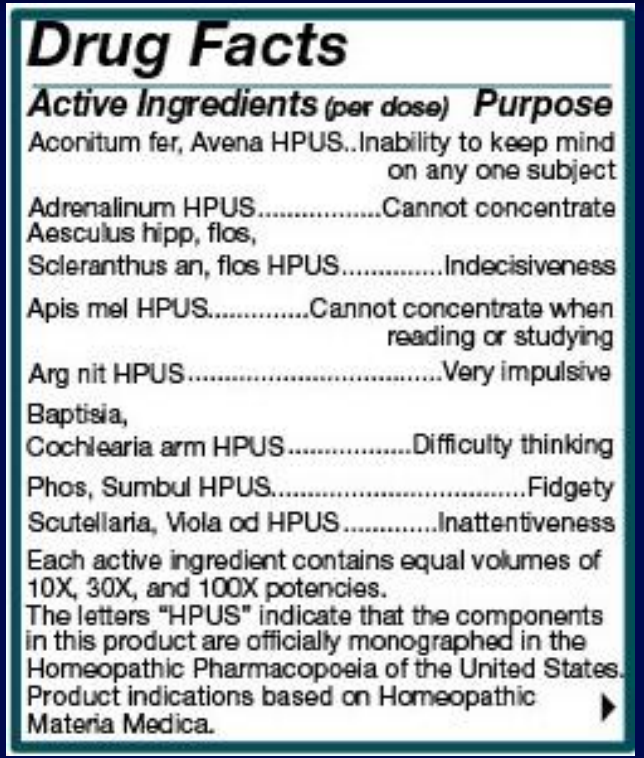

Drug Facts

Active Ingredients (per dose)	Purpose
Aconitum fer, Avena HPUS	Inability to keep mind on any one subject
Adrenalinum HPUS	Cannot concentrate
Aesculus hipp, flos, Scleranthus an, flos HPUS	Indecisiveness
Apis mel HPUS	Cannot concentrate when reading or studying
Arg nit HPUS	Very impulsive
Baptisia, Cochlearia arm HPUS	Difficulty thinking
Phos, Sumbul HPUS	Fidgety
Scutellaria, Viola od HPUS	Inattentiveness

Each active ingredient contains equal volumes of 10X, 30X, and 100X potencies.
The letters "HPUS" indicate that the components in this product are officially monographed in the Homeopathic Pharmacopoeia of the United States.
Product indications based on Homeopathic Materia Medica.

Behavioral Therapy

Behavioral Therapy

- Behavioral therapy consists of a broad array of therapeutic approaches to help individuals to change their self-defeating problematic behaviors
- Founded on the fundamental principles of operant and classical conditioning
- Operant conditioning process that utilizes techniques help to make a response become less or more likely to occur depending upon its consequences, such as using a demerit system to reduce the impulsive blurting out of answers by a student with ADHD in a classroom.

- Classical conditioning is a process that utilizes various techniques to transform a previously neutral stimulus such that it will be paired with another stimulus that already elicits a desired response; it is also referred to as Pavlovian conditioning or as respondent conditioning.

Nutritional Therapy

Nutritional Therapy

- Nutritional therapy can also be of substantial assistance in the management of ADHD and is an approach that many parents of children with ADHD are typically very willing to try. Losing excess weight through proper nutrition, along with appropriate regular physical exercise, can be particularly helpful in the prevention “of certain types of conditions which have a high association with ADHD, such as diabetes and obesity.
- A mostly vegetarian diet has been suggested to be helpful for those dealing with some of the symptoms associated with ADHD.

- Nutritional supplements, like the natural hormone melatonin, may be of some assistance in improving sleep problems for those children who take certain ADHD medications. Herbal remedies, fish oils and other nutritional approaches, like gluten free diets, have been suggested, but additional research is sorely needed before any evidence-based recommendations can legitimately be made. A balanced diet with sufficient caloric levels is clearly essential as the human brain uses about one fifth of the total energy consumed. Furthermore, a proper diet can also often decrease the amount of ADHD medications required

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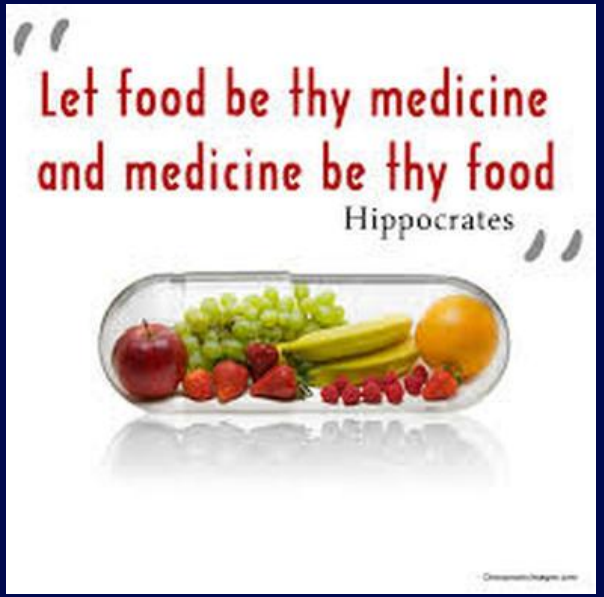


Healthier Condition

Healthier Condition

- A healthier condition, all of which can assist in the managing symptoms of ADHD. For example, tai chi is a traditional Chinese practice that is based on gentle, slow movements that can help increase flexibility and concentration;
- similarly, there are numerous types of yoga from India that people have used for millennia to help achieve a mind-body balance and for relaxation and enhanced concentration. There are many other varieties of physical therapy and myriad corrective exercises that could possibly enhance both physical and emotional health, as well as help improve concentration.

- There are many benefits demonstrated from regular physical exercise that would be helpful for managing symptoms of ADHD and promoting overall health improvement. Through the use of cardiovascular, flexibility, and strength exercises, one can possibly improve both his or her physical and psychological health and thereby possibly reduce, if not even eliminate, the use of ADHD medications. However, the wrong type of exercise or any exercise performed improperly can also lead to injury; therefore, professional guidance is recommended.”

Biofeedback & Neurofeedback

Biofeedback

- Biofeedback special equipment teach individuals to gain conscious control over involuntary physiological functions, such as their blood pressure, heart rate, muscle tension, skin temperature, and sweating.
- based on premise power of one's mind to consciously control what's happening inside of their body, they can gain better control over their state of health.
- Electromyographic (EMG) biofeedback, for instance, uses equipment to monitor muscular tension to train individuals how to more effectively and selectively relax areas of intense tension, which can clearly help to lessen stress, like that associated with anxiety disorders, back pain, and headaches.

