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DRUGS FOR BEHAVIORAL HEALTH 2

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DISCLOSURE

None

OBJECTIVES

1. Identify the appropriate drugs and drug classes for managing depression, bipolar, and schizophrenia.
2. Explain the mechanism of action of atypical antidepressants, typical (classical) antipsychotics, atypical (newer) antipsychotics, and anti-manic agents and how this relates to the underlying pathophysiology of depression, bipolar, and schizophrenia.
3. Describe adverse effects and contraindications to atypical antidepressants, typical (classical) antipsychotics, atypical (newer) antipsychotics, and anti-manic agents.
4. Describe the clinically important drug interactions of atypical antidepressants, typical (classical) antipsychotics, atypical (newer) antipsychotics, and anti-manic agents.

BEHAVIORAL HEALTH 2

- Depression
- Bipolar
- Schizophrenia

DEPRESSION

ACTIVE LEARNING

Which drug classes have we previously discussed in pharmacology for the management of depression?

What are their mechanisms of action?

SELECTED DRUG CLASSES FOR DEPRESSION

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Atypical antidepressants
- Serotonin-Dopamine Activity Modulators (Atypical Antipsychotics)
- Tricyclic antidepressants (TCAs)
- Monoamine oxidase inhibitors (MAOIs)

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ATYPICAL ANTIDEPRESSANTS

ATYPICAL ANTIDEPRESSANTS

Serotonin 5-HT2 Receptor Antagonists

- Nefazodone
- Trazodone

Alpha-2 Antagonist

- Mirtazapine

Bupropion

SEROTONIN 5-HT2 RECEPTOR ANTAGONIST MECHANISM OF ACTION: TRAZODONE/NEFAZODONE

Block the 5-HT2A receptor

- GPCR located in several CNS regions (neocortex)
- Antagonism of the 5-HT2A receptor associated with lessened anxiety and depression

Trazodone also

- Blocks alpha-1 adrenergic receptors
- Inhibits SERT (less potently than its blockade of 5-HT2A receptors)

Nefazodone primarily blocks the 5-HT2A receptor

Mirtazapine

- Potently blocks histamine H1 receptors
- Some affinity for alpha-2 adrenergic receptors

ALPHA-2 ANTAGONIST: MIRTAZAPINE

Inhibition of alpha-2 adrenergic receptors (primarily responsible for antidepressant effect)

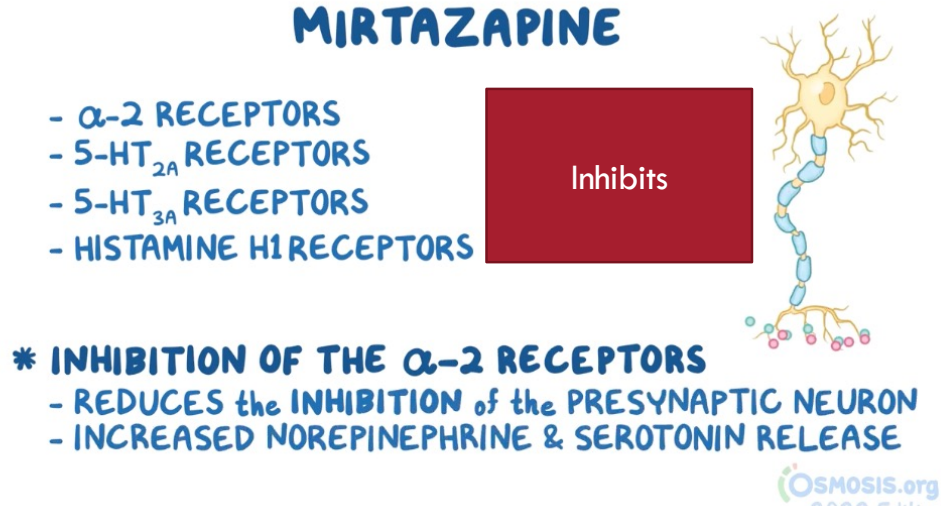
- Reduces inhibition of presynaptic neuron
- Leads to increased NE and 5-HT release

