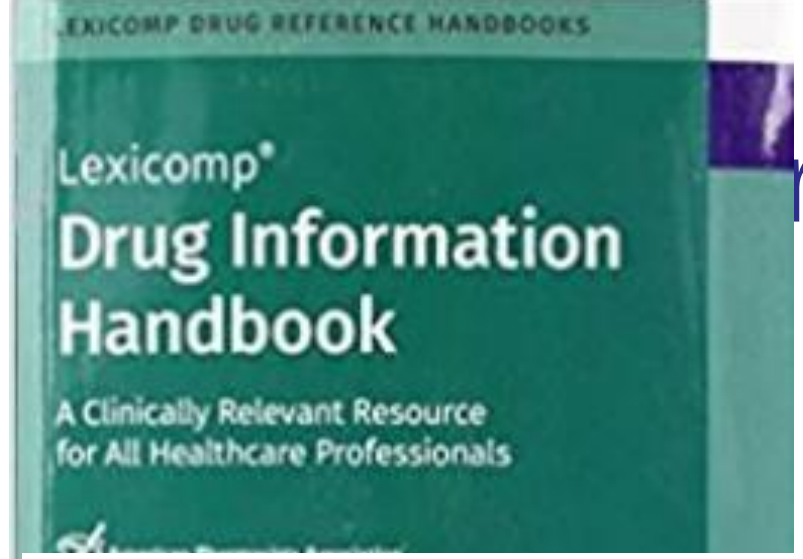
Anti-Depression Drugs
(Anti-Depressant Agents)
= Anti-Depressants

Sara Rasoul-Amini, Pharm D, PhD in Medicinal Chemistry;
Department of Medicinal Chemistry, School of Pharmacy,
Shiraz University of Medical Sciences(SUMS)- Feb2025



r Reference

The Drug Information Handbook, the flagship publication from Lexicomp, is trusted by a wide variety of healthcare professionals to deliver timely, clinically relevant pharmacotherapy knowledge.

Endorsed by the American Pharmacists Association (APhA), the Drug Information Handbook is chosen daily by healthcare professionals as their resource to help improve medication safety and enhance patient care.

This handbook follows a dictionary-like format, with drug products organized alphabetically and cross-referenced by U.S. and Canadian brand names and index terms. Healthcare professionals have access to more than 1700 drug monographs, each offering up to 48 fields of information specific to a particular medication. Supplementing the drug information is an extensive Appendix, offering helpful treatment guidelines and therapy recommendations, and a Pharmacologic Category Index.

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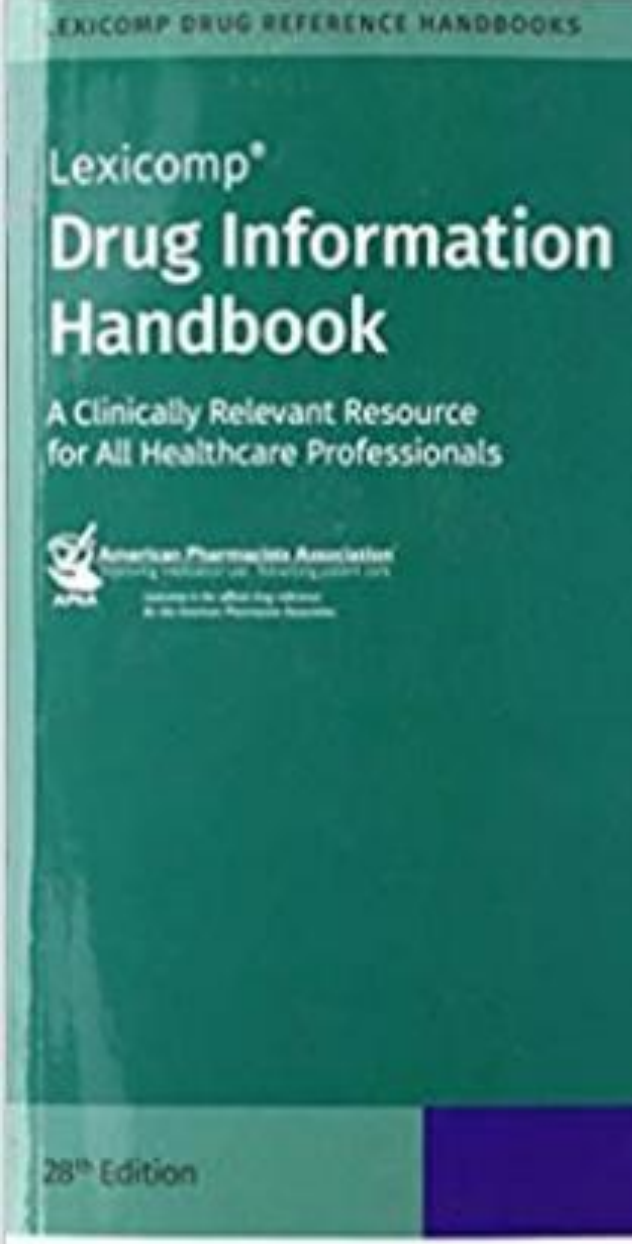