Neurofeedback

- Similarly, electroencephalographic (EEG) biofeedback, also known as neurofeedback, uses equipment to measure brain wave activity and can be particularly helpful in managing conditions such as ADHD as well as epilepsy or seizure disorders; the goal of this approach is to assist the individual with ADHD to learn how to increase his or her beta wave activity and to lessen his or her theta wave activity. In addition, galvanic skin response (GSR), also known as electrodermal activity (EDA) or[…]"

Chiropractic

Chiropractic

- Chiropractic is a type of alternative medicine that employs myriad techniques that are based on the belief that subluxations, or dislocations, in the arrangement of the vertebra of the spinal column can result in nerve impingements that are claimed to produce varied health problems, including the types of symptoms that are usually associated with ADHD, like restlessness. Realignment by manipulation is the primary technique that is used by chiropractors to supposedly adjust the structural integrity of the spinal column.

- Chiropractic treatment usually involves manual adjustments, known as manipulation therapy, delivered by means of respective techniques, such as high-velocity, low-amplitude spinal manipulation (HVLA-SM). Chiropractic practitioners may also freely dispense dietary advice, commonly advocating the use of specific nutritional supplements, as well as employing other varied treatment modalities, such as the application of hot or cold compresses, ultraviolet or infrared light, ultrasound, and traction. The benefits claimed for[…]”

Massage

Massage

- Based on manipulation of muscles and of soft body tissues to alter circulatory, lymphatic, muscular and nervous systems in the body.
- The kneading, pummeling, rubbing, and stroking of muscles and other tissues as typically practiced in respective massage therapy techniques have been clinically shown to effectively increase metabolism, enhance lymphatic “drainage, and release substances back into circulation in order to thereby create states of both physical and mental relaxation.

- Clinical studies demonstrate that massage therapy techniques promote release of endorphins produce feelings of euphoria.
- Massage encourages state of relaxation
- Appears to provide opportunities for maintaining greater concentration promote improved daily functioning.
- Demonstrated efficacy providing to improve mental concentration and focus.
- Reiki, style of Japanese massage uses light, energy healing techniques based on concept of life force energy.
- 100 different types of massage approaches including those like acupressure, Ayurvedic, reflexology, shiatsu, and Swedish forms

Hypnosis

Hypnosis

- “Hypnosis involves a set of specific techniques that are intended to help individuals to improve their focus and concentration, lessen the potential influence of distractions, and increase their responsiveness to suggestions set forth. Some individuals, however, respond better to hypnotic suggestions than do others; the motivations and the expectations that an individual brings to this form of treatment has a profound influence upon the potential effectiveness of the hypnotherapy. There are various hypnotherapeutic techniques that can be used for managing symptoms of ADHD, such as the varied interpersonal approaches and hypnoanalysis.

- Hypnotic regression is frequently employed as a technique that is generally considered the best way to get to the underlying root cause of a respective problem, recognition of which can sometimes be enough to lead to better acceptance and possibly even relief. Most hypnotic techniques are essentially designed to produce an altered state of awareness, which can usually make an individual more open to specific suggestions, such as feeling less distracted.

Relaxation

Relaxation

- “Relaxation techniques, such as guided imagery, mediation, and progressive muscle relaxation, consist of a battery of techniques that can be employed to help an individual to reduce his or her level of stress.
- These varied relaxation techniques help individuals learn how to relax specific muscle groups and to achieve a more calm mental state, also been clinically shown to reduce the levels of stress hormones in the body.
- Respective meditation techniques are intended to help produce a state of mind-body inner focus and more peaceful, concentrated awareness, which can assist one in maintaining his or her focus and attention.

- Various relaxation approaches: yoga, autogenic training, mindfulness meditation, rhythmic breathing practices, transcendental meditation, and visualization exercises.
- Most relaxation and meditation techniques help to lower blood pressure, slow metabolism, and lessen anxiety, all of which are things that can help an individual with ADHD to become less distractible
- Fundamental purpose of relaxation techniques = help individual systematically reach homeostatic physiological state opposite that of the stress response.
- Several relaxation therapies clinically shown to reduce feelings of anxiety. Mediating, increases ability to maintain focus and decrease the use of ADHD medications

Acupuncture

- Acupuncture is an ancient medical technique from China that involves inserting thin needles at specific anatomical points on the body along what are referred to as the meridian lines of 12 energy channels that purportedly flow below the surface of the body.
- Acupuncture is known to have been practiced at least as far back as 4,500 years ago in ancient China.
- There are at least 365 of these specific acupuncture sites along the meridians where the specialized needles can be inserted and manipulated by an acupuncturist in specific ways and for specific periods of time to produce the desired therapeutic results.
- Acupuncture can definitively change brain activity, particularly in the dorsomedial prefrontal cortex, which has been implicated in hyperactivity."

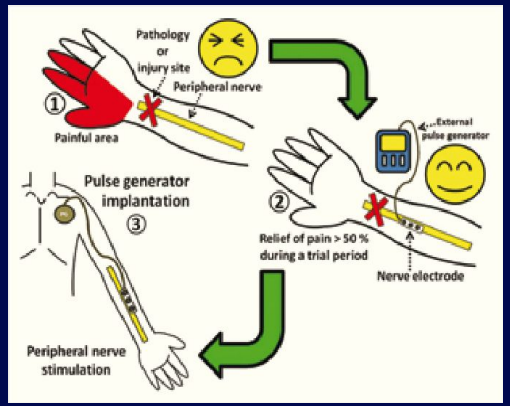
- Chinese medicinal specialists who perform this revered practice are said to help bring balance the life forces, known as the complementary cosmic energies of yin and yang, which are believed to flow through the human body as ch'i.
- These small acupuncture needles can easily produce a slight tingling feeling and can even make a selected body part feel numb,
- Changing signals sent to and from the brain; suggested that mechanism of action is to selectively block the transmission of impulse signals
- Also suggested by some that acupuncture might actually work by stimulating the release of endorphins and other neurotransmitters that, in turn, could block signals from being delivered either to the brain or, conversely, back to the extremities.

Electrotherapy

Electrotherapy

- Various types of electrotherapy have been developed control sensations and excessive locomotor activity as sometimes exhibited by individual's with ADHD.
- Approaches utilize assorted technological devices that can be used to help control and manage muscle tension and related sensations.
- Transcutaneous electrical nerve stimulation (TENS), for instance, utilizes safe, relatively mild electrical signals that are released by small, battery powered devices which can be attached to the surface of the skin, while spinal cord stimulation (SCS), on the other hand, uses an electrode that is surgically implanted near the spinal cord of an individual to block neurotransmission signals by means of neuro-modulation.