Block the 5-HT2A receptor, 5-HT3A recepto

- Allows more 5-HT to bind to 5-HT1A receptors (stronger link to depression)
- Inhibition of 5-HT3A receptors reduces nausea and vomiting

Inhibits histamine H1 receptors

- Leads to sedation
  - Desirable in insomnia



TRAZODONE/NEFAZODONE & MIRTAZAPINE

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Trazodone Nefazodone	MAOI use within 14 days Linezolid, methylene blue Cautions: Serotonin syndrome Trazodone/nefazodone: Cardiac disease	Sedation Dizziness Dry mouth Nausea Orthostatic hypotension Priapism Ventricular arrhythmias	Strong CYP3A4 inhibitors (ketoconazole, clarithromycin, itraconazole, fluconazole) may require trazodone dose reduction Increases risk of bleeding with anticoagulants Enhances CNS depressant effects of other drugs
Mirtazapine	Mirtazapine: Anticholinergic effects Seizure disorder	Sedation Increased appetite Weight gain Dry mouth	Enhances serotonergic and CNS depressant effects of other drugs Diminishes antihypertensive effects of alpha-2 agonists

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

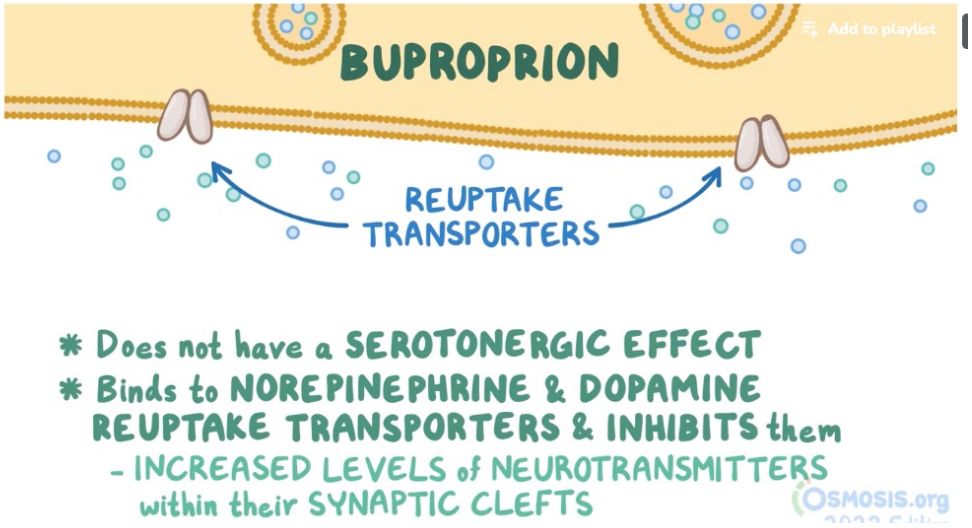
BUPROPION MECHANISM OF ACTION

Inhibits NET and DAT (not as potent effects on DAT)

- Increases concentration of NE and DA within synaptic clefts
- Does NOT have a serotonergic effect

Blocks nicotinic (ACh) receptors

- Useful in smoking cessation



BUPROPION

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Bupropion (Wellbutrin)	MAOI use within 14 days Linezolid, methylene blue Seizure history History of anorexia/bulimia Patients undergoing abrupt discontinuation of ETOH or sedatives	Stimulant effects (tachycardia, insomnia) Headache Lowers seizure threshold	Bupropion is a substrate of CYP2B6 Bupropion inhibits CYP2D6 and may inhibit metabolism of some SSRIs, beta blockers, and haloperidol
Boxed warning for increased risk of suicidal thoughts & behaviors in pediatric and young adult patients			

ATYPICAL ANTIDEPRESSANT CLINICAL USE

Trazodone/Nefazodone

- Major depressive disorder
- Insomnia (off-label)