Includes:

-1745 Drug Monographs
-Up to 48 Fields of Information per Monograph
-More than 50 Pages of Appendix Information

Updates to this edition:

-65 New Drug Monographs
-6 New/Revised Monograph Fields
-Dosing: Renal Impairment: Adult
-Dosing: Hepatic Impairment: Adult
-Dosing: Renal Impairment: Pediatric
-Dosing: Hepatic Impairment: Pediatric
-6 Updated Appendix Topics
-Immunization Schedules
-Immunization Administration Recommendations
-Opioid Conversion Table and Morphine Equivalent Dose Table
-Oral Anticoagulant Comparison Chart

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Monograph Template for This File Following Lexi's Format

- Title: pharmacologic classification (pharmacologic category)
- Generic name
- Brand/Trade name/s
- Dosage form/s: tab.; cap.; inj.
- Mechanism Of Action (MOA)
- ✓ Labeled & un-labeled use (indication)
- ✓ Administration
- Metabolism
- Drug-Drug Interactions
- Avoid concomitant use
- Side effect/s
- Monitoring
- Company names:

Followed Monograph Format in This Course

Generic Name		**Chemical Structure**	**نام ژنریک دارو**
Trade Name			**نام / های تجاری رایج**
Available Market Dosage Forms (Iran/ International Market)			**فرم های دارویی موجود در ایران/جهان**
Any Particular Point in the Available Dosage Form			**نکته قابل توجه درباره فرمولاسیون رایج**
Stability			**پایداری فرم دارویی**
Pharmacologic Category			**دسته فارماکولوژیکی**
Mechanism of Action			**مکانیسم عمل**
Labeled Use			**کاربرد درمانی اصلی**
Unlabeled Use			**کاربرد درمانی فرعی**
Administration			**نحوه مصرف (تجویز)**
Onset of action			**شروع اثر**
Metabolism			**متابلیسم**
Minimum Efficient Dose			**حداقل دوز موثر**
Maximum Efficient Dose			**حداکثر دوز موثر**
Monitoring			**مانیتورینگ (پایش)**
Pregnancy Limitations			**محدودیت مصرف در بارداری**

