

# Pediatric Mental Health Pharmacology

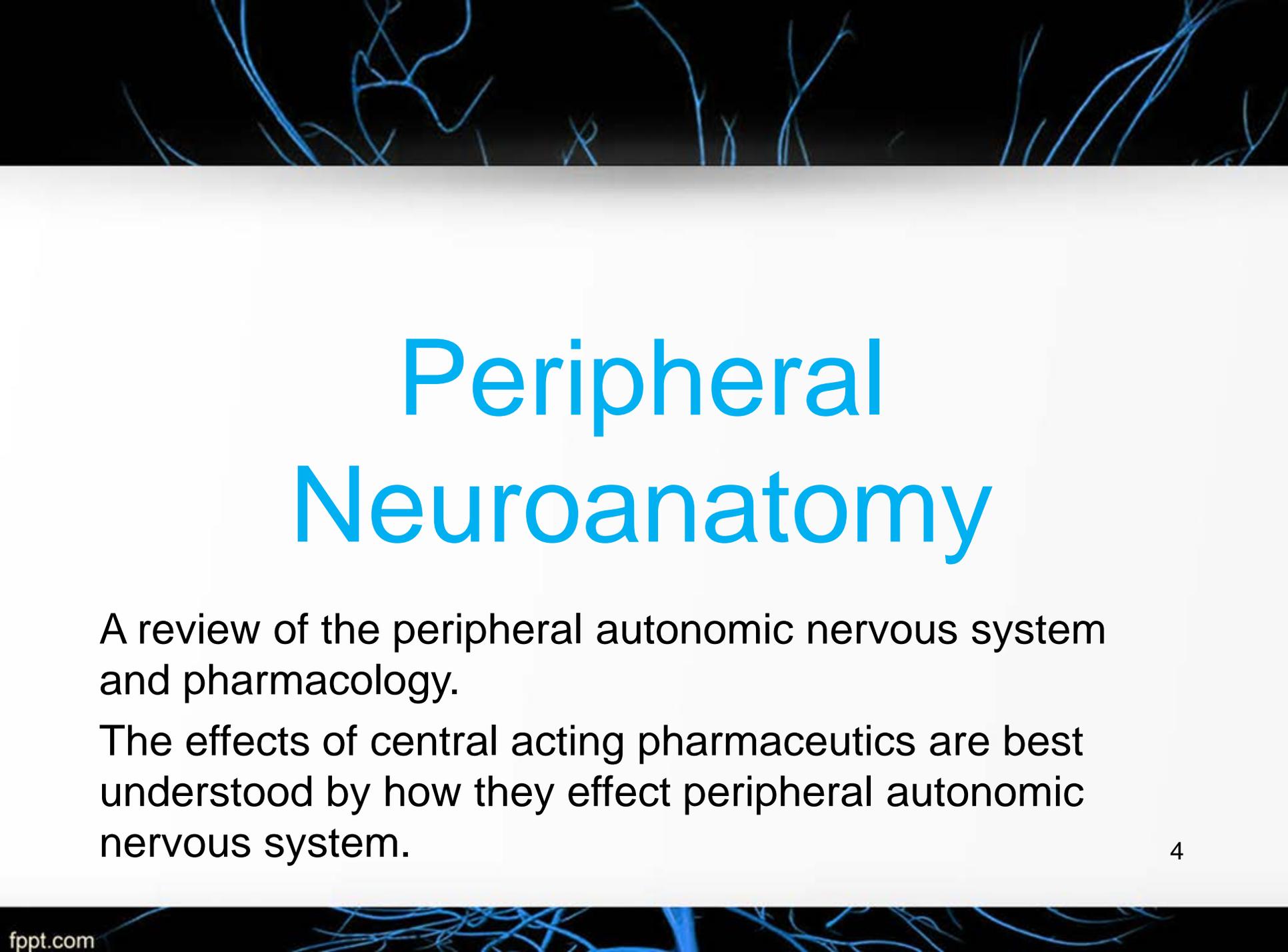
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# Disclaimer

- The presenter has no invested interest in any product or organization described in this presentation.
- No funding has been provided by any pharmaceutical company, healthcare organization, or other source to support this presentation.

# Overview

- Neurotransmitter anatomy and physiology
- Developmental principles
- Common childhood mental illnesses
- Classes of psychotropic medications
- Specific psychotropic medications
- Adverse effects and emergency interventions



# Peripheral Neuroanatomy

A review of the peripheral autonomic nervous system and pharmacology.

The effects of central acting pharmaceuticals are best understood by how they effect peripheral autonomic nervous system.

# Peripheral Receptors

- Four primary neurotransmitters found in the peripheral autonomic nervous system.
  - Acetylcholine
  - Epinephrine
  - Norepinephrine
  - Dopamine
- Each activates selective receptors on different cells to produce effects.

# Neurotransmitters of the Peripheral Nervous System

Acetylcholine

- Employed at most junctions of the peripheral nervous system

Norepinephrine

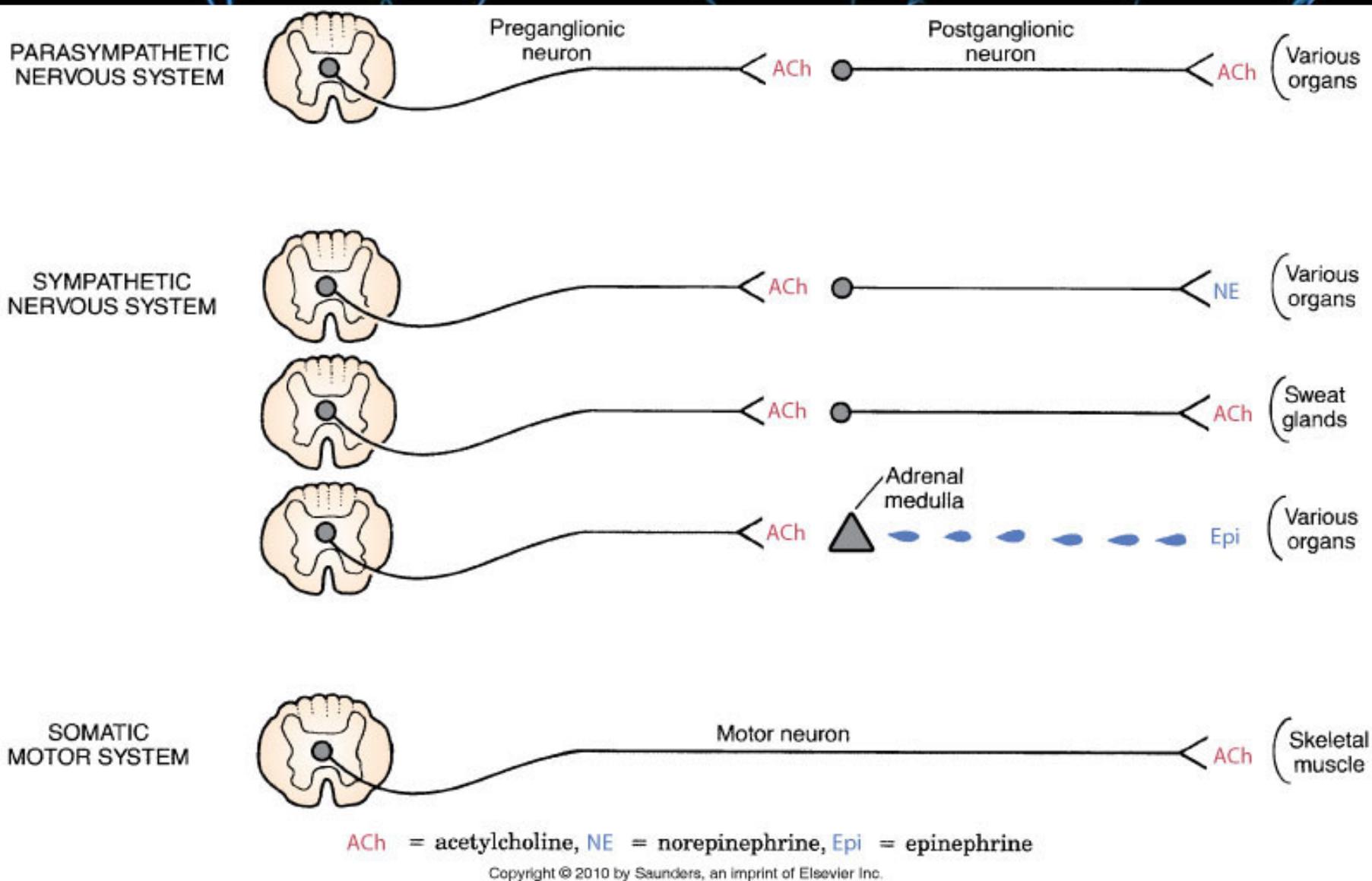
- Released by most postganglionic neurons