Mirtazapine

- Major depressive disorder

Bupropion

- Major depressive disorder
  - May have less sexual adverse effects
- Seasonal affective disorder
- Smoking cessation

BIPOLAR

SELECTED DRUG CLASSES FOR BIPOLAR

Classic Drug	Newer Drugs	
Lithium	Aripiprazole, asenapine, carbamazepine, cariprazine, clonazepam, iloperidone	Lurasidone, olanzapine, quetiapine, valproate, ziprasidone, others

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LITHIUM

LITHIUM MECHANISM OF ACTION

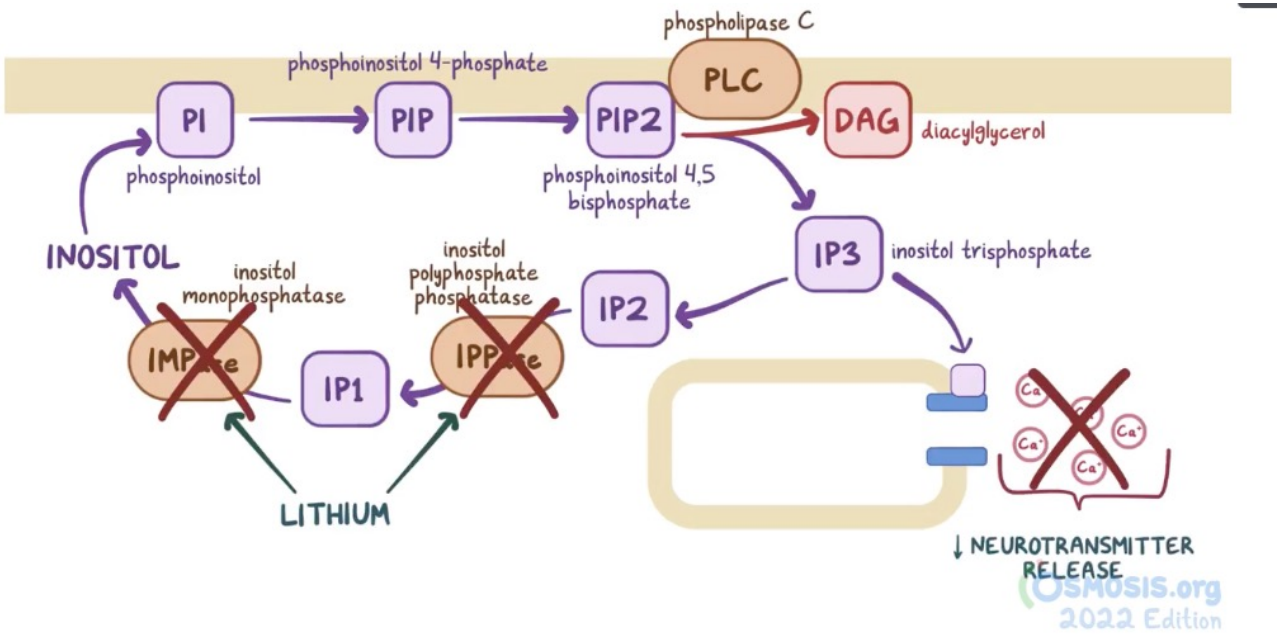
Not well defined

May regulate release of neurotransmitters

Possibly related to inhibition of phosphoinositol cascade

- Inositol → PI → PIP → PIP2 → IP3 or DAG
- IP3 soluble and diffuses through the cytoplasm into the ER
  - Opens calcium channels to released stored calcium in the cytoplasm and triggers release of neurotransmitters into synaptic cleft
- IP3 is then recycled back to inositol
  - Mediated by inositol IPPase and IMPase, which require magnesium as a co-factor
  - Lithium displaces magnesium and IP3 does not get recycled back into inositol
    - Decreased neurotransmitter release