Neurotransmitter Deficiency Syndromes

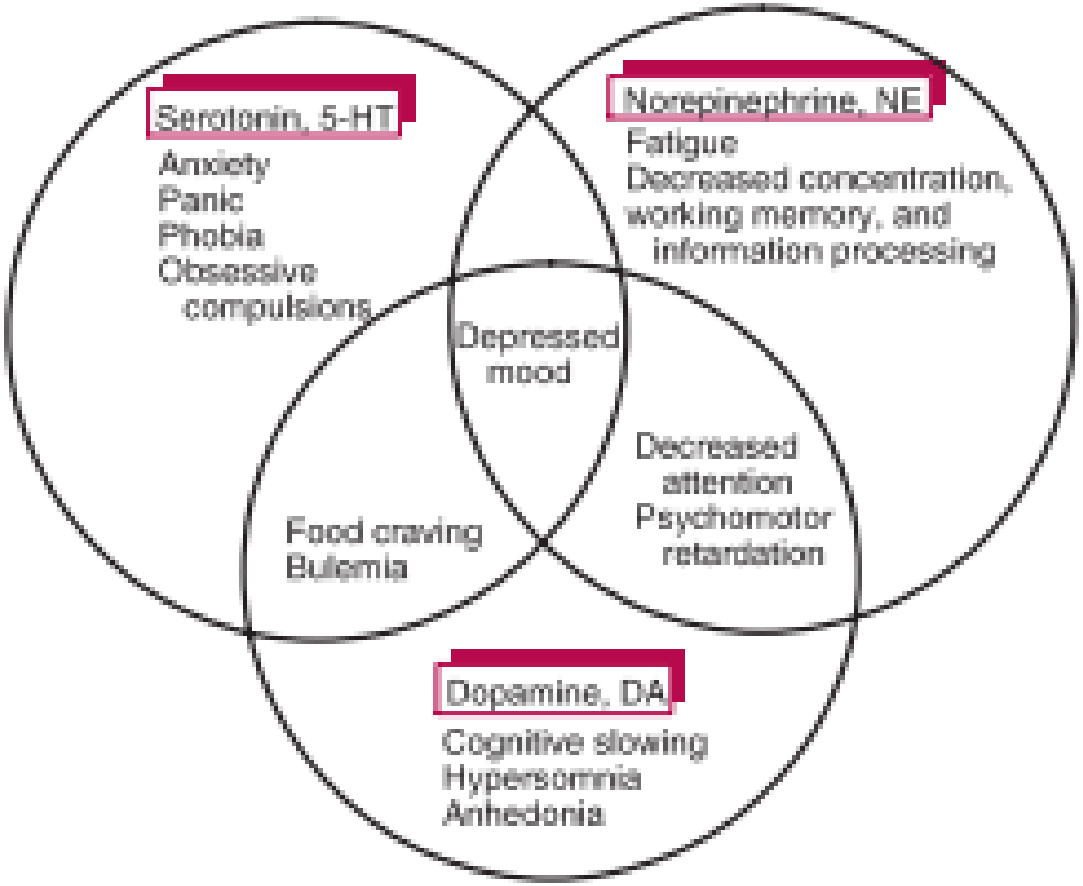
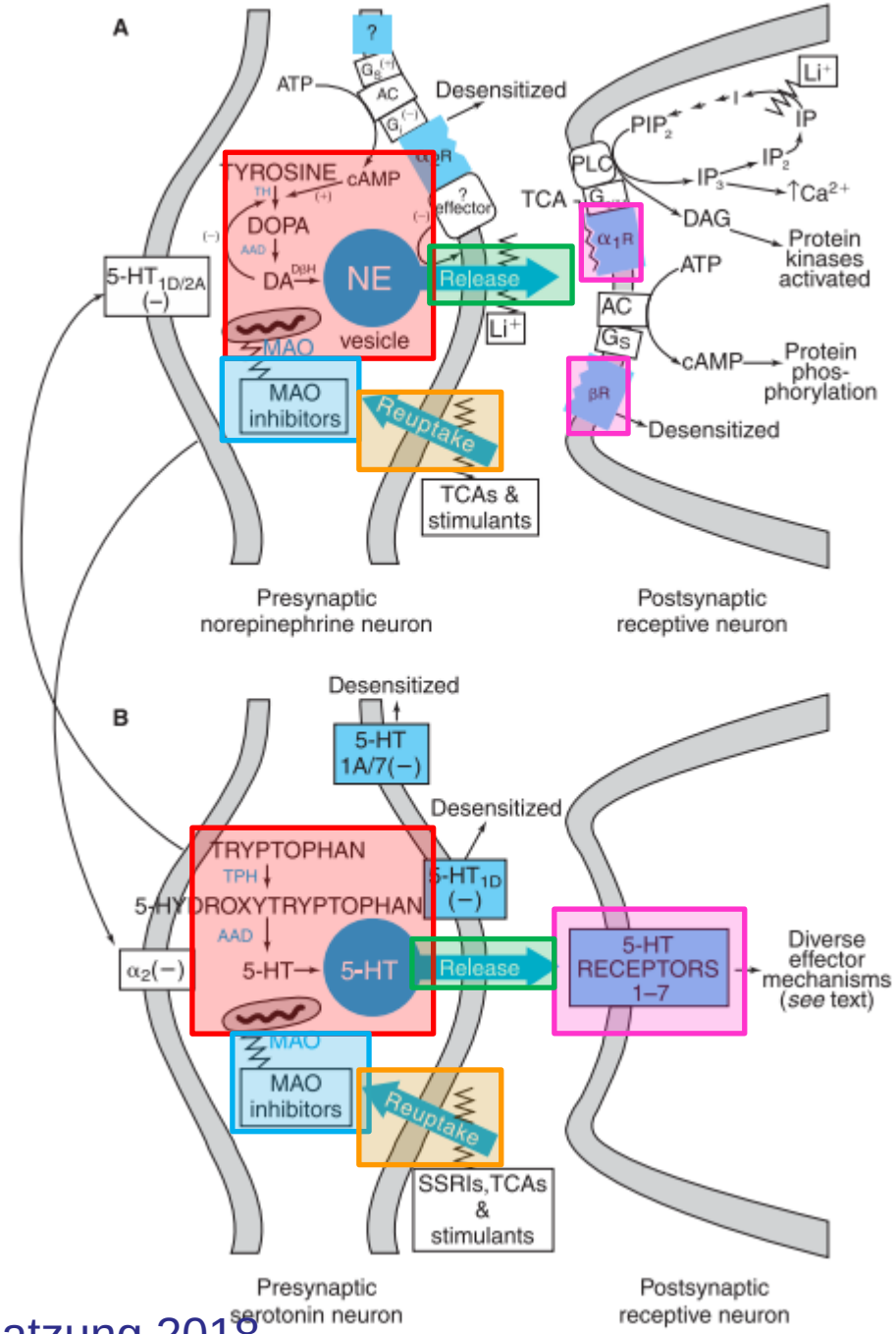