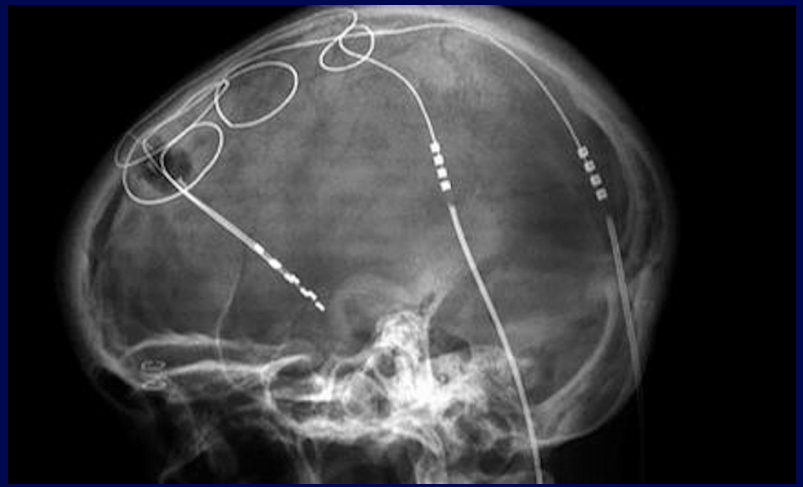
- Peripheral nerve stimulation (PNS), uses an electrode that is inserted through a small surgical incision and then placed on a nerve,
- Peripheral nerve field stimulation (PNFS) slightly less invasive approach in which an electrode is inserted under the skin by means of a needle.



Deep Brain Stimulation & Transcranial Magnetic Stimulation

Peripheral Nerve Stimulation

- Deep brain stimulation (DBS) = most invasive: which electrodes are placed directly into the brain, usually in either the periacueductal gray and sensory thalamus regions.
- (DBS) in which electrodes are placed directly into the brain, usually in either the periacueductal gray and sensory thalamus regions.
- Transcranial magnetic stimulation (TMS) is “magnetic induction is used to impart electrical stimulation in order to better manage excessive locomotor activity



Aromatherapy

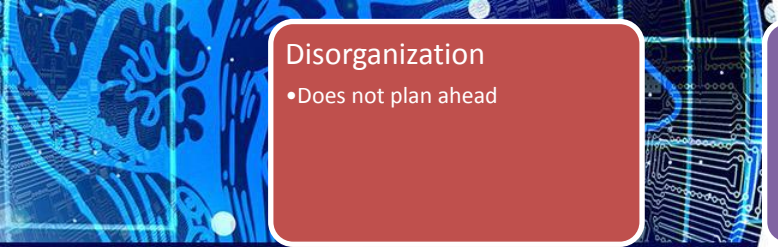
Aromatherapy

- “Aromatherapy is an approach that uses scents from the essential oils of selected plants; the essential oils are the compounds that help produce a plant’s fragrance. These essential oils, usually in diluted formulations, can be applied directly to the skin, such as by facials or body wraps, inhaled, or bathed with. Essential oils of substances are sometimes recommended for relief of symptoms commonly associated with ADHD, such as the use of ”
- Peppermint for feelings of depression. Essential oils appear to help provide the most relief for minor and occasional symptoms.
- It is another not very well understood complementary technique that has been used for thousands of years by people in many different cultures around the world to manage and control emotions and actions; at the very least, aromatherapy can probably be quite helpful in assisting some individuals with ADHD to achieve a more tranquil, calm state of mind.”

PTBM
Parent Training

PTBM

- PTBM is the recommended primary intervention for preschool-aged children with ADHD as well as children with ADHD-like behaviors whose diagnosis is not yet verified. This type of training helps parents learn age-appropriate developmental expectations, behaviors that strengthen the parent-child relationship, and specific management skills for problem behaviors.



Disorganization
- Does not plan ahead

Low boredom threshold
- Gets bored easily once the novelty of an activity has worn off

Low self esteem
- Often associated with life-long functional impairments

nent

Forgetfulness
- Misses appointments, loses things

Mood lability
- Irritable or labile moods and low tolerance of frustration

Variable performance
- Both under- and over-focused on tasks, or focuses only on immediately rewarding tasks

Procrastination
- Starts projects but does not complete

Time management problems
- Always late

Criminal offences
- Speeding, road traffic accidents, taking illegal drugs

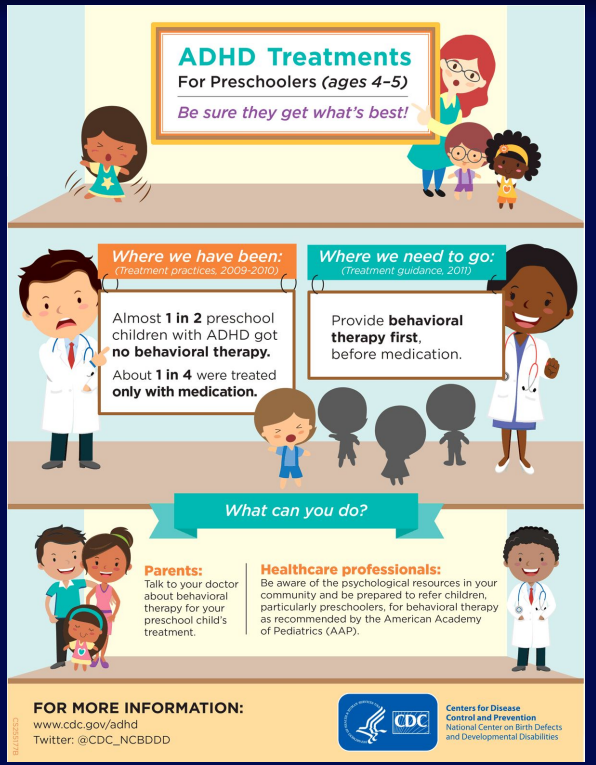
Impulsive decisions
- Spending, taking on projects, travelling, jobs, or social plans

Premature shifting of Activities
- Starts something but then is quickly distracted by something else

Unstable jobs and relationships
- Unable to keep a job or maintain long-term relationships