Epinephrine

- Released by the adrenal medulla

Dopamine

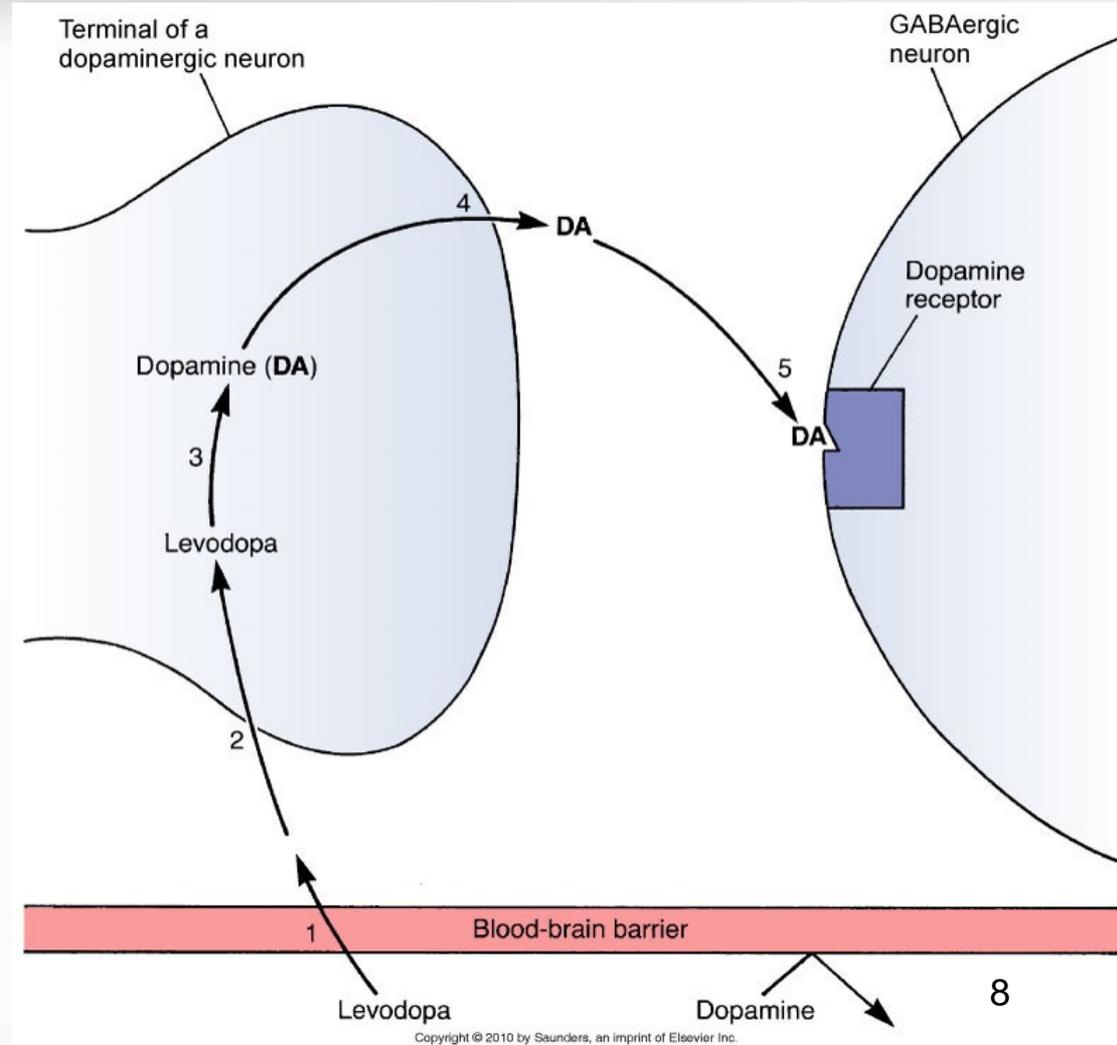
- Serves as a local chemical messenger at limited sites



Transmitters employed at specific junctions of the peripheral nervous system.

# Dopamine

- Does not cross the blood-brain barrier so peripheral systemic action is independent of functions in the brain
- Dopamine is a metabolite of L-DOPA which does cross the blood-brain barrier



# Two Forms of Dopamine

- Dopamine sulphate has no known biological function and is excreted in the urine. May be a filter for ingested dopamine
- Unconjugated dopamine may be produced by the sympathetic nervous system, the digestive system or possibly some other organs

# Peripheral Availability of Dopamine

- 95% of dopamine is dopamine sulfate, produced by sulfotransferase 1A3/1A4 converting unconjugated (free) dopamine
- Unconjugated dopamine may be produced by the sympathetic nervous system, the digestive system, or other unknown organs
- Released by the carotid body in conditions of low oxygen

