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DRUGS FOR BEHAVIORAL HEALTH I

Skye McKennon, PharmD, BCPS, ACSM-GEI
Thread Director, Interprofessional Education & Pharmacology
Clinical Associate Professor
Elson S. Floyd College of Medicine
skye_mckennon@wsu.edu

DISCLOSURE

None

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OBJECTIVES

1. Identify the appropriate drugs and drug classes for managing attention deficit hyperactivity disorder (ADHD), anxiety, and obsessive compulsive disorder (OCD).
2. Explain the mechanism of action of central nervous system stimulants, selective norepinephrine reuptake inhibitors, tricyclic anti-depressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and benzodiazepines and how this relates to the underlying pathophysiology of ADHD, anxiety, and OCD.
3. Describe adverse effects and contraindications to of central nervous system stimulants, selective norepinephrine reuptake inhibitors, tricyclic anti-depressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and benzodiazepines.
4. Describe the clinically important drug interactions of central nervous system stimulants, selective norepinephrine reuptake inhibitors, tricyclic anti-depressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and benzodiazepines.

BEHAVIORAL HEALTH I

- Anxiety
- Obsessive Compulsive Disorder (OCD)
- Attention Deficit Hyperactivity Disorder (ADHD)

ANXIETY

AMINE HYPOTHESIS OF MOOD

Amine hypothesis of mood postulates amines (particularly norepinephrine and serotonin) are neurotransmitters in pathways that function in mood expression

- Functional decrease in amine activity → mood depression
- Functional increase in amine activity → mood elevation

SELECTED DRUG CLASSES FOR ANXIETY

First-line

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)

Second- or third-line

- Benzodiazepines
- Tricyclic antidepressants (TCAs)
- Other antidepressants
- Beta-blockers (performance anxiety)

Treatment refractory and/or comorbid conditions

- Atypical antipsychotics
- Monoamine oxidase inhibitors (MAOIs)

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SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

ACTIVE LEARNING

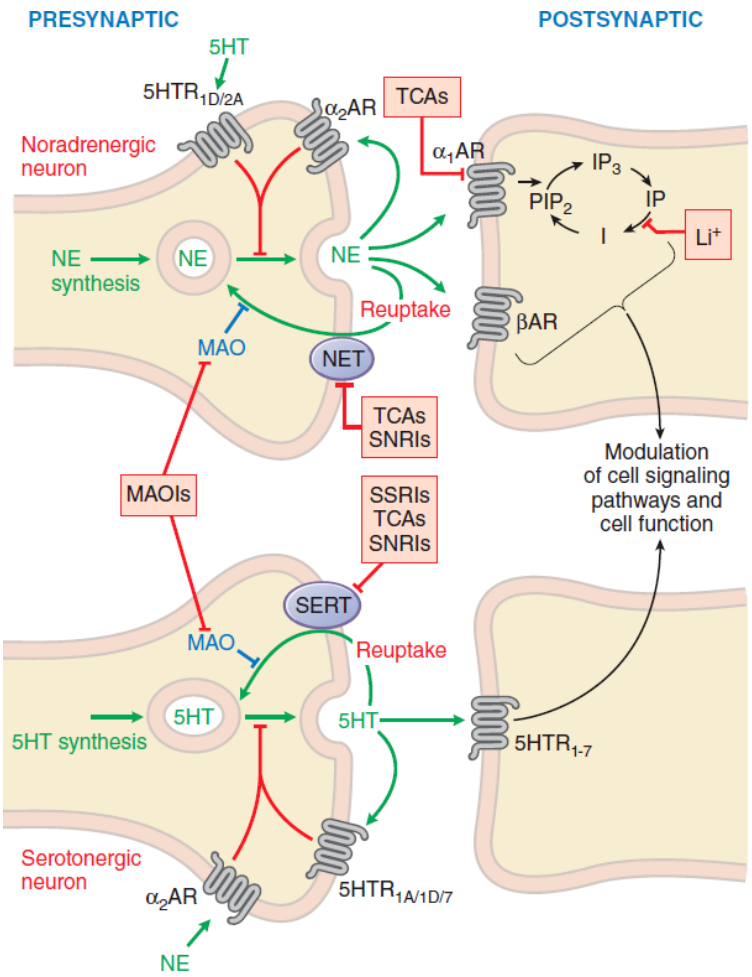
Consider serotonin and norepinephrine. What functions are each neurotransmitter involved in? How are they synthesized? How are their effects terminated?