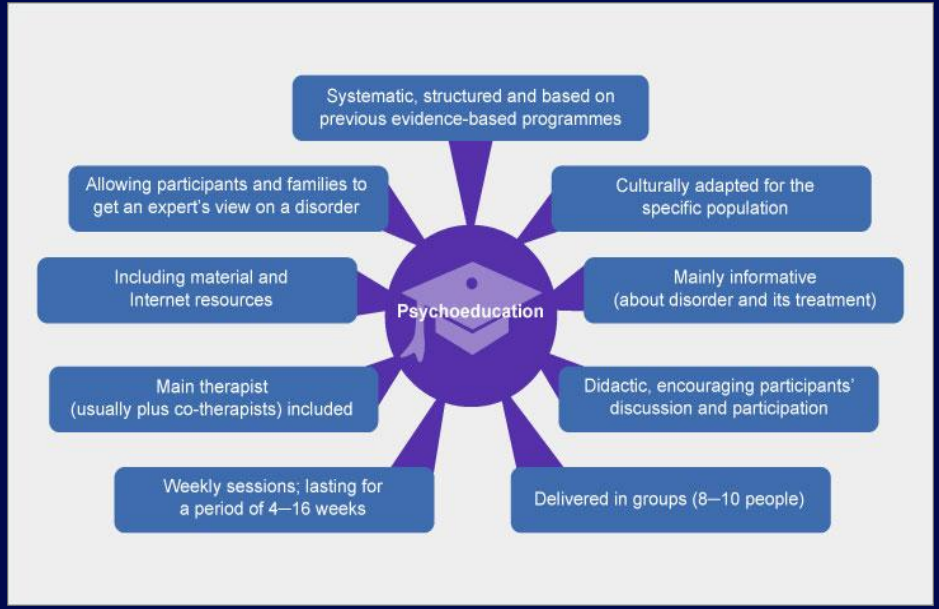
Therapy Treatment

- Not just directed at the core symptoms of ADHD.
- Therapy sessions may include techniques that will help the patient:
  - to improve emotional control;
  - to self-impose structure;
  - to develop organizational skills;
  - to plan and manage time;
  - to improve social skills and manage interpersonal relationships
  - with peers and family;
  - to improve conduct;
  - to stop and think about consequences;
  - to develop critical thinking and reasoning skills.



Psychoeducation

- Providing psychoeducation about ADHD is an essential component of treatment in order to promote knowledge and understanding about the disorder and what can be expected in the years to come, and to dispel lay beliefs and/or incorrect assumptions.
- This education needs to include
- explanations about:
  - the etiology of ADHD;
  - ADHD symptoms;
  - common psychiatric comorbidities;
  - psychosocial problems;
  - treatment options and side effects;
  - outcome research data;
  - longer-term prognosis.



Treatment

ADHD Treatment Guide by Age Group

	Considerations & challenges	Recommended treatment	Prescribing considerations
Preschool	• High rate of any comorbidity • Few studies with ADHD medications in preschool-aged children • Pharmacokinetic differences compared with older children	• **First-line**: psychosocial therapy • **Second-line**: add pharmacotherapy, with MPH as the first choice • **Other options:** AMP, DEX, ATX	• Titrate starting with lowest dose • Higher rate of AEs than older children • Irritability, emotional outbursts, and repetitive behaviors/thoughts common

ADHD Treatment Guide by Age Group

	Considerations & challenges	Recommended treatment	Prescribing considerations
School	• Girls less likely to be diagnosed • ADHD treatment can improve school performance and reduce risk of developing some comorbidities	• **First-line:** psychosocial therapy combined with pharmacotherapy, with MPH as the first choice • **Other options**: AMP, DEX, ATX, GXR and CXR	• Lower tolerability of AMP • Safety: closely monitor height and weight of children for signs of growth issues

ADHD Treatment Guide by Age Group

	Considerations & challenges	Recommended treatment	Prescribing considerations
Adolescents	• Inattentive symptoms more prevalent • Increased risk-taking behaviors • Difficulties at school can be escalated • Poor treatment adherence	• **First-line:** psychosocial therapy combined with pharmacotherapy, with 50/50 MPH and AMP as the first choice • **Other options**: Long-acting AMP, ATX, GXR	• Long-acting formulations with once-daily dosing can improve adherence and decrease misuse

ADHD Treatment Guide by Age Group

	Considerations & challenges	Recommended treatment	Prescribing considerations
College	• Transition to independent living • At risk for general psychological distress, depression, substance use • Higher risk of ADHD medications misuse/abuse • Poor treatment adherence	• **First-line**: pharmacotherapy with long-acting AMP as first-choice • **If misuse/abuse is a concern:** nonstimulant • **Other option:** Long-acting MPH	• Preplan time and location to receive medication in college • Openly discuss the social and academic benefits of taking medication • Emphasize importance of daily structure, exercise, sleep, and positive peer relations

Treatment

ADHD Treatment Guide by Age Group

	Considerations & challenges	Recommended treatment	Prescribing considerations
Adults	• ADHD often undiagnosed and undertreated • High rate of comorbid disorders • Inability to effectively modulate emotions • Excessive mind-wandering	• **First-line**: pharmacotherapy, with AMP as first-choice • **Other options**: MPH, ATX • **If misuse/abuse is a concern**: ATX	• Determine if ADHD can be treated simultaneously with other comorbid disorder(s) • Consider potential drug-drug interactions of medications for ADHD and comorbid disorders

ADHD Treatment Guide by Comorbid Condition

Substance use disorder

Substance use disorder (SUD)

Considerations & challenges

- Risk of abuse or diversion of stimulant ADHD medication is a concern
- Treatment can reduce ADHD symptoms without exacerbating SUD

People with ADHD are 5x more likely to develop SUD

Prescribing recommendations

- Avoid short-acting stimulants
- Use long-acting formulations that minimize "rush and rebound"
- Some alternative formulations may be less likely to be abused: Concerta (OROS-MPH), Vyvanse (LDX, a prodrug of dexamphetamine), Cotempla (MPH XR-ODT), ATX

ADHD Treatment Guide by Comorbid Condition

Autism spectrum disorder (ASD)

Considerations & challenges

- Swallowing issues are common
- Sensitive to adverse effects from ADHD treatment

~75% of children with ASD are also diagnosed with ADHD

Prescribing recommendations

- Low and slow titration of ADHD medication to monitor adverse effects
- Liquid formulations allow for the smallest dose increments
- To address swallowing issues, prescribe liquid, orally disintegrating tablet, or sprinkle formulations
- Any class of ADHD medication can be beneficial, and response varies for each patient

ADHD Treatment Guide by Comorbid Condition

Epilepsy

Considerations & challenges

- Limited guidance on the treatment of ADHD in these patients

~1/3 of children with active epilepsy have ADHD

Prescribing recommendations

- MPH is the first-choice ADHD treatment, as it did not significant increase the frequency or severity of seizures
- ATX can also be used, but less is known about safety in epileptic patients