# Non-Neuro Actions of Dopamine

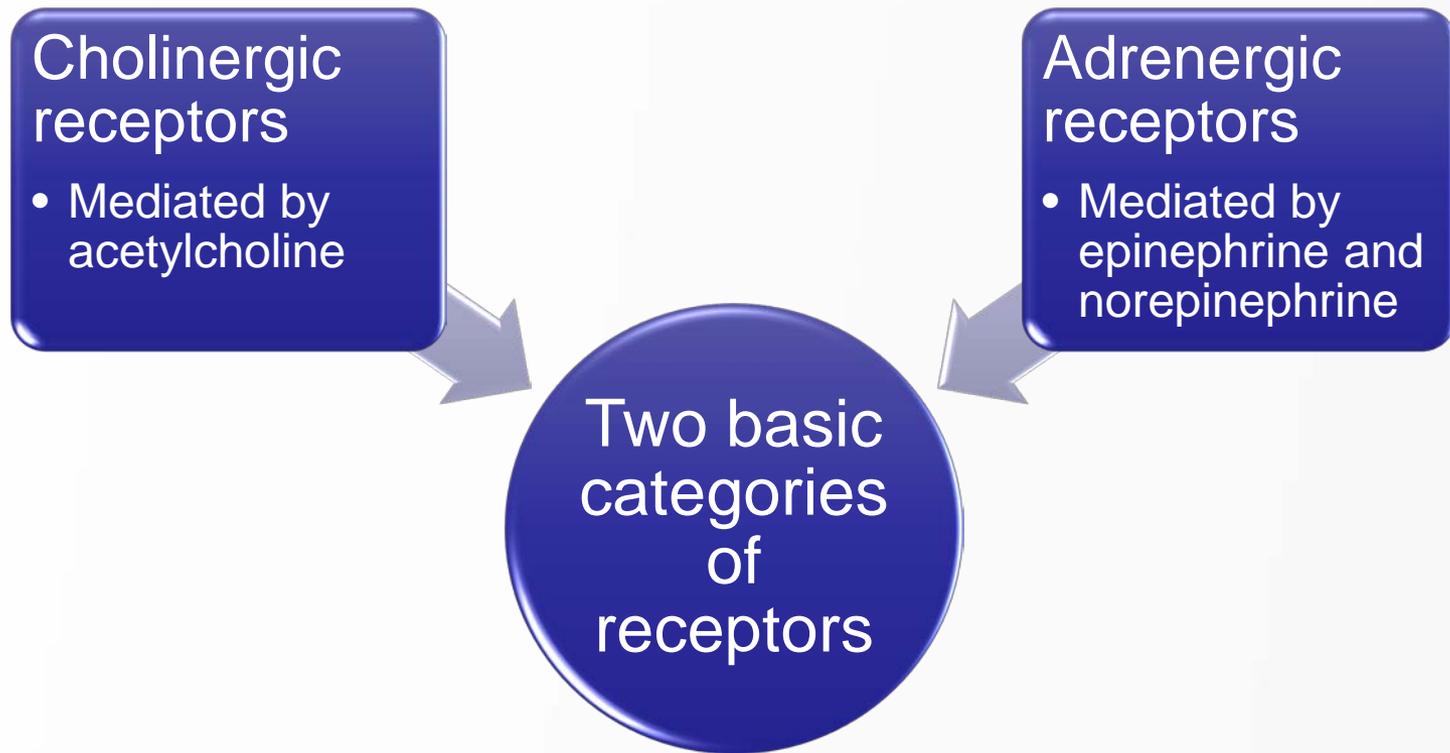
- Vascular – inhibits norepinephrine release and acts as a vasodilator
- Renal – increases urine output and sodium excretion
- GI – reduces gastrointestinal motility
- Immune – reduces activity of lymphocytes

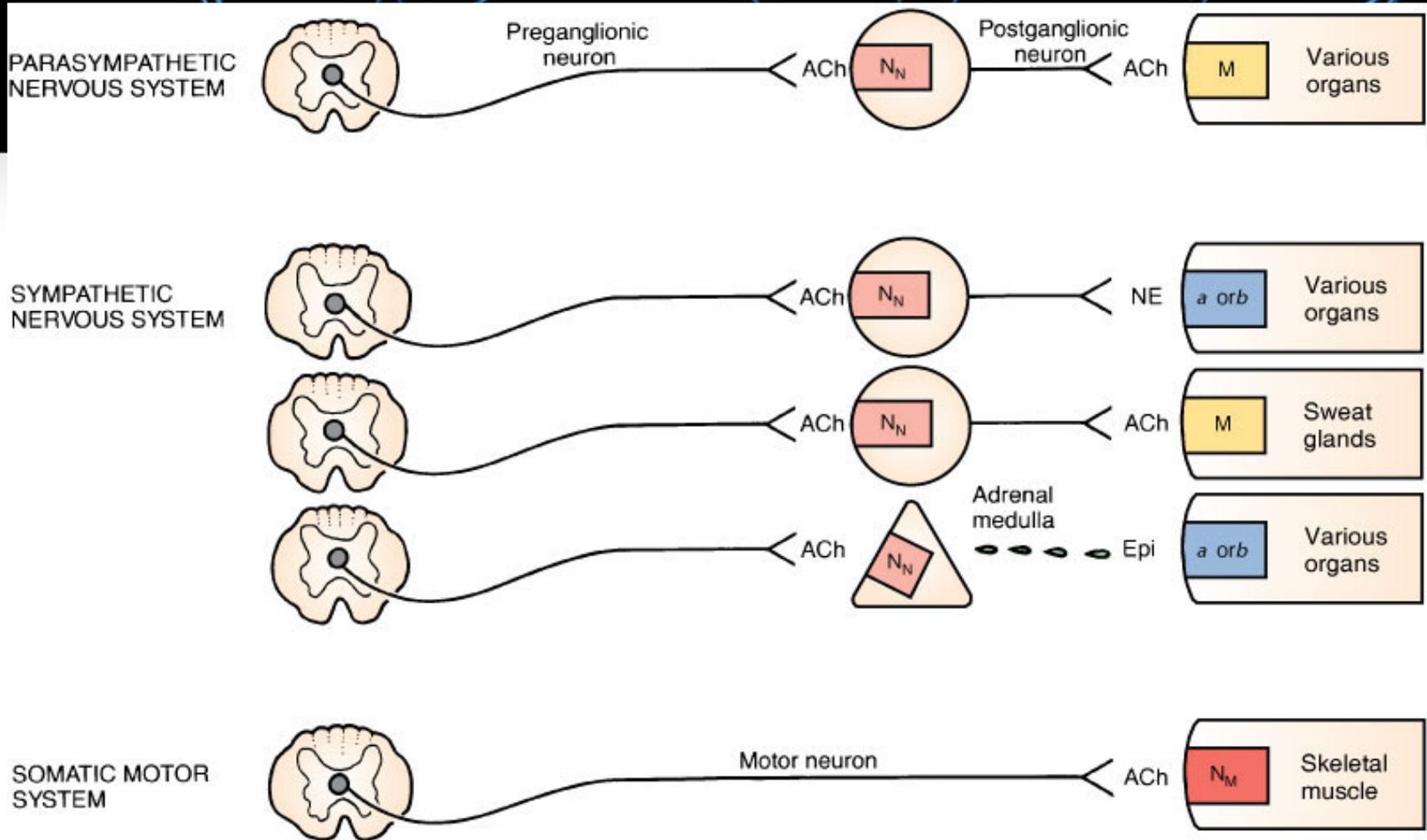
Except in the blood vessels dopamine acts locally in a “paracrine” function

# Sympathetic Actions of Dopamine

- May be enzymatically converted to norepinephrine by dopamine beta hydroxylase released by the adrenal medulla
- Dopaminergic receptors on walls of arteries may trigger vasodilation and inhibit norepinephrine release
- In high doses, Beta<sub>1</sub> adrenergic receptors are activated

# Autonomic Receptors





Cholinergic receptor subtypes:  $N_N$  = nicotinic<sub>N</sub>,  $N_M$  = nicotinic<sub>M</sub>, and M = muscarinic.  
 Adrenergic receptor subtypes:  $\alpha$  = alpha and  $\beta$  = beta.

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## Locations of cholinergic and adrenergic receptor subtypes.