SEROTONIN (5HT) & NOREPINEPHRINE (NE)

Parameter	Serotonin	Norepinephrine
Involved in	Mood, behavior, memory	Mood, appetite, alertness
Synthesis	Tryptophan → 5-hydroxytryptophan (5HTP) → 5 hydroxytryptamine (5HT or serotonin)	Tyrosine → DOPA → dopamine (DA) DA secreted into the bloodstream OR undergoes hydroxylation to NE NE can be secreted into the bloodstream (release stimulated by ACh) OR modified by a methyltransferase to epinephrine (EPI)
Neurotransmission termination	Reuptake	
Degradation	Monoamine oxidase (MAO)	Monoamine oxidase (MAO) OR catechol-o-methyltransferase (COMT)

ACTIVE LEARNING

If your pharmacologic goal were to increase serotonin and/or norepinephrine levels, which mechanisms might your use?



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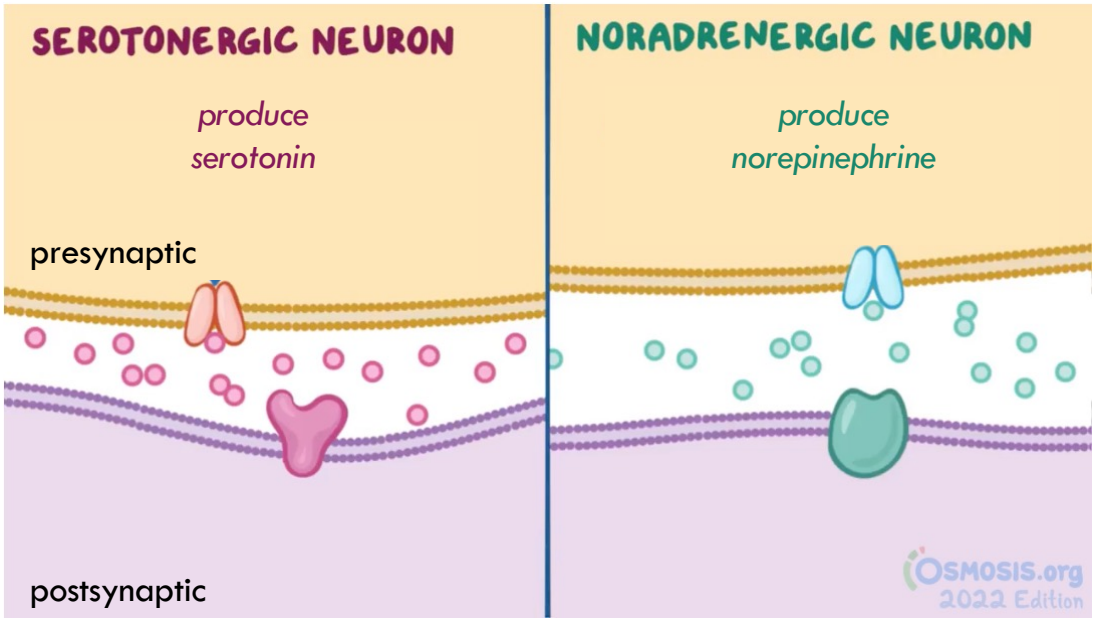
SEROTONERGIC & NORADRENERGIC NEURONS

Each neuron synthesizes and stores their neurotransmitters in small vesicles

Action potential reaches presynaptic membrane → neurotransmitters released in synaptic cleft → bind to receptors on postsynaptic membrane

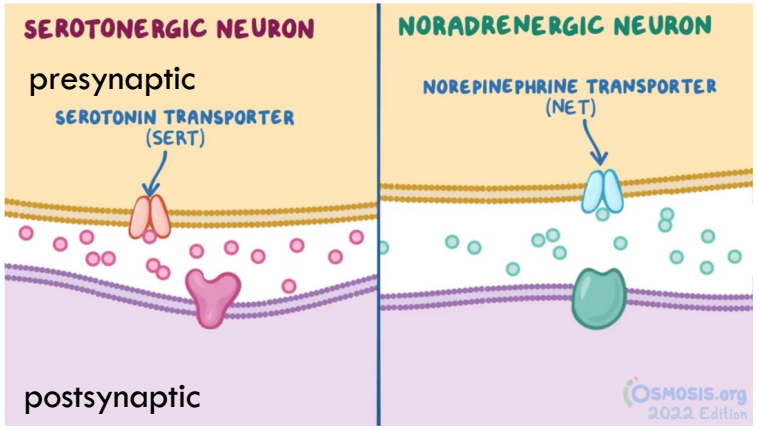
As long as synaptic cleft neurotransmitter concentrations high enough → postsynaptic neurons continue to fire