ADHD Treatment Guide by Comorbid Condition

Tic disorders

Considerations & challenges

- Reduced the patient's quality of life

5%–15% of children with ADHD also have a tic disorder

Prescribing recommendations

- Stimulants can be effective, but monitoring for worsening of tics is necessary
- ATX can be considered if stimulants exacerbate tics
- GXR and clonidine are often effective at treating ADHD, and may improve tics

ADHD Treatment Guide by Comorbid Condition

Anxiety

Considerations & challenges

- Anxiety exacerbates ADHD-related impairment

Comorbid with ADHD in ~15% of children and ~47% of adults

Prescribing recommendations

- Stimulants can be effective, especially when ADHD symptoms contribute to anxiety
- Long-acting, smooth-release formulations are preferred vs those with distinct phases of drug release
- Titrate slowly, and monitor anxiety as well as ADHD symptoms
- First-choice: MPH
- Other options: AMP, ATX, GXR (children only)

ADHD Treatment Guide by Comorbid Condition

Bipolar disorder

Considerations & challenges

- This combination of disorders worsens and complicates each

Comorbid with ADHD in 19% of adults, also co-occurs in children

Prescribing recommendations

- Based on recent studies in children, treat bipolar disorder and ADHD concurrently
- Monitor for any worsening of bipolar symptoms

ADHD Treatment Guide by Comorbid Condition

Depression

Considerations & challenges

- Incidence increases with age

MDD occurs in 19% of adults with ADHD

Prescribing recommendations

- Severe or suicidal cases: Treating depression takes precedent over ADHD treatment
- Mild cases: Treat ADHD and depression concurrently
- Taking both a stimulant and a serotonin reuptake inhibitor is well-tolerated, and may address both ADHD and depressive symptoms
- ATX is also effective for treating ADHD

ADHD Treatment Guide by Comorbid Condition

Insomnia

Considerations & challenges

- Sleep issues are common in patients with ADHD, independent of medication
- Insomnia and sleep issues may improve or worsen with ADHD medication
- Insomnia can occur when initiating an ADHD medication, but may subside over time

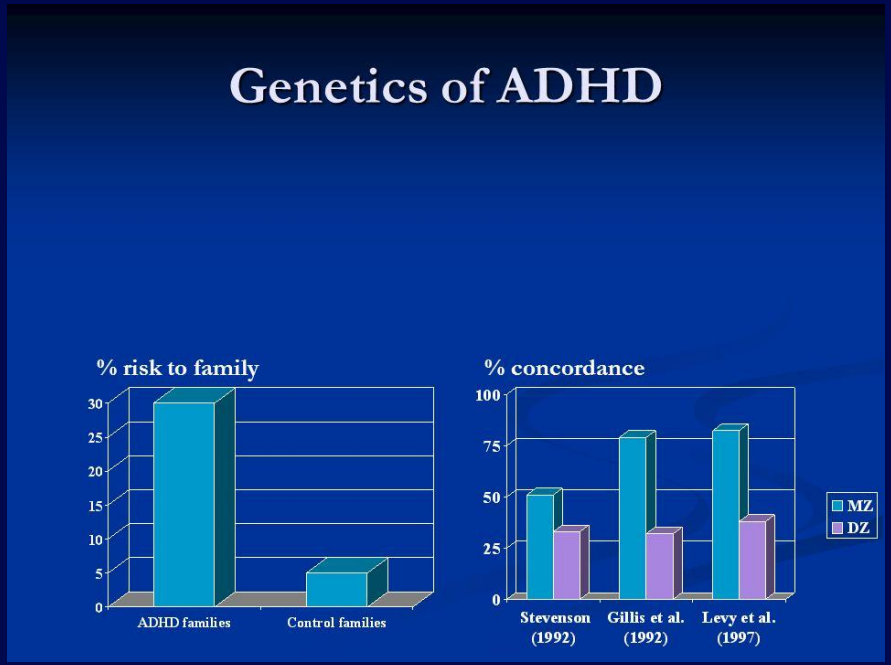
55%–80% of adults, >80% of children with ≥1 sleep issue

Prescribing recommendations

- Monitor how the patient responds to different long-acting formulations: Does release at end of day induce or help insomnia?
- With stimulants, adjust dose or try different delivery formulation to address insomnia
- ATX is less likely to cause insomnia
- GXR or clonidine have a sedative effect: use alone or with a stimulant
- Melatonin supplement may help address sleep issues

Genetic Risk Factor

- Familial risk for ADHD
- Rate of ADHD among first-degree 10–20% for the siblings and parents of a child with ADHD

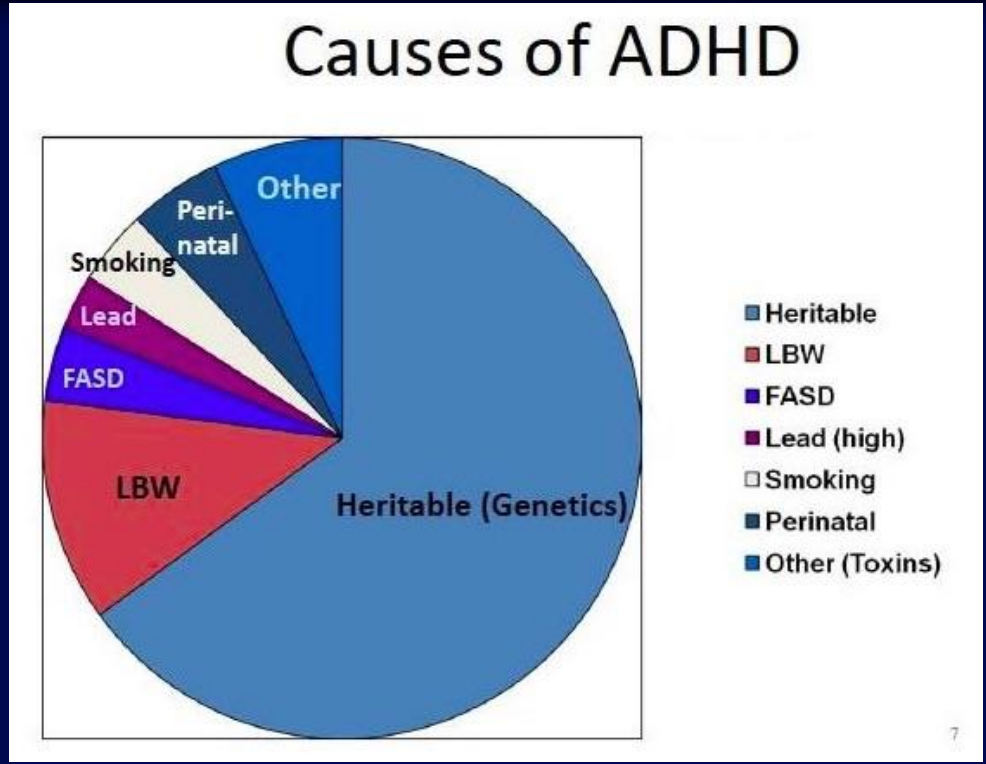


ADHD and Pregnancy

- There are two main considerations when it comes to ADHD and pregnancy: •
  - decision whether or not to continue drug treatment for ADHD during pregnancy (or when expecting a pregnancy);
  - the impact of maternal behavior during pregnancy on the future child.