# Adrenergic Receptor Subtypes

- Alpha1
  - Vasoconstriction
  - Ejaculation
  - Contraction of bladder neck and prostate
- Alpha2
  - Located in presynaptic junction
  - Minimal clinical significance

# Adrenergic Receptor Subtypes

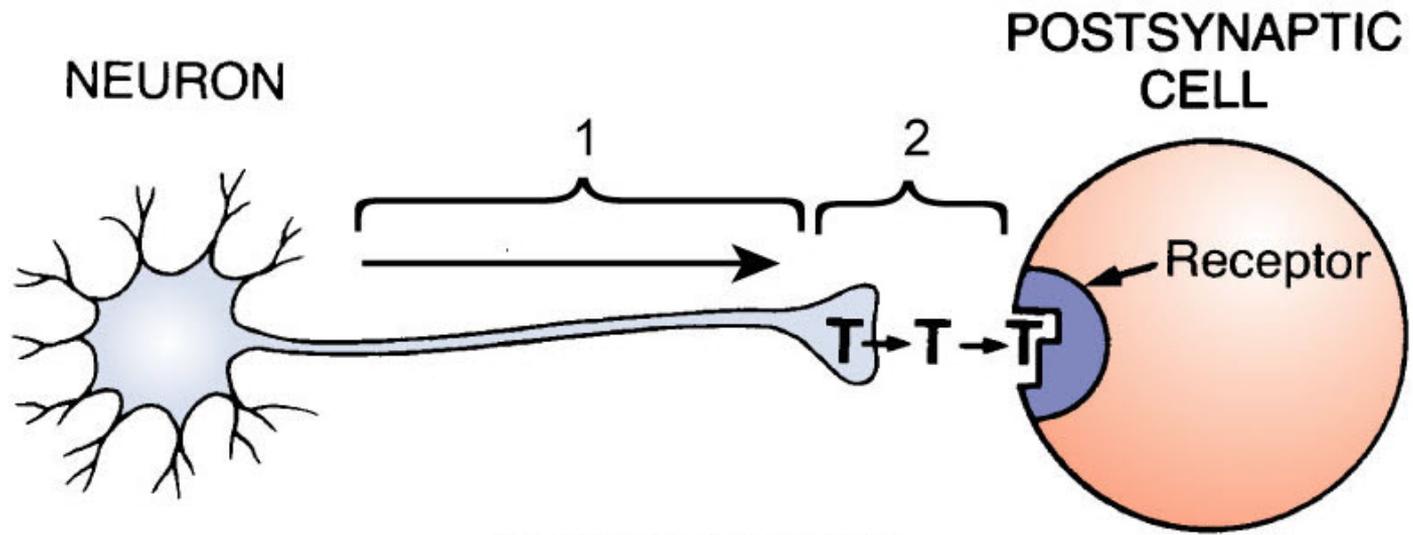
- Beta<sub>1</sub>
  - Heart
    - Increases heart rate (positive chronotropic effect)
    - Increases force of contraction (positive inotropic effect)
    - Increases velocity of conduction in atrioventricular (AV) node
  - Kidney
    - Renin release
- Beta<sub>2</sub>
  - Bronchial dilation
  - Relaxation of uterine muscle
  - Vasodilation
  - Glycogenolysis
- Dopamine
  - Dilates renal blood vessels

# Receptor Specificity of the Adrenergic Neurotransmitters

- Epinephrine can activate all alpha and beta receptors, but not dopamine receptors.
- Norepinephrine can activate alpha1, alpha2, and beta1 receptors, but not beta2 or dopamine receptors.
- Dopamine can activate alpha1, beta1, and dopamine receptors.
- Note: Dopamine is the only neurotransmitter capable of activating dopamine receptors.

# Basic Mechanism of Neuropharmacological Agents

- Sites of action: axons vs. synapses
  - Axonal conduction – 1
  - Synaptic transmission – 2
  - Receptors
  - Neurotransmitter storage or lifecycle - T



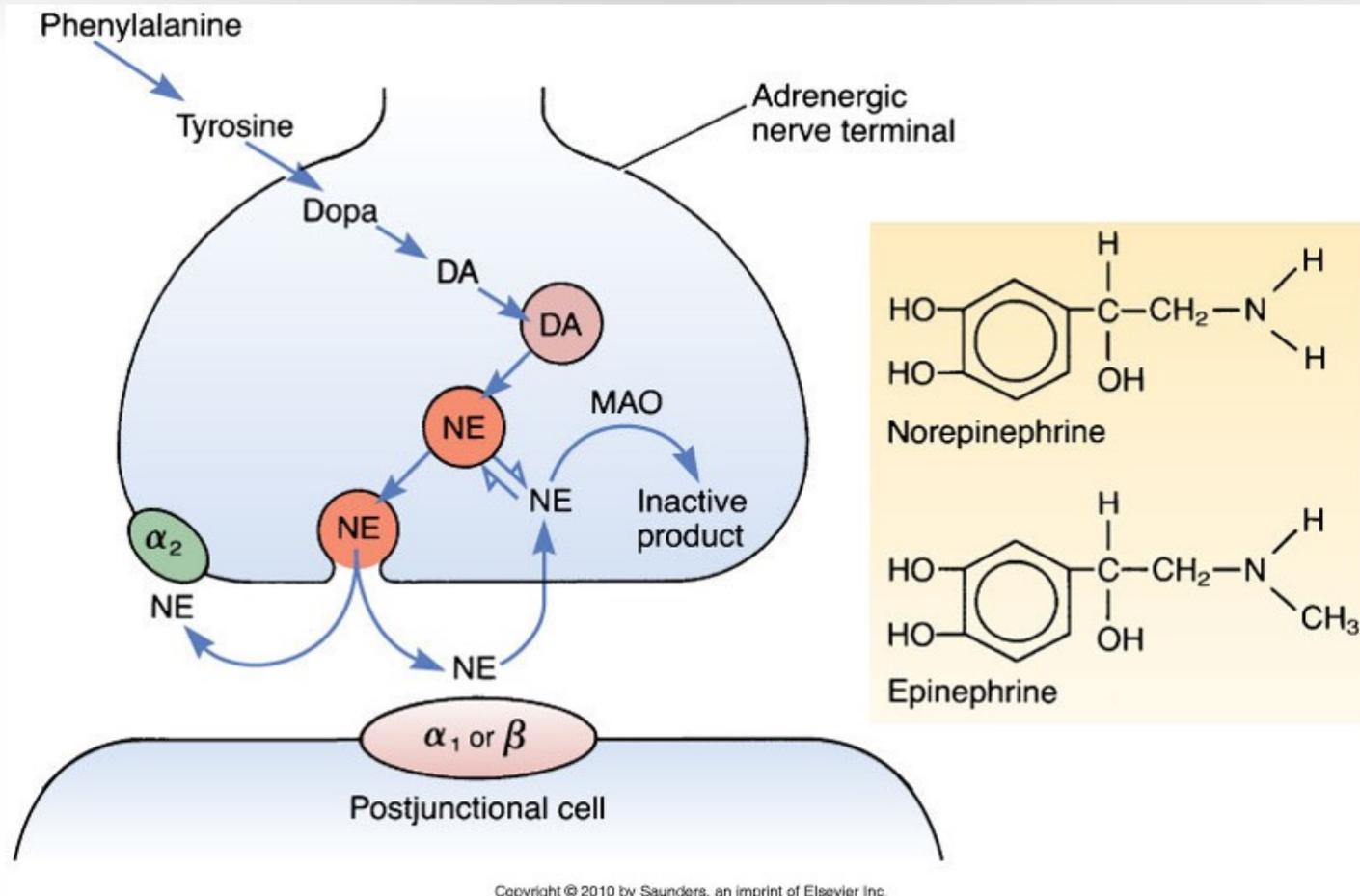
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# Neuropharmacologic Agents