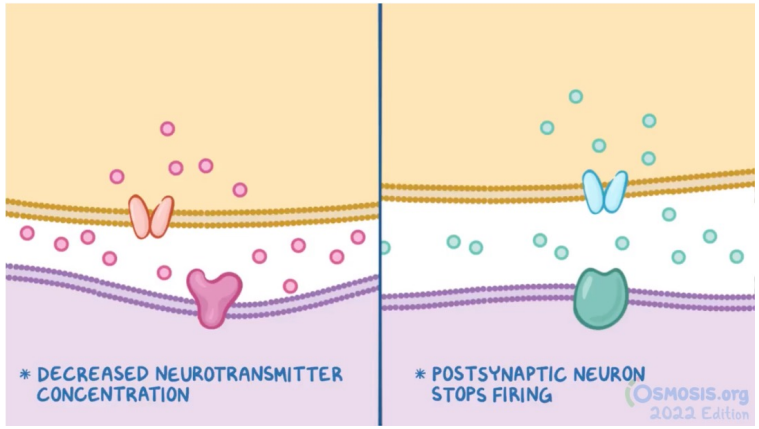


SEROTONERGIC & NORADRENERGIC NEURONS

SERT & NET transport 5HT & NE back into presynaptic neurons

↓ 5HT & NE in synaptic cleft → postsynaptic neurons stop firing





SNRI MECHANISM OF ACTION

SNRIs allosterically inhibit SERT and NET transporters (bind at site other than serotonin or norepinephrine)

- Have little to no affinity for other receptors

Blocks reuptake of 5HT and NE

This enhances/prolongs 5HT and NE neurotransmission

SNRIs

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Venlafaxine (Effexor) Desvenlafaxine (Pristiq) Duloxetine (Cymbalta) Levomilnacipran (Fetzima) Milnacipran (Savella)	MAOI use intended to treat psychiatric disorders (concurrently or within 14 days of discontinuing either SSRI or the MAOI) Cautions: Serotonin syndrome Withdrawal symptoms with abrupt discontinuation	Hypertension Stimulant effects Sedation Anticholinergic Sexual dysfunction Liver enzyme elevation	MAOIs increase risk of hypertensive crisis Duloxetine potent CYP2D6 inhibitor

Boxed warning for increased risk of suicidal thoughts & behaviors in pediatric and young adult patients

SNRI ADME & CLINICAL USE

ADME

Venlafaxine is a pro-drug (converted to the active desvenlafaxine by CYP2D6)

Takes 2 - 4 weeks for therapeutic response

Clinical Use

Generalized anxiety disorder

Depression

Diabetic neuropathy

Venlafaxine: Panic disorder , social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder

Duloxetine/milnacipran: Fibromyalgia

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SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

SSRI MECHANISM OF ACTION

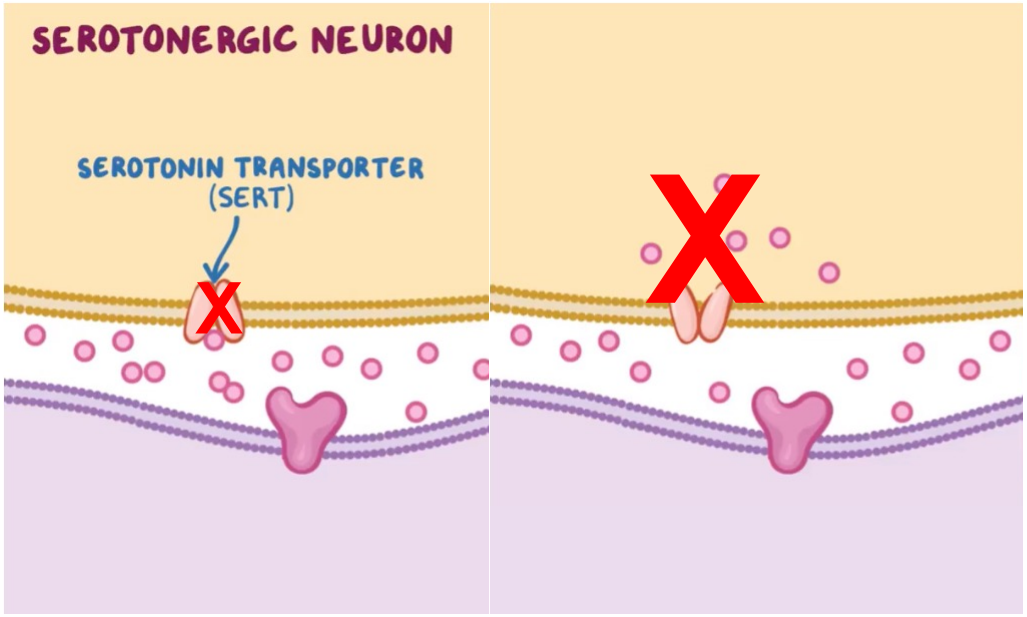
SSRIs allosterically inhibit SERT transporter (bind at site other than serotonin)