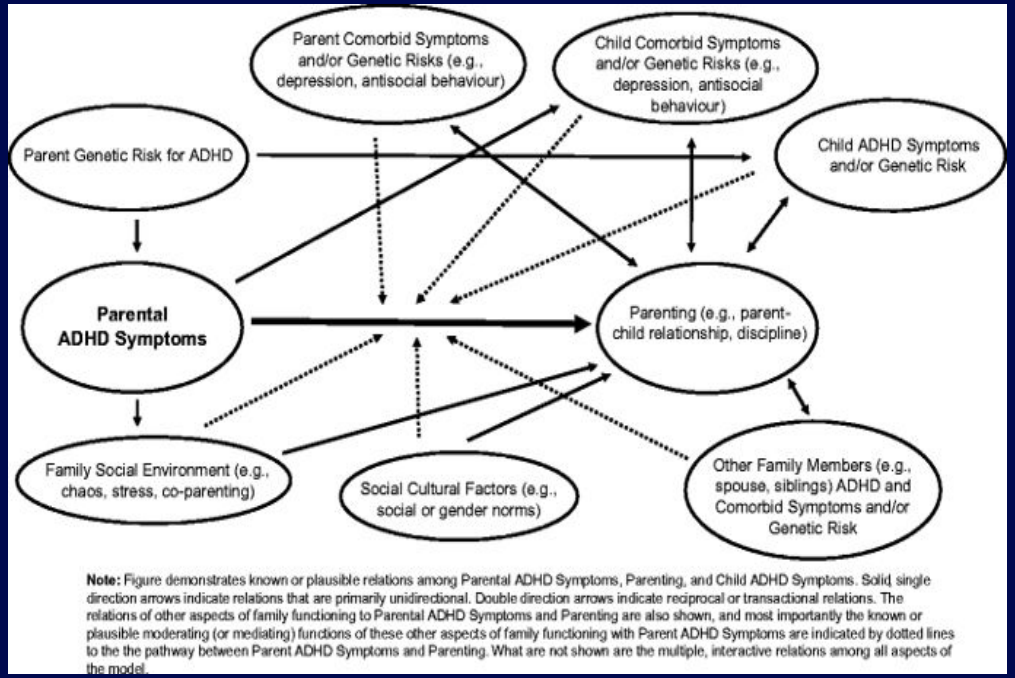
ADHD in Pregnancy

- Maternal behavior during pregnancy. Maternal factors that have been associated with an increased risk of ADHD include:
  - exposure to nicotine in utero [5,6];
  - alcohol use during pregnancy [7];
  - maternal caffeine intake [5];
  - exposure to psychosocial stress [7,8].
- Smoking during possible risk factor for the later development of ADHD, but not certain that this is a direct toxic effect of smoking.
  - smoking has other detrimental effects on the developing fetus and should be avoided



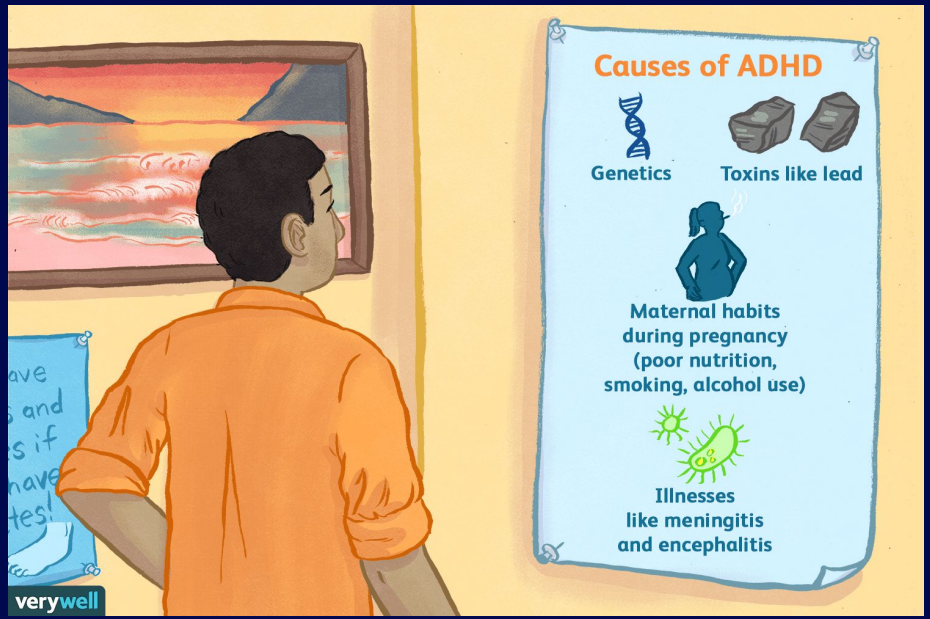
ADHD in Pregnancy

- Data regarding caffeine exposure & ADHD are weak
- Maternal stress exposure in pregnancy and correlation to ADHD more consistent,
  - Level of maternal stress associated with the severity of ADHD symptoms among offspring
  - Stress exposure = risk factor independent of maternal smoking,
  - Stress and maternal smoking closely related [



ADHD in Pregnancy

- Low birth weight and prematurity associated with development of ADHD [
- Complications during pregnancy, delivery, and infancy = increased risk of ADHD independently of possible genetic factors.
- Pregnancy risks greatest for complications of a chronic nature such as, family psychosocial problems, and illicit drug use.
  - Complications associated with impaired cognitive functioning & poor school performance associated with ADHD



ADHD Treatment in Pregnancy

- Treatment and nontreatment bear risks.
- Discontinuation medication reduces risk of chemical harm, but potentially harmful behaviors related to the mother's mental state.
- Possible decline mother's mental health, including erratic, impulsive, & disorganized behavior, poor risk management (such as dangerous driving or the use of drugs, alcohol, or tobacco during pregnancy).
- Lack of data on risks to offspring from exposure to ADHD drug general recommendation that treatments for ADHD during pregnancy considered individually and decided once all risks are considered and the patient has been fully informed.