LITHIUM MECHANISM OF ACTION



LITHIUM

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Lithium	Significant renal impairment Sodium depletion Dehydration Significant cardiovascular disease <u>Cautions:</u> Narrow therapeutic window Psoriasis	Nausea/vomiting Tremor Blocks TSH from binding to receptor → hypothyroidism (weight gain, cold sensitivity, slower heart rate) Mild hypercalcemia Blocks ADH → Polyuria (nephrogenic diabetes insipidus) Leukocytosis Teratogenesis (Ebstein anomaly) Weight gain	↑ lithium levels: thiazide diuretics, ACEIs, tetracycline, metronidazole ↓ lithium levels: potassium-sparing diuretics, SGLT2 inhibitors, theophylline, caffeine, May ↑ or ↓ lithium levels: loop diuretics, calcium channel blockers

Boxed warning for lithium toxicity

EBSTEIN ANOMALY

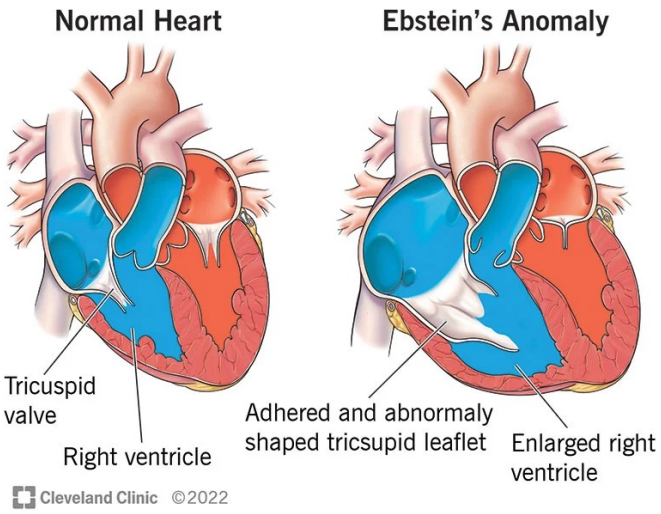


Image credit: Cleveland Clinic

ACTIVE LEARNING

What is therapeutic index?

What does it mean if the therapeutic index of a medication is high?

What does in mean if the therapeutic index of a medication is low?

THERAPEUTIC INDEX

Measure of drug safety

- Drug with a higher therapeutic index is safer than one with a low therapeutic index
- Can use lethal dose or toxic dose
  - The toxic dose is the dose that is toxic to 50% of those that receive it
  - The lethal dose is the dose that is lethal to 50% of those that receive it

$$Therapeutic\ Index = \frac{median\ toxic\ dose}{median\ effective\ dose} = \frac{TD_{50}}{ED_{50}}$$

ADME & CLINICAL USE

ADME

Half-life ~20 hours

Almost exclusively excreted by kidneys

Plasma levels should be monitored

- Acute symptoms: 0.8 – 1.2 mEq/L
- Maintenance: 0.4. – 0.7 mEq/L
- Plasma levels may be altered by changes in total body water

Clinical Use

Mood stabilizer for bipolar disorder

Treats acute manic episodes

Prevents mania relapses

LITHIUM TOXICITY

Acute renal failure

Severe neurological symptoms (ataxia)

Confusion

Dysarthria (inability to speak clearly)

Coma

Death

SCHIZOPHRENIA

SELECTED DRUG CLASSES FOR SCHIZOPHRENIA

Antipsychotics

Typical (Classical)
D2 >>>5HT2 affinity

- High Potency
  - Haloperidol, trifluoperazine, fluphenazine
- Low Potency
  - Thioridazine, chlorpromazine,

Atypical (Newer)

- Aripiprazole, asenapine, carbamazepine, cariprazine, clozapine, iloperidone
- Olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, others

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TYPICAL (CLASSICAL) ANTIPSYCHOTICS

DOPAMINE HYPOTHESIS & TYPICAL ANTIPSYCHOTICS

Does not fully explain schizophrenia

Proposes schizophrenia caused by **relative excess of DA** functional activity

- Increased density of DA receptors in prefrontal cortical brain regions of untreated individuals with schizophrenia

Many antipsychotic drugs block brain DA receptors (D2)