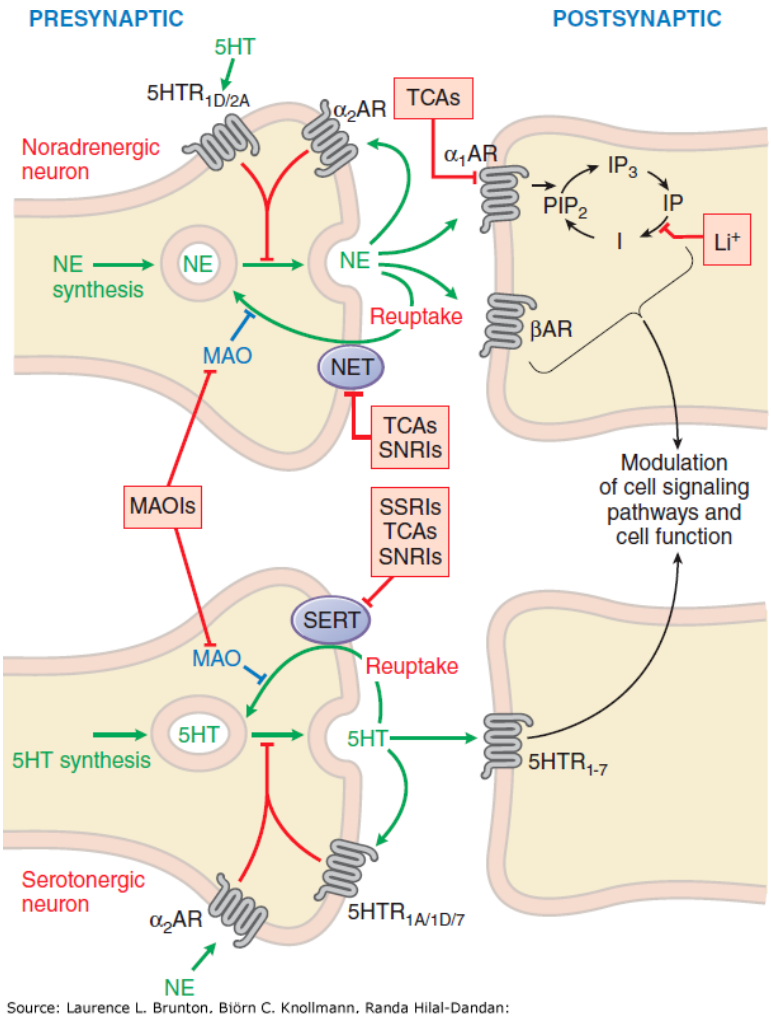
- Highly selective action on serotonin transporter (SERT)

Blocks reuptake of 5HT

This enhances/prolongs 5HT neurotransmission

- Minimal inhibitory effects on NE transporter





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SSRIs

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Fluoxetine (Prozac) Fluvoxamine (Faverin) Paroxetine (Paxil) Sertraline (Zoloft) Escitalopram (Lexapro) Citalopram (Celexa)	MAOI use intended to treat psychiatric disorders (concurrently or within 14 days of discontinuing either SSRI or the MAOI) Cautions: Serotonin syndrome Withdrawal symptoms with abrupt discontinuation	Initial anxiety/jitteriness Serotonin syndrome GI distress SIADH Sexual dysfunction (anorgasmia, erectile dysfunction, ↓ libido) Mania precipitation if underlying bipolar disorder	**Fluoxetine and paroxetine are potent CYP2D6 inhibitors** Fluvoxamine is a potent CYP1A2 inhibitor

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ACTIVE LEARNING

Hydrocodone is a pro-drug that requires bioactivation by CYP2D6 to the active metabolite hydromorphone to produce analgesia. How would the use of fluoxetine or paroxetine impact hydrocodone's analgesic efficacy?