- The decision-making process depends on several factors including:
  - risk for the developing baby from detrimental maternal behavior or maternal stress during the pregnancy;
  - efficacy of the present treatment and its side effects;
  - the nature and severity of the ADHD symptoms and the impact of medication on controlling these and associated comorbidities;
  - individual circumstances including social support and adjustment, engagement with health care professionals (eg, midwife, health visitor) and self-care during the pregnancy.

ADHD Treatment in Pregnancy

- Available risk data for prenatal exposure to stimulant medication is limited.
- Amphetamines, methylphenidate, atomoxetine, bupropion, and modafinil were designated **category C by the FDA**.
  - This category = animal studies have reported some harm without there being any robust evidence in humans, or where no human or animal studies have been performed.
- Methylphenidate and dexamphetamine: few data available.
  - At therapeutic doses, does not seem to be an increased rate of fetal malformations.
  - Well-established that illicit use of stimulants prematurity, low birth weight, and increased morbidity

CSN STIMULANTS AND PREGNANCY

Research done on CNS Stimulants and pregnancy is not fully understood and is not always clear because either there aren't enough studies, or the current studies do not have well defined or properly matched pregnancy populations. Studies can also be contaminated there are poor nutrition, living conditions, and lifestyles, and other drug use such as alcohol was present during pregnancy. These symptoms are what may happen…

Daughtery, R., & O'Bryan, T. (2014). *Prime for life.* (8.0 ed.). Lexington, Kentucky, USA: Prevention Research Institute.

Amphetamines – If a pregnant mother are taking prescription medicine, she should talk to her doctor about further taking medication.

"Amphetamine Facts." *Amphetamines.* Australian Drug Foundation, 27 Jan. 2013. Web. 10 Apr. 2014.

Caffeine - Pregnant mothers should have less than 200 mg/day. Mothers who chose to drink caffeine are at higher risk of miscarriage and stillbirth. There can be slight reduction in weight of baby at birth.

"Caffeine during Pregnancy." *BabyCenter.* BabyCenter, L.L.C., Apr. 2012. Web. 15 Apr. 2014.

MDMA (Ecstasy) - There has not been enough research in this area.

Pappas, Stephanie. "Ecstasy in Pregnancy Is Bad for Baby, Study Finds." *LiveScience.* TechMedia Network, 08 Mar. 2012. Web. 15 Apr. 2014.

Methamphetamine – Low birth weight, Cleft palates, Premature birth, Mental and physical birth defects, Increased risk of miscarriage

Chait, Jennifer. "What Are the Effects of Crystal Meth on Pregnancy?" *LoveToKnow.* LoveToKnow Corp., 24 Mar. 2014. Web. 15 Apr. 2014.

Cocaine "Cocaine Babies" - Low birth weight, Premature birth, Small head, Increased irritability, Cognitive defects, Problems with motor skills and language development, Problems gathering info, short attention span. There is a high rate of mother's abandoning their babies after birth.

Crack Cocaine "Crack Babies" – Similar defects to Cocaine Babies

"Cocaine." *NIDA for Teens.* National Institute on Drug Abuse, 24 Mar. 2014. Web. 12 Apr. 2014.

ADHD Treatment in Pregnancy

- Atomoxetine: Data more limited.
  - Single cases of atomoxetine use during pregnancy, no teratogenicity was reported.
  - In animal models, atomoxetine exposure, in high doses can result in negative effects, including decreased survival rates, lower birth weight, delayed ossification, and abnormal angiogenesis.
- Buproprion:
  - higher incidence of cardiac abnormalities but recent study failed to show any increased risk compared with other antidepressants
- No adequate studies of modafinil in pregnancy that allow an evaluation of its teratogenic potential.

ADHD Treatment in Pregnancy

Best Practices

- Adjust dosage to the minimum amount that produces good control of symptoms.
- During pregnancy both volume of distribution and liver enzymatic activity are increased. less active drug being available
- Some report spontaneous improvement in attentional and dose reduction may be easier to achieve.
- Titrate down or stop stimulant dosage prior to delivery to avoid potential for acute withdrawal symptoms in the newborn.
- Liaise closely with the obstetric team
- Increase frequency of follow-ups in pregnancy and PostPartum period

ADHD Treatment and Breastfeeding

- All psychotropic drugs excreted through breast milk around 1% of that in blood
- If child exposed psychotropic drug in utero, not necessary to stop medication during breastfeeding.
- Ideally, drug given as a once-a-day formulation before the child's longest period of sleep avoids a feed occurring during peak secretion.
- Drugs licensed for children general less risky than those not tested.
- If medication in breastfeeding, monitor child's development & pediatrician informed of changes in medication dosage or formulation.
-

- Specific effects unknown stimulant & nonstimulant medication breastfeeding,
- Some case reports suggest methylphenidate relatively innocuous, particularly after the morning
- Caution with atomoxetine & amphetamines.
- Modafanil is contraindicated in women who are breastfeeding.
- Buproprion accumulates in breast milk and ^ risk of seizures in newborn pregnancy & Post Partum period.

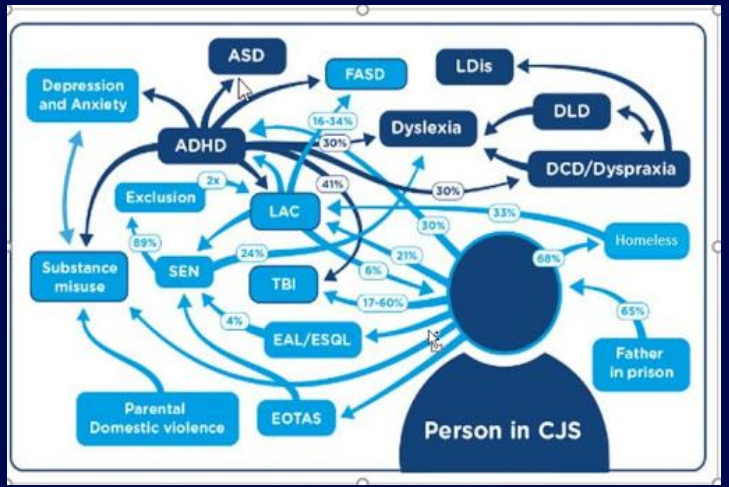
ADHD Postnatal Period

- Postnatal period = istressful and challenging time
- Great deal of organization and planning is required for demands of a new child.
- Many women with ADHD request to be restarted on medication after delivery.