- Block the reception of neurotransmitters
- Directly stimulate receptors
- Increase or decrease availability of neurotransmitters by
  - Affecting axonal secretion
  - Affecting the destruction or reuptake of neurotransmitters
- Can change rates but not function of cells

# Neurotransmitter Lifecycle

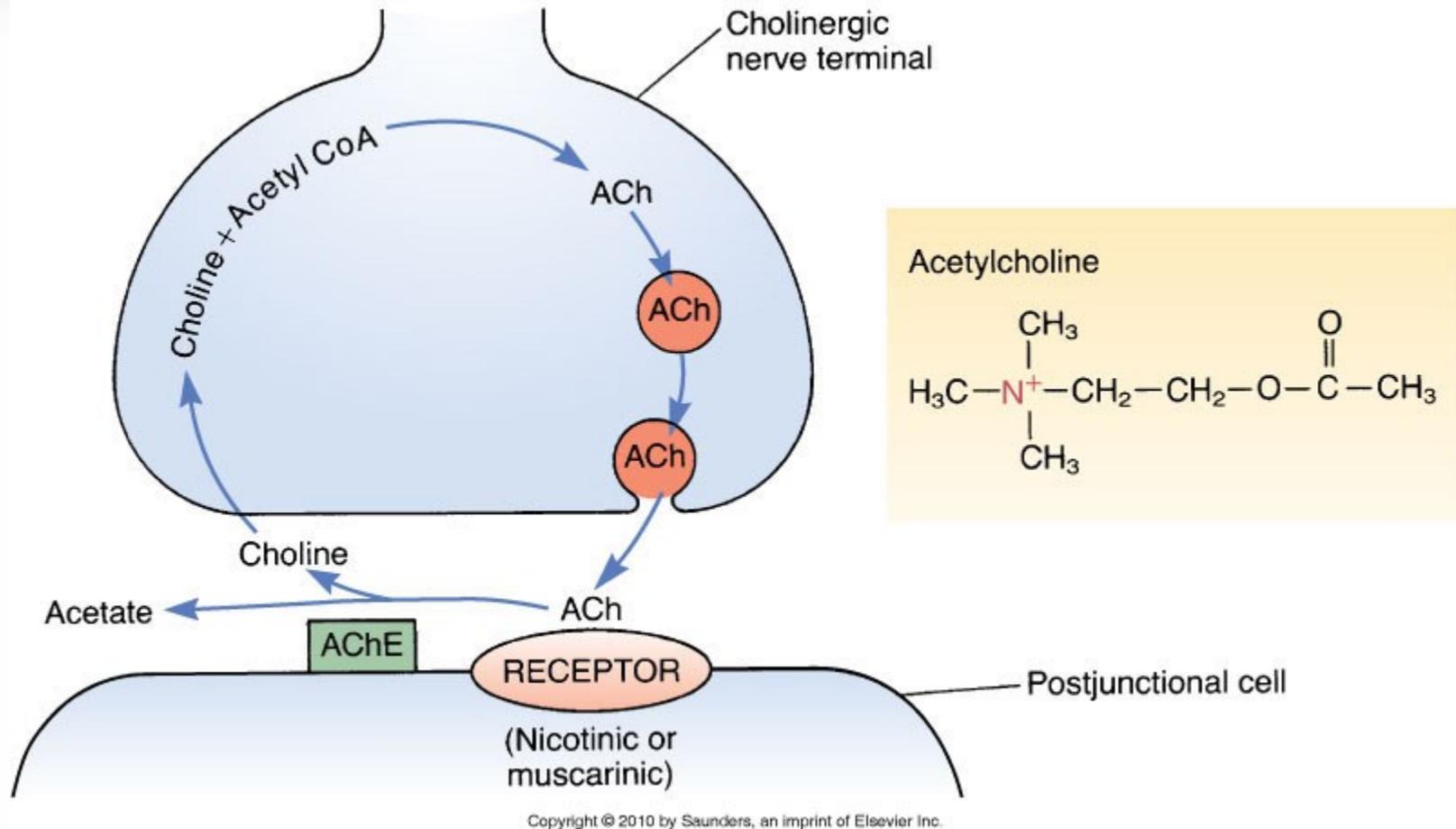
## Norepinephrine



MAO – L-Monoamine oxidases

Dopa – L-DOPA | DA – Dopamine | NE - Norepinephrine

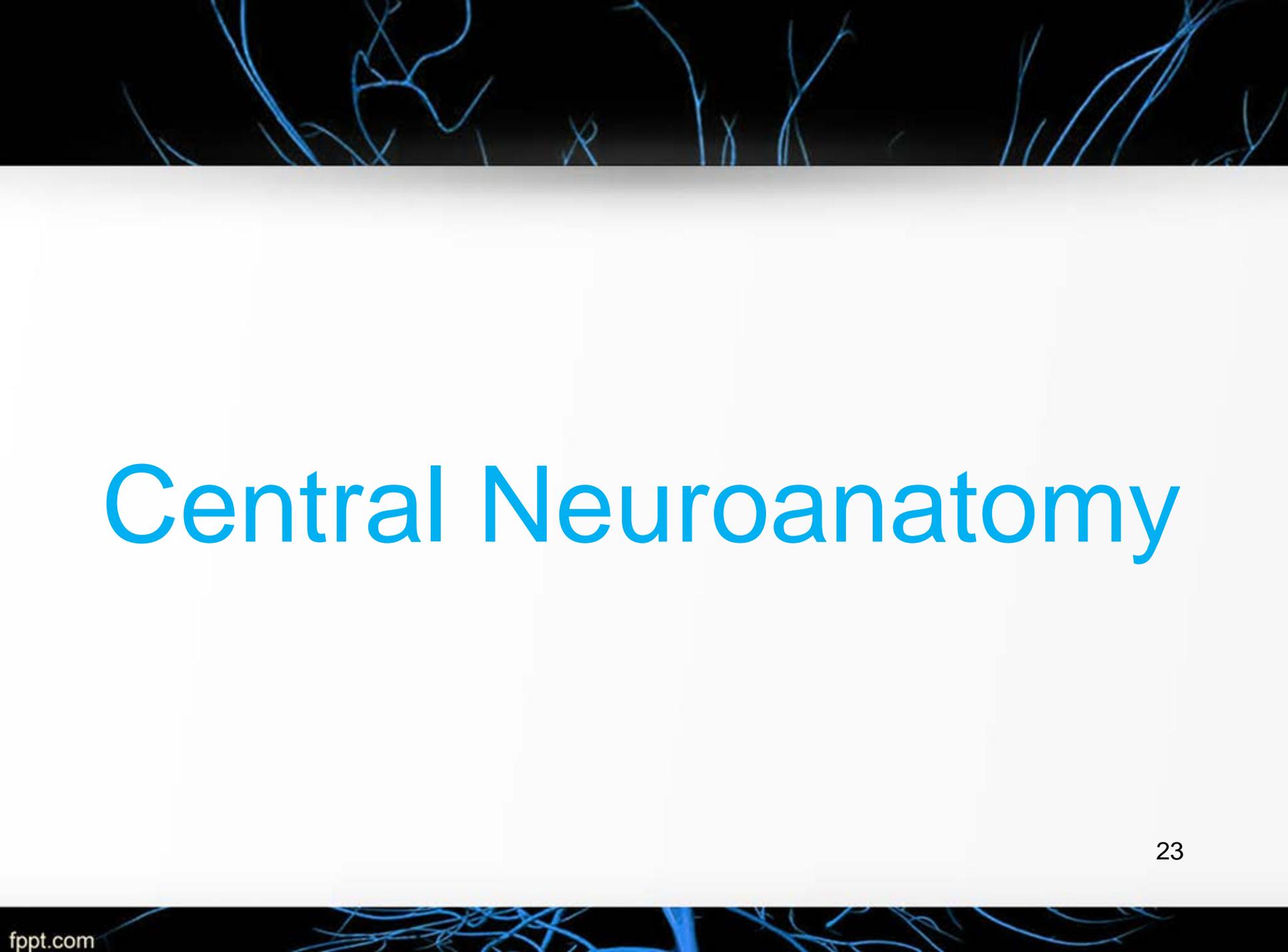
# Neurotransmitter Lifecycle Acetylcholine