DA agonist drugs (amphetamine, levodopa) exacerbate schizophrenia

DOPAMINE

Five different DA receptors (D1-D5); GPCRs with 7 transmembrane domains

Receptor Type	Receptor Mechanisms	Relevant Drugs
D2	Inhibitory (presynaptic); ↓ Ca2+ conductance Inhibitory (postsynaptic); ↑ K+ conductance; ↓ cAMP	Blocked by phenothiazines and haloperidol

SALIENT PHYSIOLOGY RELATED TO PHARM

Dopaminergic Tract in Brain	Responsibilities	Effect of DA Receptor Blockade
Mesocortical-mesolimbic	Mentation, mood, behavior	Antipsychotic effects
Nigrostriatal tract	Coordination of voluntary movement (motor neurons that bypass the medullary pyramids)	Extrapyramidal dysfunction
Tuberoinfundibular pathway	Inhibits prolactin release from anterior pituitary	Hyperprolactinemia
Chemoreceptor trigger zone	Nausea, vomiting	Block nausea, vomiting

TYPICAL ANTIPSYCHOTIC MECHANISM OF ACTION

Block dopamine D2 receptors

- Mesolimbic system
  - High levels of DA in mesolimbic system in schizophrenia → "positive symptoms"
    - Hyperactivity, bizarre ideation, hallucinations, delusions
  - Blocking DA receptors **alleviates positive symptoms** of schizophrenia
- Mesocortical system
  - May be low levels of DA in mesocortical system in schizophrenia → "negative symptoms"
    - Emotional blunting, social withdrawal, lack of motivation
  - Blocking DA receptors **may worsen negative** symptoms of schizophrenia

TYPICAL ANTIPSYCHOTIC MECHANISM OF ACTION

Many also block

- Alpha-1 adrenergic receptors → orthostatic hypotension
- Histamine (H1) receptors → sedative, antipruritic
- Muscarinic receptor inhibition → anticholinergic (atropine-like) side effects such as dry mouth, blurred vision, urinary retention, constipation

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NOTABLE ADVERSE EFFECTS OF TYPICAL ANTIPSYCHOTICS

REVERSIBLE NEUROLOGIC EFFECTS

EXTRAPYRAMIDAL EFFECTS (PARKINSON-LIIKE SX)

TARDIVE DYSKINESIAS

AUTONOMIC EFFECTS

BLOCKADE OF PERIPHERAL MUSCARINIC & ALPHA-1 RECEPTORS

ENDOCRINE AND METABLOIC EFFECTS

HYPERPROLACTINEMIA, GYNECOMASTIA, AMENORRHEA-GALACTORRHEA SYNDROME, INFERTILITY

NEUROLEPTIC MALIGNANT SYNDROME

SEDATION

EXTRAPYRAMIDAL SYMPTOMS

Hours to Days

- Dystonia
  - Muscle spasms
  - Oculogyric crisis

Days to Weeks

- Neuroleptics malignant syndrome

Days to Months

- Akathisia
  - Restlessness and urge to move the limbs
- Pseudoparkinsonism

Months to Years

- Tardive dyskinesia
  - Constant, involuntary, rhythmic movements

Reversible

Irreversible

NEUROLEPTIC MALIGNANT SYNDROME

Result of rapid blockade of postsynaptic DA receptors

Associated with

- Antipsychotic drugs
- Antiemetic drugs
- Levodopa or dopamine agonist medication withdrawal

Symptoms

- Confusion, coma, agitation, muscle rigidity, seizures, hyperthermia (similar to serotonin syndrome)
- Hyporeflexia, normal pupils (unlike serotonin syndrome)
- Rhabdomyolysis

NEUROLEPTIC MALIGNANT SYNDROME TREATMENT

Life threatening

Treatment

- Stop causative agent
- Dantrolene (direct-acting skeletal muscle relaxant)
- Diazepam (seizures, agitation, muscle relaxation)
- DA agonists such as bromocriptine (restore lost dopaminergic tone)
  - Amantadine, levodopa

