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 pharmaceutics 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

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Acetylcholine</td>
<td>Employed at most junctions of the peripheral nervous system</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Released by most postganglionic neurons</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Released by the adrenal medulla</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Serves as a local chemical messenger at limited sites</td>
</tr>
</tbody>
</table>
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
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, Beta₁ adrenergic receptors are activated
Autonomic Receptors

Two basic categories of receptors

Cholinergic receptors
• Mediated by acetylcholine

Adrenergic receptors
• Mediated by epinephrine and norepinephrine
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\(_1\)**
  - 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\(_2\)**
  - 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
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)
Catacholamine 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
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
ADHD / ADD

- Hyperactivity
- Failure to concentrate
- Difficulty in completing school work
- Lack of attention
- Distractible
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
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

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Therapeutic Class</th>
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<tr>
<td>Attention Deficit Disorder (ADD) / Attention Deficit Hyperactivity Disorder (ADHD)</td>
<td>Psychostimulants</td>
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<tr>
<td></td>
<td>Centrally acting Alpha$_2$ adrenergic agonists</td>
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<td>Oppositional Defiant Disorder</td>
<td>Antipsychotics</td>
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<td>Conduct Disorder</td>
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<td>Autism Spectrum Disorder</td>
<td>Antipsychotics for irritability</td>
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<tr>
<td>Mood Disorders</td>
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<td>Anxiety</td>
<td>Anxiolytics</td>
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<tr>
<td>Sleep Disorders</td>
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<td></td>
<td>Hypnotics</td>
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</tbody>
</table>

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 ©Il
  (Adderall, Adderall XR)
- Atomoxetine (Strattera)
- Caffeine
- Dexamphetamine (Focalin) ©Il
- Dextroamphetamine (Dexedrine) ©Il
- Lisdexamfetamine (Vyvanse) ©Il
- Methylphenidate (Ritalin, Methylin, Metadate, Concerta, Daytrana) ©Il
- Cocaine
## Psychostimulant Drug Actions

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drugs</th>
</tr>
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<tr>
<td>Dopamine reuptake inhibitor</td>
<td>methylphenidate</td>
</tr>
<tr>
<td></td>
<td>dextroamphetamine + amphetamine</td>
</tr>
<tr>
<td></td>
<td>lisdexamfetamine</td>
</tr>
<tr>
<td></td>
<td>cocaine</td>
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<td>Norepinephrine reuptake inhibitor</td>
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<td>Serotonin reuptake inhibitor</td>
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<tr>
<td></td>
<td>cocaine</td>
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<td>Adenosine antagonist</td>
<td>caffeine</td>
</tr>
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*Adenosine antagonist*
Psychostimulant Side and Adverse Effects

- Hypervigilence
- Euphoria
- Hypertension
- Tachycardia
- Sudden cardiac death
Centrally Acting Alpha$_2$ Adrenergic Agonists

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

- Clonidine (Kapvay, Catapres)
- Guanfacine (Tenex, Intuniv)
- Metyldopa

- 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 or combinations of SSRI’s with other medications
  - 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°F or 41.1°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
Sero
to
nin
Norepinephrine Reuptake Inhibitors

• 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.
Isoniazid is a first line treatment for tuberculosis.
MAO – L-Monoamine oxidases
dopamine (DA) and norepinephrine (NE) are metabolized by MAO

**Phenylalanine** → **Tyrosine** → **Dopa** → **DA** → **NE** → **Inactive product** → **α₂** → **NE** → **α₁ or β** → **Postjunctional cell**

MAO: Mitochondrial enzymes that catalyze the oxidative deamination of biogenic amines.
MAOIs and Tyramine
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

- Benzodiazepines – 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 $D_{2,3,4}$ 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 D₂ 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

- 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
Extrapyrmdidal 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.
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


• Images: https://hrexach.wordpress.com