AChE – Acetylcholinesterase | Acetyl CoA – Acetyl coenzyme A (Hub of Metabolism) 21

# Catecholamine Inactivation

- Catechol-O-methyl transferase (COMT)
  - Epinephrine
  - Norepinephrine
  - Dopamine
  - COMT protein is encoded by the COMT gene
- L-Monoamine oxidase (MAO)
  - Catalyze the oxidation of monamines
  - Found bound to the outer membrane of mitochondria in most cell types of the body
  - Breaks down serotonin, melatonin, norepinephrine, epinephrine, dopamine, tyramine, tryptamine, phenethylamine, benzylamine



# Central Neuroanatomy

# Development

A key principle of development is that all people develop in exactly the same progression. They only do so at different rates.

Some mental health issues are differences which will decrease with age.

# Neurotransmitters, Neuroregulators, and Neuromodulators

- Approximately 50 known substances
- Human DNA genome library suggests the possibility of more than 200
- Three primary neurotransmitters with common pharmacotherapeutic agents
  - Norepinephrine
  - Dopamine
  - Serotonin

# Classes of Therapy

- Psychostimulants
- Mood stabilizers – Anti-psychotics
- Anti-depressants
- Anti-anxiety
- Anti-epileptics
- Somnolence enhancers

# Common Disorders

- Attention Deficit Disorder (ADD) / Attention Deficit Hyperactivity Disorder (ADHD)
- Oppositional Defiant Disorder
- Conduct Disorder
- Autism Spectrum Disorder
- Mood Disorders
  - Major Depressive Disorder
  - Bipolar Disorder
- Schizophrenia
- Anxiety
- Disorders of Sleep

# ADD/ADHD

## Attention Deficit Disorder (ADD) Attention Deficit Hyperactivity Disorder (ADHD) / Hyperkinetic Disorder

Lack of focus, impulsivity, easily distracted, hyperactive in ADHD, trouble completing tasks, poor school performance

- Currently affects 6-7% of the population
- Affects boys three times more than girls
- Possible impairment in norepinephrine and dopamine pathways

# Oppositional Defiant Disorder

## Social interaction disorder exhibiting

- Anger
- Irritability
- Defiance
- Argumentative
- Frequent temper tantrums

No destruction of property or aggressiveness is involved

Thought to be an imbalance between the behavioral activation system (BAS), and underactive behavioral inhibition system (BIS).

# Conduct Disorder

Behaviors of childhood or adolescence that present in a repetitive pattern in which the rights of others or significant social norms are violated

- Complex etiology involving executive function and other reductions in brain responsiveness
- Chemically described as reductions in serotonin and cortisol levels
- Inability to regulate mood, impulsive behaviors, weakened signals of anxiety and fear, and decreased self-esteem are common
- 1-10% prevalence in the general population
- 23-87% prevalence in juvenile detention facilities

# Autism Spectrum Disorders

## Pervasive Developmental Disorders

Autism - Asperger Syndrome - Childhood Disintegrative Disorder

- Communication disorder with possible
  - Antisocial behaviors
  - Repetitive behaviors
  - Cognitive Delays
- Cause and pathophysiology is unknown
- 6 per 1,000 for autism spectrum disorders as a whole
- Many are present without recognition in the general population

Daryl Hannah

# Mood Disorders

## Moods of depression or mania

Bipolar, major depressive disorder (MDD)

Less severe are dysthymic and cyclothymic disorders

- In 2011, mood disorders were the leading cause of hospital admissions for children ages 1-17 with approximately 112,000 stays
- May be substance-induced or the result of a medical condition

# Schizophrenia

Abnormal social behavior and the inability to recognize what is real

Confused thinking, incongruent expression, auditory hallucinations

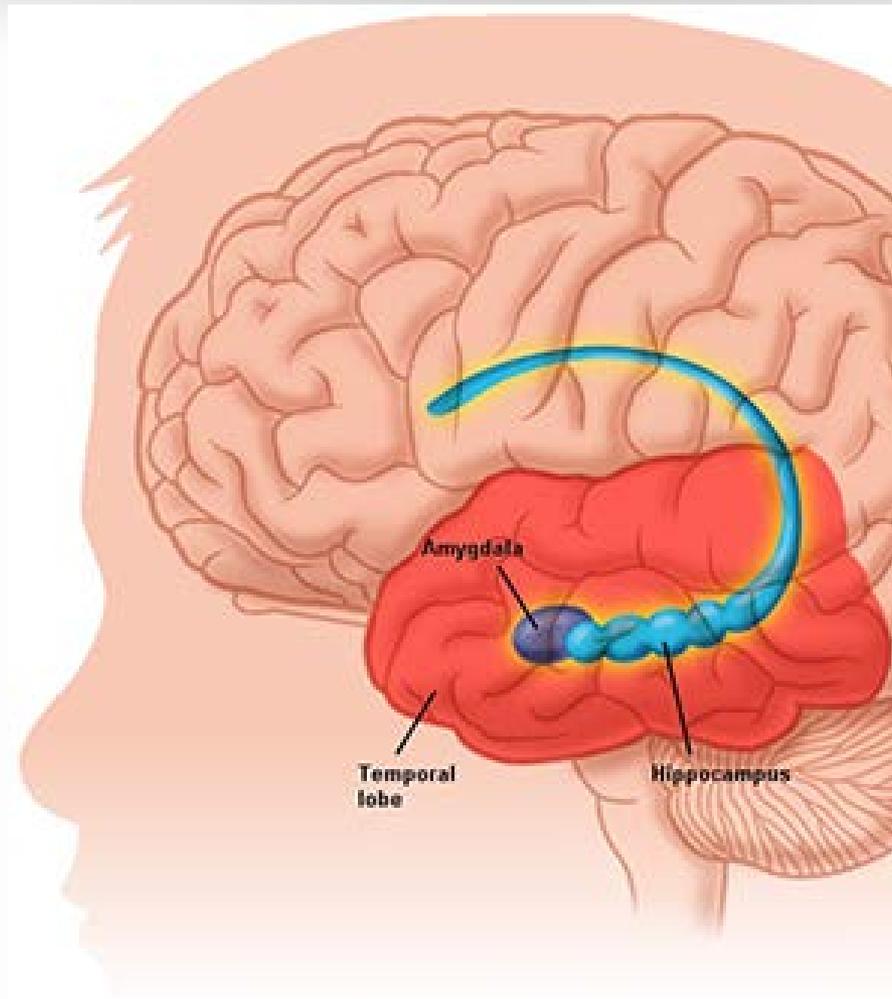
- Typically begins in young adulthood with rare presentation in children
- May be linked to overstimulation of dopamine receptors