SSRIs

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Fluoxetine (Prozac) Fluvoxamine (Faverin) Paroxetine (Paxil) Sertraline (Zoloft) Escitalopram (Lexapro) Citalopram (Celexa)	MAOI use intended to treat psychiatric disorders (concurrently or within 14 days of discontinuing either SSRI or the MAOI) Cautions: Serotonin syndrome Withdrawal symptoms with abrupt discontinuation	Initial anxiety/jitteriness Serotonin syndrome GI distress SIADH Sexual dysfunction (anorgasmia, erectile dysfunction, ↓ libido) Mania precipitation if underlying bipolar disorder	**Fluoxetine and paroxetine are potent CYP2D6 inhibitors** • Tamoxifen (pro-drug metabolized to active form by CYP2D6) → decreased tamoxifen efficacy • Prodrug opioids (codeine, hydrocodone, tramadol) → worsened pain control Fluvoxamine is a potent CYP1A2 inhibitor
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SSRI ADME & CLINICAL USE

ADME

Half-lives 15+ hours

Takes 2 - 4 weeks for therapeutic response

Clinical Use

Generalized anxiety disorder

Depression

Panic disorder

Obsessive compulsive disorder

Bulimia

Binge-eating disorder

Social anxiety disorder

PTSD

Premature ejaculation

Premenstrual dysphoric disorder

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BENZODIAZEPINES

Anxiety

BENZODIAZEPINES

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Alprazolam Diazepam Flurazepam Lorazepam Midazolam Oxazepam Temazepam Triazolam ***-zepam or -zolam***	**Pregnancy (cleft lip or cleft palate)** Hepatic disease Respiratory disease or sleep apnea Older adults (CNS adverse effects ↑ d/t prolonged $t_{1/2}$)	Tolerance **Daytime sedation and performance impairment** **Anterograde amnesia** Rebound insomnia Paradoxical CNS stimulation Hangover Dependence after prolonged use (can lead to withdrawal)	CNS depressants enhance CNS depression of benzos

CONCERNS WITH BENZODIAZEPINES

Not recommended first-line for anxiety

Risk versus benefit

- Physical and psychological dependence
- Potential for misuse
- Overdose mortality

OBSESSIVE COMPULSIVE DISORDER

SALIENT PATHOPHYSIOLOGY RELATED TO PHARM

Exact cause of OCD unknown

Likely dopaminergic and glutamatergic overactivity in frontostriatal pathways and diminished serotonergic and GABAergic neurotransmission in frontolimbic systems

DRUG CLASSES FOR OCD

- SSRIs
- Tricyclic antidepressants

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TRICYCLIC ANTIDEPRESSANTS (TCAs)

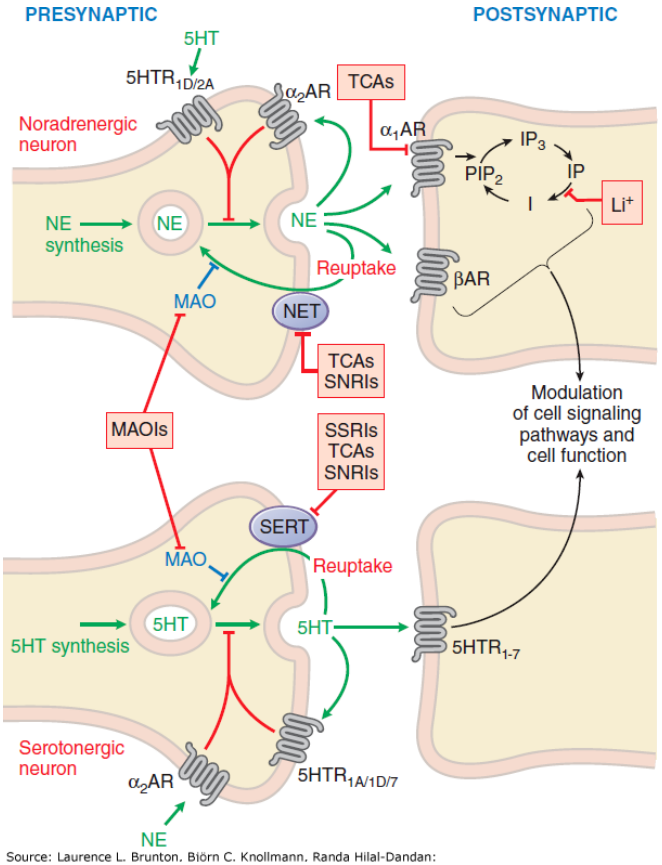
TCA MECHANISM OF ACTION

Block reuptake of 5HT and NE in presynaptic nerve terminals

- Inhibit SERT and NET
- This enhances/prolongs 5HT and NE neurotransmission

Act as competitive antagonists on post-synaptic

- Alpha adrenergic (alpha1 and alpha2)
- Muscarinic
- Histaminergic receptors (H1)
- Structure influences affinity of particular TCA for each receptor



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ACTIVE LEARNING

Both SNRIs and TCAs inhibit the reuptake of 5HT and NE in presynaptic nerve terminals. When might SNRIs be preferred compared to TCAs? When might TCAs be preferred over SNRIs?