TYPICAL (CLASSICAL) ANTIPSYCHOTICS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Chlorpromazine Fluphenazine Haloperidol Thioridazine Trifluoperazine	Use of CNS depressants Anticholinergic medications Severe cardiac abnormalities History seizure disorder Narrow angle glaucoma Tardive dyskinesia	Extrapyramidal effects Tardive dyskinesia Autonomic effects (orthostatic hypotension, tachycardia) Endocrine (hyperprolactinemia, gynecomastia) QT prolongation	Additive effects may occur when these drugs are combined with others that have sedative effects, alpha-adrenergic blocking action, anticholinergic effects

Boxed warning for increased all cause mortality in older adult patients with dementia-related psychosis

ATYPICAL ANTIPSYCHOTIC MECHANISM OF ACTION

Target multiple receptors

Most have higher affinity for other receptors than D2
- Block 5-HT2A receptors > DA D2 receptors

Mesolimbic pathway
- Block D2 receptors → alleviates positive symptoms

Mesocortical pathway
- Block 5-HT2A receptors → alleviates negative symptoms

Other receptors
- May be partial agonist at at 5-HT1A receptor
- Some antagonize alpha-1 and/or alpha-2 adrenergic receptors
- Some block muscarinic receptors
- Some block histamine receptors

ATYPICAL (NEWER) ANTIPSYCHOTICS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Aripiprazole, asenapine, carbamazepine, cariprazine, clozapine, iloperidone Olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, others	Seizure risk Withdrawal symptoms	Weight gain Hyperglycemia, T2DM Hyperlipidemia Sedation Hyperprolactinemia Neuroleptic malignant syndrome Orthostatic hypotension Sudden death Extrapyramidal symptoms and tardive dyskinesia (less than typicals) QT prolongation	Additive effects may occur when these drugs are combined with others that have alpha-adrenergic blocking action, anticholinergic effects Some interact with SSRIs Carbamazepine, valproate, phenobarbital, and phenytoin may decrease atypical antipsychotic concentrations

Boxed warning for increased all cause mortality in older adult patients with dementia-related psychosis

CLINICAL USE OF ANTIPSYCHOTICS

Schizophrenia

- Typical primarily treat positive symptoms
- Atypical primarily treat positive and negative symptoms

Disorders with concomitant psychosis (bipolar)

Tourette syndrome

OCD

Huntington disease

ACTIVE LEARNING

Compare and contrast typical and atypical antipsychotics by completing the table below.

Parameter	Typical (Classical) Antipsychotic	Atypical (Newer) Antipsychotic
Mechanism of action (consider impact on specific receptors)		
Adverse Effects (consider EPS, weight gain, sedation, etc.)		

MANAGING TOXICITIES OF ANTIPSYCHOTICS

Toxicity	Treatment	Notes
Dystonia	Antihistamines (diphenhydramine) Antimuscarinics (benztropine, trihexyphenidyl)	Muscarinic agents generally increase severity of tardive dyskinesia
Akathisia	Antimuscarinics (benztropine, trihexyphenidyl) Beta-blocker (propranolol)	
Tardive dyskinesia	Discontinue medication Withdrawal of antimuscarinics Injection of botulinum toxin for facial dyskinesia	Irreversible Atypical antipsychotics usually cause fewer EPSs than typical antipsychotics
Parkinsonism	Drugs for Parkinson's including: • Antimuscarinics (benztropine, trihexyphenidyl) • Amantadine • Dopamine agonists • Levodopa	

MANAGING TOXICITIES OF ANTIPSYCHOTICS

Toxicity	Treatment	Notes
Hyperprolactinemia	Consider switching antipsychotic (risperidone strongly associated with hyperprolactinemia) Dopamine agonists Metformin	DA normal inhibitory regulator of prolactin secretion
Neuroleptic malignant syndrome *(life threatening)*	Discontinue medication Dantrolene Diazepam DA agonists	Life threatening emergency

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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?