# Anxiety

An unpleasant state of inner turmoil frequently presenting with nervous behavior and somatic complaints and focused attention on the symptoms of distress

- Anxiety is thought to be a function of neural pathways involving the amygdala and the hippocampus
- Increased blood flow is noticed in the amygdala in response to unpleasant sensations
- It may be a protective mechanism with a high level of false positive reactions

# Amygdala



# Disorders of Sleep

A common comorbidity in mental health

- Delayed sleep phase disorder (DSPD) a disorder of circadian rhythms
- Insomnia disorder
- Parasomnias – Disruptive sleep events

# Pharmacotherapeutics

Disorder	Therapeutic Class
Attention Deficit Disorder (ADD) / Attention Deficit Hyperactivity Disorder (ADHD)	Psychostimulants Centrally acting Alpha <sub>2</sub> adrenergic agonists
Oppositional Defiant Disorder	Antipsychotics
Conduct Disorder	Antipsychotics
Autism Spectrum Disorder	Antipsychotics for irritability
Mood Disorders	Antidepressants Antipsychotics Antimanics
Schizophrenia	Antipsychotics
Anxiety	Anxiolytics
Sleep Disorders	Centrally acting Alpha <sub>2</sub> adrenergic agonists Hypnotics

Multiple comorbidities are frequently present in mental health patients. There is no one recipe for the pharmacological management of many mental health disorders. Frequently the medication choices are based upon clinical resolution of the behaviors that are interfering with the activities of daily living.

# Psychostimulants

- Dextroamphetamine + amphetamine ©II  
(Adderall, Adderall XR)
- Atomoxetine (Strattera)
- Caffeine
- Dexmethylphenidate (Focalin) ©II
- Dextroamphetamine (Dexedrine) ©II
- Lisdexamfetamine (Vyvanse) ©II
- Methylphenidate (Ritalin, Methylin, Metadate, Concerta, Daytrana) ©II
- Cocaine

# Psychostimulant Drug Actions

Mechanism	Drugs
Dopamine reuptake inhibitor	methylphenidate dexmethylphenidate (d-threo-methylphenidate) cocaine
Norepinephrine reuptake inhibitor	methylphenidate dexmethylphenidate (d-threo-methylphenidate) atomoxetine cocaine
Dopamine receptor activator	dextroamphetamine + amphetamine lisdexamfetamine
Norepinephrine receptor activator	dextroamphetamine + amphetamine Lisdexamfetamine
Serotonin reuptake inhibitor	dextroamphetamine cocaine
Adenosine antagonist	caffeine

# Psychostimulant Side and Adverse Effects

- Hypervigilance
- Euphoria
- Hypertension
- Tachycardia
- Sudden cardiac death

# Centrally Acting Alpha<sub>2</sub> Adrenergic Agonists

Reduces brainstem vasomotor CNS activation – systemic vasodilation by activation of norepinephrine  $\alpha_{2A}$  receptors

- Clonidine (Kapvay, Catapres)
- Guanfacine (Tenex, Intuniv)
- Methyldopa
  
- Side effect – hypotension
- Adverse effect – sudden cardiac death

# Antidepressants

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Tricyclic antidepressants (TCAs)
- Monoamine oxidase inhibitors (MAOIs)
- St. John's wort
- Antipsychotics are also used in low doses

# SSRIs

## Second generation antidepressants

- citalopram (Celexa)
- dapoxetine (Priligy)
- escitalopram (Lexapro)
- fluoxetine (Prozac, Sarafem)
- fluvoxamine (Luvox)
- paroxetine (Paxil)
- sertraline (Zoloft)

# SSRI Side and Adverse Effects

- Cardiac events are not suggested in SSRI overdose with a few rare exceptions
  - QT interval prolongation with escitalopram
  - Sinus tachycardia, MI, junctional rhythms, trigeminy
- Serotonin syndrome
- Suicide risk is higher in children and adolescents using SSRIs however some studies indicate that it lowers suicide rates
- Platelet dysfunction may occur especially in those on anticoagulants

# Serotonin Syndrome

Onset within minutes of elevated serotonin levels and potentially life-threatening

- Cognitive effects – headache, agitation, confusion, hallucinations, coma
- Autonomic effects – tachycardia, shivering, hyperthermia ( $>106.0^{\circ}\text{F}$  or  $41.1^{\circ}\text{C}$ ), vasoconstriction, hypertension, diarrhea, nausea
- Somatic effects – twitching (myoclonus), hyperreflexia (clonus), tremor

Management consists of treating the symptoms and possibly administering a serotonin antagonist (quetiapine, cyproheptadine, risperidone, trazodone). All are oral and may be ineffective in the presence of activated charcoal.

# SNRIs

## Second generation antidepressants

- Venlafaxine (Effexor)
- Desvenlafaxine (Pristiq)
- Duloxetine (Cymbalta, Yentreve)
- Levomilnacipran (Fetzima) – Approved in July, 2013
- Sibutramine (Meridia, Reductil) – first weight loss and appetite suppressant drug approved by the FDA to treat obesity in 30 years
  
- Adverse and side effects are similar to SSRIs however the norepinephrine aspect produces more intense effects when starting the drugs

# Tricyclic Antidepressants (TCAs)

First generation antidepressants - SNRIs  
(Less selective than second generation)

Clomipramine (Anafranil)

Imipramine (Tofranil, Janimine,  
Praminil)

Desipramine (Norpramin, Pertofrane)

Nortriptyline (Pamelor, Aventyl,  
Norpress)

Protriptyline (Vivactil)

Amitriptyline (Tryptomer, Elavil, Endep)

Amitriptylinoxide (Amioxid, Ambivalon,  
Equilibrin)

Amoxapine (Asendin)

Doxepin (Adapin, Sinequan)

Trimipramine (Surmontil)

TCAs behave like class 1A Antiarrhythmics. In overdose they can be cardiotoxic, increasing myocardial irritability.