TCAs

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Secondary amines: Desipramine Nortriptyline	MAOI use (concurrently or within 14 days of discontinuing either SSRI or the MAOI) Family history of QTc prolongation, sudden cardiac death) Cautions: Heart disease Seizures Narrow angle glaucoma Serotonin syndrome Mania risk in bipolar	Alpha-1 blocking effects (orthostatic hypotension, dizziness) Anticholinergic effects (tachycardia, urinary retention, constipation dry mouth)* - 3° > 2° Histamine blocking effects (sedation, increased appetite, weight gain, confusion) Convulsions Coma Respiratory depression Hyperpyrexia QTc prolongation	Less likely to be involved in clinically significant interactions
Tertiary amines: Amitriptyline Clomipramine Doxepin Imipramine			Tertiary amines are CYP2C19 inhibitors
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ACTIVE LEARNING

A patient with a diagnosis of OCD is prescribed desipramine (a substrate of CYP2C19). The patient is found to be an ultra-rapid metabolizer of CYP2C19. How might his impact desipramine's efficacy?

TCA ADME & CLINICAL USE

ADME

Often dosed at night due to sedating effects

Desipramine and nortriptyline lack active metabolites

Takes 2 - 4 weeks for therapeutic response

Clinical Use

Major depressive disorder

Peripheral neuropathy

Chronic neuropathic pain

Migraine prophylaxis

Obsessive compulsive disorder (clomipramine, imipramine)

Nocturnal enuresis (imipramine)

TCA POISONING

Sedation, confusion, delirium, or hallucinations

Cardiac conduction delays, arrhythmias, hypotension, and anticholinergic toxicity (eg, hyperthermia, flushing, dilated pupils)

Patients who present immediately after ingestion may initially be well-appearing, only to deteriorate rapidly, due to the variable absorption kinetics

TCA ingestions of 10 to 20 mg/kg lead to significant cardiovascular and central nervous system (CNS) toxicity

The “3 Cs” - coma, convulsions, and cardiac problems

TCA POISONING MANAGEMENT

- ABCs
- Cardiac: Sodium bicarbonate
  - Refractory: magnesium, lidocaine
- Hypotension: Isotonic saline to treat hypotension
  - Refractory: vasopressors, hypertonic saline
- Seizures: Benzodiazepines
- GI decontamination
- Contraindicated: flumazenil; physostigmine; Class IA (ie, procainamide) and Class IC antiarrhythmics (ie, flecainide)

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

SALIENT PATHOPHYSIOLOGY RELATED TO PHARM

ADHD associated with cognitive/functional deficits related to diffuse abnormalities in brain

Anterior cingulate gyrus and dorsolateral prefrontal cortex (DLFPC) are found to be small in individuals with ADHD

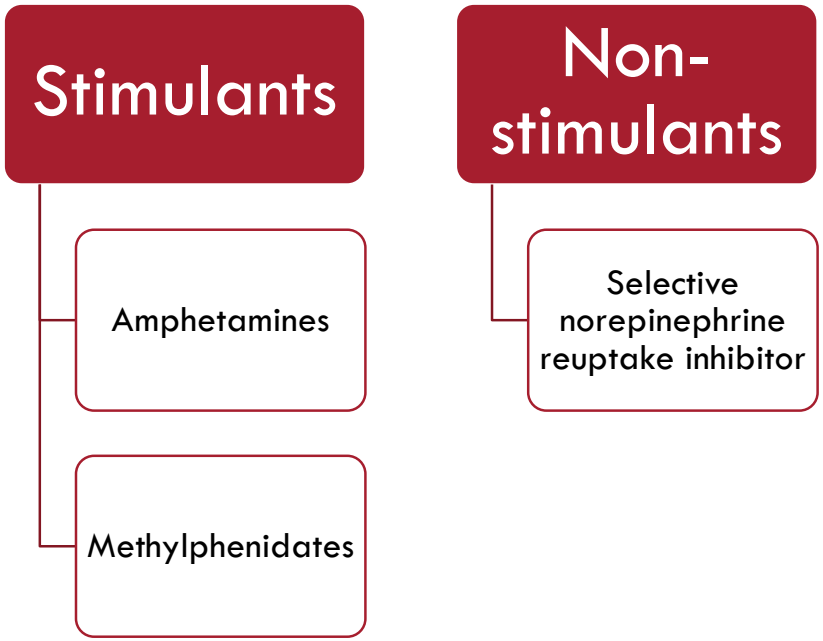
- These changes may account for the deficits in goal-directed behavior