ADHD Criminal Justice

- The age-dependent decline of (ADHD) symptoms suggests by young adulthood full diagnosis will persist in around 15% of cases and 50% will be in partial remission
  - many individuals, although within the subthreshold of criteria, still experience functional impairment
- Trajectory for some is a progression of comorbid conduct problems into antisocial and criminal behavior.
  - Those diagnosed & treated in childhood = better outcomes than untreated
- International studies suggest that 2/3 youths and ½ young adults in prison screen positive for ADHD.
- ADHD associated with early onset criminal behavior prior to age 11 years & high rates of recidivism.

- Rates in female prisoners are around 10%
- In the UK, study conducted on personality disorder wards found 1/3 with ADHD
- UK prison studies found rates of 43% in 14-year-old youths and 14% in adults



ADHD Criminal Justice

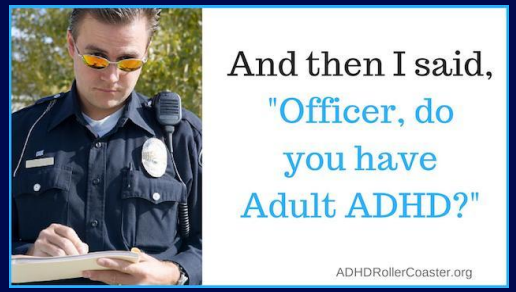
- All studies have limitations but those with ADHD in forensic settings far exceed general population.
- ADHD and crime likely to be associated with ADHD symptoms & personality factors:
  - recklessness and risk taking; sensation seeking behavior; poor behavioral control; absentmindedness or forgetfulness; compliant personality traits; labile temperament; and a confrontational interpersonal style.
- Chronic substance misuse among the most prolific offenders is of major concern and the motivation behind offending

- Vulnerability in police interviews Individuals with ADHD may be at risk of making admissions or giving factually incorrect information during police interviews for several reasons:
  - maladaptive coping strategies,
  - a desire for immediate gratification,
  - attention and memory problems
  - symptoms of restlessness and impulsiveness = highly motivated to escape the confinement of custody

Criminal Justice
Police Interviewing Issues

- May not pay full attention
- May require concentration for long periods of time under pressure.
- One coping mechanism responding with ‘don’t know’ responses (even for questions posed for which they should know the answer)
  - Law may suspect not cooperating fully with the interview process.
  - May be perceived as being evasive or deliberately misleading, they may unintentionally provide the police with misleading accounts of events due to them not fully understanding the significance of the questions put to them or the implications of their answers.

- ADHD decreases resilience in resisting pressure from police a false confession even after controlling for gender, age, emotional lability, and conduct disorder
- Sometimes parents also genetically ADHD encouraging the child to agree or ‘own up’ so that they can get out of the police station and go home.



Criminal Justice Fitness for Trial

- In England and Wales, the criteria for fitness to plead and stand trial (R v Pritchard, [1836] 7 C. & P. 303) Billy Jo Friend appealed conviction related to pleading inability to stand trial related to severe ADHD symptoms.
- Usually only special considerations are needed to be adopted by the courts, (eg, the provision of brief regular breaks, that counsel pose one question at a time and avoid using complex language).
- Emotional lability may be a particular problem when testifying as they may become distressed and/or angry under cross examination.
- Unless these vulnerabilities are explained, they are likely to be misinterpreted by a jury.

- Criminal responsibility and mitigation of sentence Mens rea refers to the defendant's state of mind at the time of the alleged offence and court assessments may be commissioned to establish whether the diagnosis of ADHD has relevance to an offence (ie, to negate criminal responsibility and/or to mitigate punishment). The legal issues relate to:
- Intent: the planning and desire to perform an act. People with ADHD will most likely have the ability to form intent but the key issue may relate more to recklessness (eg, carelessness). Recklessness shows less culpability than intention.
- • Duress and coercion: knowledge of the wrongfulness of the act but robbed of free will by a perceived threat.

Criminal Justice Criminal Responsibility & Sentencing

- Mens rea refers to the defendant's state of mind at the time of the alleged offence The legal issues relate to:
  - Intent: with ADHD will most likely have ability to form intent but key issue may relate more to recklessness (eg, carelessness). Recklessness shows less culpability than intention.
  - Duress and coercion: knowledge of the wrongfulness of the act but robbed of free will by a perceived threat.
  - Provocation: knowledge of the wrongfulness of the act but robbed of self-control.
- In law, there are two types of provocation:
  - Instantaneous
  - accumulative over time.

- ADHD vulnerable d/t poor emotional regulation expressed by a labile, reactive temperament and susceptibility to losing behavioral control.
- Diminished responsibility: 'malice aforethought' (ie, intention to kill another person or inflict grievous bodily harm).
  - Involves question of mitigating circumstances Decrease the charge of murder to manslaughter.
  - One must demonstrate 'substantial impairment' in perception, judgment, or willingness and this has been argued successfully in cases of depression, psychosis and personality disorder.
- Issue relates to impulsiveness and planning deficits (ie, a tendency to act on the spur of the moment and without considering the consequences of action).

Criminal Justice Post-Conviction

- Association with conduct disorder may be the key vulnerability for ADHD youths and adults to become involved in crime
- ADHD symptoms may keep them longer in the system by reducing the likelihood of early release, perhaps due to an association with aggressive incidents

Treatment of offenders with attention deficit

- hyperactivity disorder
- With respect to their ADHD symptoms, offenders with ADHD are unlikely
- to differ greatly in their response to treatment with medication than
- nonoffenders with ADHD. A Swedish randomized controlled trial reported
- large treatment effects for stimulant medication in prisoners; however,

ADHD Quick Check Question

Which is true about Medications for ADHD in Pregnancy?

- A) Women who are pregnant should never be given stimulant medications.
- B) The safest treatment for ADHD in Pregnancy is Straterra
- C) At therapeutic dosing methylphenidate causes and increased risk of fetal malformations
- D) Bupropion in recent studies has shown no increased risk of cardiac abnormalities compared to other antidepressants

Answer:

- D) Bupropion in recent studies has shown no increased risk of cardiac abnormalities compared to other antidepressants

Summary

- ADHD is a multifactorial condition that has genetic, environmental, biological, and other factors.
- There are many treatment options both on and off-label for the treatment of ADHD.
- Treatments should be considered individually given other genetic, biologic, and comorbid factors a patient is experiencing.
- Special populations such as pregnancy or people in the criminal justice system require even more special considerations for treatment.

ADHD Questions


Thank you!