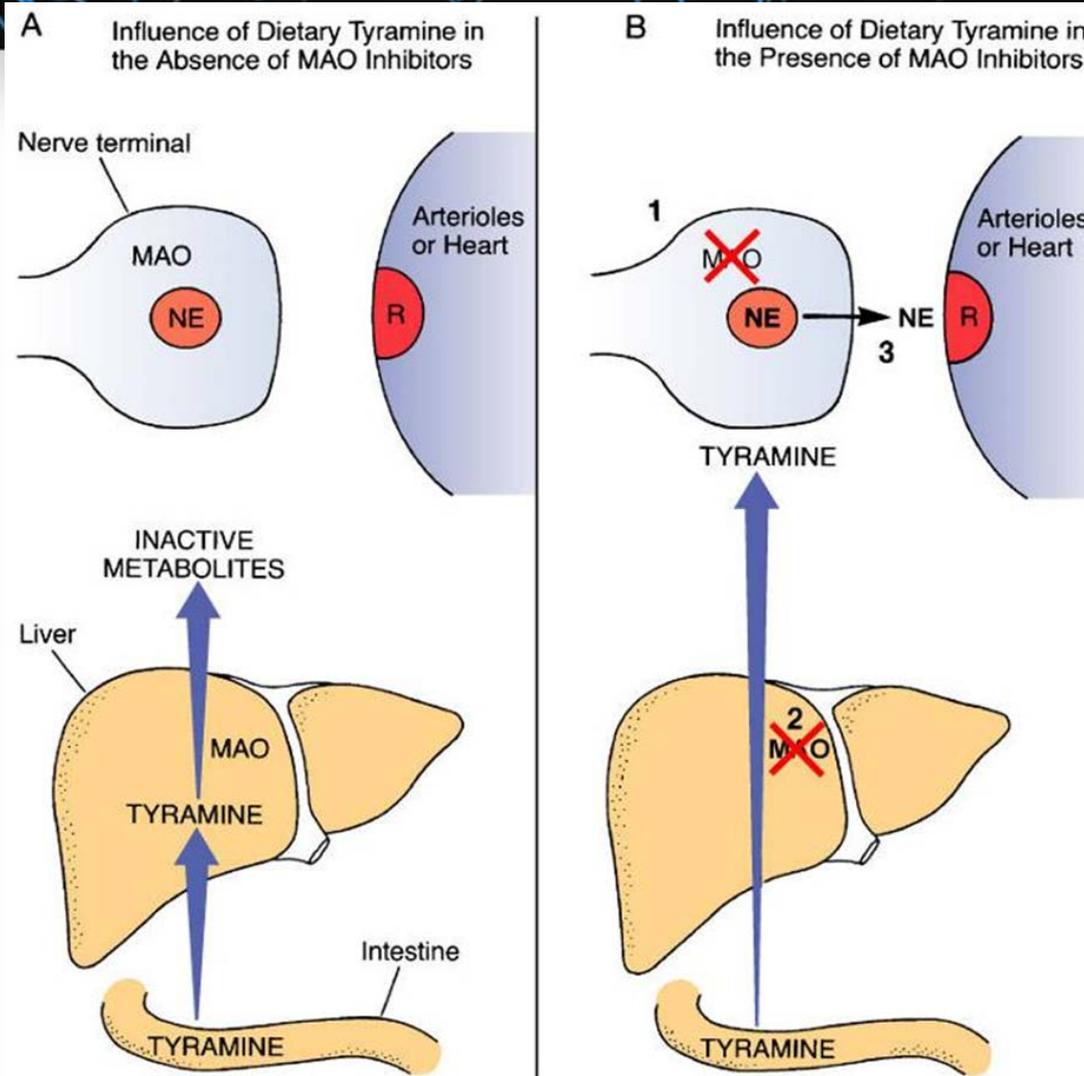
# MAO Inhibitors

- Nonselective MAO-A/MAO-B Inhibitors
  - Hydrazines
  - Isocarboxazid (Marplan)
  - **Isoniazid (Laniazid, Nydrazid)**
  - Nialamide (Niamid)
  - Phenzelzine (Nardil, Nardelzine)
  - Procarbazine
  - Hydracarbazine
- Non-Hydrazines
  - Tranylcypromine (Parnate, Jatrosom)
- Selective MAO-A Inhibitors
  - Moclobemide (Aurorix, Manerix)
- Selective MAO-B Inhibitors
  - Rasagiline (Azilect)
  - Selegiline (Deprenyl, Eldepryl, Emsam)

Isoniazid is a first line treatment for tuberculosis.



# MAOIs and Tyramine



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# Other Antidepressants

- Bupropion (Wellbutrin) – thought to affect dopamine transmission
- Mirtazapine (Remeron)
- Trazodone (Desyrel, Oleptro) – commonly used for insomnia, affects serotonin transmission

# St. John's Wort

Serotonin, norepinephrine, and dopamine, GABA, and glutamate reuptake inhibitor

- Inactivates estrogen in birth control pills
- Has a high risk for serotonin syndrome
- Has a high incidence of reaction with a wide range of antidepressants, tramadol, meperidine, stimulants, and triptans

# Anxiolytics

## Drugs that inhibit anxiety

- Benzodiazapines – short term use
- SSRIs – first line for most anxiety
- Barbiturates – rarely prescribed anymore
- Hydroxyzine (Atarax) – antihistamine with antianxiety effects
- Beta blockers – not approved
- Melatonin – has been studied for preoperative anxiety without general use

# Benzodiazepines

Antianxiety, amnesia effects in low dose. Hypnotic effects in high doses.

- Alprazolam (Xanax)
  - Bromazepam (Lectopam, Lexotan)
  - Chlordiazepoxide (Librium)
  - Clonazepam (Klonopin, Rivotril)
  - Clorazepate (Tranxene)
  - Diazepam (Valium)
  - Flurazepam (Dalmane)
  - Lorazepam (Ativan)
  - Oxazepam (Serax, Serapax)
  - Temazepam (Restoril)
  - Triazolam (Halcion)
- 
- Respiratory depression is a common adverse effect in high doses
  - Rebound syndrome including seizures may occur when discontinued
  - Addictive

# Other Anxiolytics

- Buspirone (BuSpar, Vanspar) – anxiety
  - Serotonin receptor agonist
  - Dopamine <sub>2,3,4</sub> receptor antagonist
  - Partial  $\alpha_1$  receptor agonist
- Chloral hydrate – insomnia
- Eszopiclone (Lunesta) – insomnia
- Ramelteon (Rozerem) – insomnia
- Zaleplon (Sonata) – insomnia
- Zolpidem (Ambien) – insomnia

# Antipsychotics

All tend to block D<sub>2</sub> receptors with atypicals also blocking serotonin receptors

## First Generation

Chlorpromazine (Thorazine)  
Fluphenazine (Prolixin)  
Haloperidol (Haldol)  
Pimozide (Orap)

Thioridazine (Mellaril)  
Thiothixene (Navane)  
Trifluoperazine (Stelazine)

## Second Generation

Atypical antipsychotic

Aripiprazole (Abilify)  
Asenapine (Saphris)  
Clozapine (Clozaril)  
Iloperidone (Fanopt)  
Lurasidone (Latuda)

Olanzapine (Zyprexa)  
Paliperidone (Invega)  
Quetiapine (Seroquel)  
Risperidone (Risperdal)  
Ziprasidone (Geodon)

Beware extrapyramidal symptoms (EPS)

# Antipsychotic Agents

- Top-selling medications in the United States in 2009
- Total sales of \$14.6 billion
- FGA higher risk of EPS
- SGA higher risk of metabolic effects (diabetes, dyslipidemia)

# Antimanic

Mania – mood of abnormally elevated energy levels

- Lamotrigine (Lamictal)
- Lithium (Eskalith, Lithobid)
- Topiramate (Topamax)
- Valproic acid (Depakote)

Beware Stevens-Johnson Syndrome

# Extrapyramidal Symptoms

## Drug induced movement disorders

- Dystonia (continuous spasms and muscle contractions)
- Akathisia (motor restlessness)
- Parkinsonism (rigidity, tremor, bradykinesia)
- Tardive dyskinesia (irregular, jerky movements)

# Stevens-Johnson Syndrome

A milder form of toxic epidermal necrolysis, it is a rare skin disorder caused by the adverse reaction to a medication.



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# Emergent Care

- Follow protocols for the ABC's
- Cardiac monitoring
- IV normal saline at a KVO rate
- Nothing by mouth
- Hold activated charcoal for direction
- Antidotes may cause more problems than solutions
- Rapid transportation
- **BRING IN THE BOTTLES!!**

# Questions?



# References

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