Frontostriatal region reduced in ADHD

Pathophysiological mechanisms relate to pharmacotherapy

Evidence of role or noradrenergic receptor involvement

MEDICATIONS FOR ADHD



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CENTRAL NERVOUS SYSTEM STIMULANTS

ADHD

CNS STIMULANT MECHANISM OF ACTION

Exact MOA in ADHD is unknown

Stimulants affect the dopaminergic and noradrenergic systems, causing the release of catecholamines from storage sites at the central nervous system synapses

Neuronal dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2) are principal targets of amphetamine's actions

Amphetamine-induced exchange diffusion, reverse transport, channel-like transport phenomena, and effects resulting from the weakly basic properties of amphetamine

Amphetamine analogues affect monoamine transporters through phosphorylation, transporter trafficking, and the production of reactive oxygen and nitrogen species

CNS STIMULANT MECHANISM OF ACTION

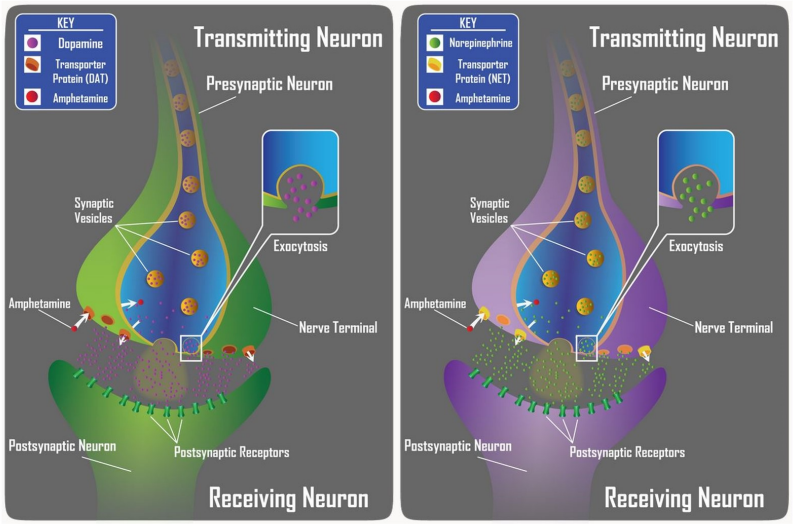
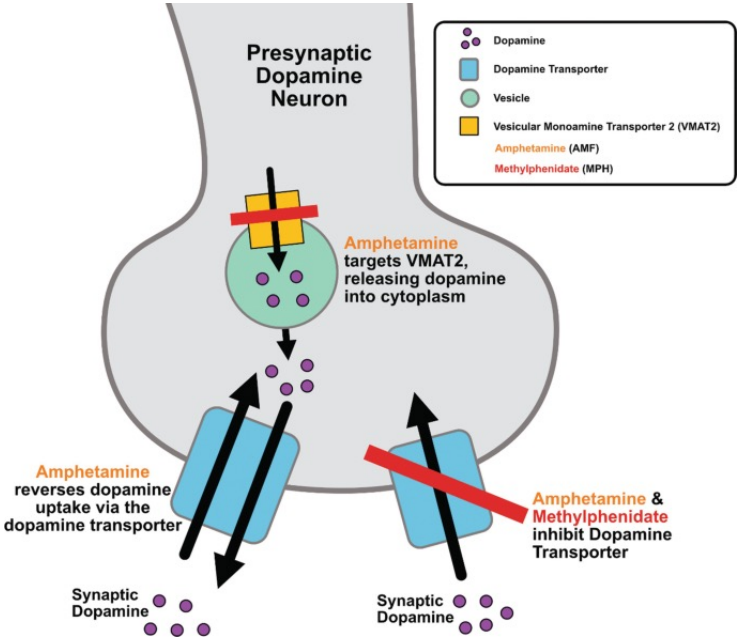


Figure 8.6. Amphetamine-Induced Neuronal Release of Norepinephrine and Dopamine

Original drawing by Nathan Olivier

AMPHETAMINE VERSUS METHYLPHENIDATE



CNS STIMULANT MECHANISM OF ACTION

Amphetamine is potent sympathomimetic amine

Stimulates medullary respiratory center (may increase rate and depth of respiration)

Lessens degree of central depression caused by various drugs

Suppresses food intake — Mediated by release of NE from central noradrenergic neurons

Increases alertness — Presumably mediated by release of NE from central noradrenergic neurons

Locomotor stimulation action — Mediated by release of NE and DA

D-isomer (dextroamphetamine) is more potent

CNS STIMULANTS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Amphetamine (Dyanavel) Dextroamphetamine (Dexedrine) Dextroamphetamine/ amphetamine (Adderall) Methylphenidate (Ritalin, Methylin, Concerta, Daytrana) Dexmethylphenidate (Focalin)	MAOI use within 14 days (hypertensive effects) Pregnancy Cardiovascular disease Abrupt withdrawal Cautions: HTN Hyperthyroidism Glaucoma Motor tics or Tourette's Psychosis Bipolar Substance use disorder	Insomnia Abdominal pain Anorexia Weight loss Restlessness Dizziness Changes in libido Tics Fatigue/depression upon discontinuation	Alkalinizing agents may decrease the excretion of amphetamines May enhance hypertensive and tachycardic effects of other drugs MAOIs
Boxed warning for high potential for abuse and dependence			

ADME & CLINICAL USE

ADME

Various dosage forms

- Tablet, chewable tablets, orally disintegrating tablets, liquid, patch
- Short-acting, long-acting
- Osmotic release
  - Immediate release coating and include pump to gradually release
- Prodrug options

Clinical Use

ADHD

Narcolepsy

Obesity secondary to hypothalamic-pituitary dysfunction

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SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS

ADHD

SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS MECHANISM OF ACTION

Selective, presynaptic, NE reuptake inhibitor

Inhibits presynaptic NET

Prevents reuptake of NE throughout the brain

Inhibits DA reuptake in specific brain regions such as the prefrontal cortex

SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Atomoxetine (Strattera)	MAOI use within 14 days (hypertensive effects) Narrow-angle glaucoma Pheochromocytoma Cardiovascular disease Abrupt withdrawal Cautions: Poor CYP2D6 metabolizers HTN Bipolar	Abdominal pain Weight loss Somnolence/fatigue Irritability	Dose adjustment may be needed with strong inhibitors of CYP2D6 (paroxetine, fluoxetine)

Boxed warning for increased risk of suicidal thoughts & behaviors in pediatric and young adult patients

ADME & CLINICAL USE

ADME

Oral capsule

Efficacy better with morning dosing, adverse effects better with evening dosing

Onset of action 1 – 4 weeks

Reduced dose in CYP2D6 poor metabolizers

Clinical Use

ADHD

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REFERENCE LIST

Antidepressants. In: Katzung BG, Kruidering-Hall M, Tuan R, Vanderah TW, Trevor AJ. eds. Katzung & Trevor's Pharmacology: Examination & Board Review, 13e. McGraw Hill; 2021. Accessed January 23, 2023. https://accessmedicine.mhmedical.com/content.aspx?bookid=3058&sectionid=255305966

Bamalan OA, Moore MJ, Al Khalili Y. Physiology, Serotonin. [Updated 2022 Jul 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545168/

Brock H, Hany M. Obsessive-Compulsive Disorder. [Updated 2022 Aug 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553162/

Chu A, Wadhwa R. Selective Serotonin Reuptake Inhibitors. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554406/

DeBattista C. Antidepressant Agents. In: Katzung BG, Vanderah TW. eds. Basic & Clinical Pharmacology, 15e. McGraw Hill; 2021. Accessed January 23, 2023. https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250598963

Drugs Used in Mood Disorders. In: Stringer JL. eds. Basic Concepts in Pharmacology: What You Need to Know for Each Drug Class, 5e. McGraw Hill; 2017. Accessed January 23, 2023. https://accessmedicine.mhmedical.com/content.aspx?bookid=2147&sectionid=161351670

Fedder D, Patel H, Saadabadi A. Atomoxetine. [Updated 2022 May 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493234/

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REFERENCE LIST

Magnus W, Nazir S, Anilkumar AC, et al. Attention Deficit Hyperactivity Disorder. [Updated 2022 Aug 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441838/

Moraczewski J, Aedma KK. Tricyclic Antidepressants. [Updated 2022 Nov 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557791/

O'Donnell JM, Bies RR, Shelton RC. Drug Therapy of Depression and Anxiety Disorders. In: Brunton LL, Hilal-Dandan R, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e. McGraw Hill; 2017. Accessed January 23, 2023. https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=169518711

Sheffler ZM, Patel P, Abdijadid S. Antidepressants. [Updated 2022 Nov 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538182/

Sibley DR, Hazelwood LA, Amara SG. 5-Hydroxytryptamine (Serotonin) and Dopamine. In: Brunton LL, Hilal-Dandan R, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e. McGraw Hill; 2017. Accessed January 23, 2023. https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=170105881

Westfall TC, Macarthur H, Westfall DP. Adrenergic Agonists and Antagonists. In: Brunton LL, Hilal-Dandan R, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e. McGraw Hill; 2017. Accessed January 19, 2023. https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=167890123

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ANY QUESTIONS?