Figure 11.25 Neurotransmitter deficiency syndromes and their interactions.



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Synthesis

Metabolism

Release

Postsynapthic Effect

Presynapthic Reuptake

FIGURE 17–1 ***Sites of action of antidepressants. A.*** In varicosities ("terminals") of norepinephrine (NE) neurons projecting from brainstem to forebrain, L-tyrosine is oxidized to dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase (TH), then decarboxylated to dopamine (DA) by aromatic L-amino acid decarboxylase (AAD) and stored in vesicles, where side-chain oxidation by dopamine β-hydroxylase (DβH) converts DA to NE. Following exocytotic release by depolarization in the presence of Ca^{2+} (inhibited by lithium), NE interacts with postsynaptic α and β adrenergic receptor (R) subtypes as well as presynaptic α_2 autoreceptors. Regulation of NE release by α_2 receptors is principally through attenuation of Ca^{2+} currents and activation of K^+ currents. Inactivation of trans-synaptic communication occurs primarily by active transport ("reuptake") into presynaptic terminals (inhibited by most tricyclic antidepressants [TCAs] and stimulants), with secondary deamination (by mitochondrial monoamine oxidase [MAO], blocked by MAO inhibitors). Blockade of inactivation of NE by TCAs initially leads to α_2 receptor–mediated inhibition of firing rates, metabolic activity, and transmitter release from NE neurons; gradually, however, α_2 autoreceptor response diminishes and presynaptic activity

Sites of Action for Antidepressants

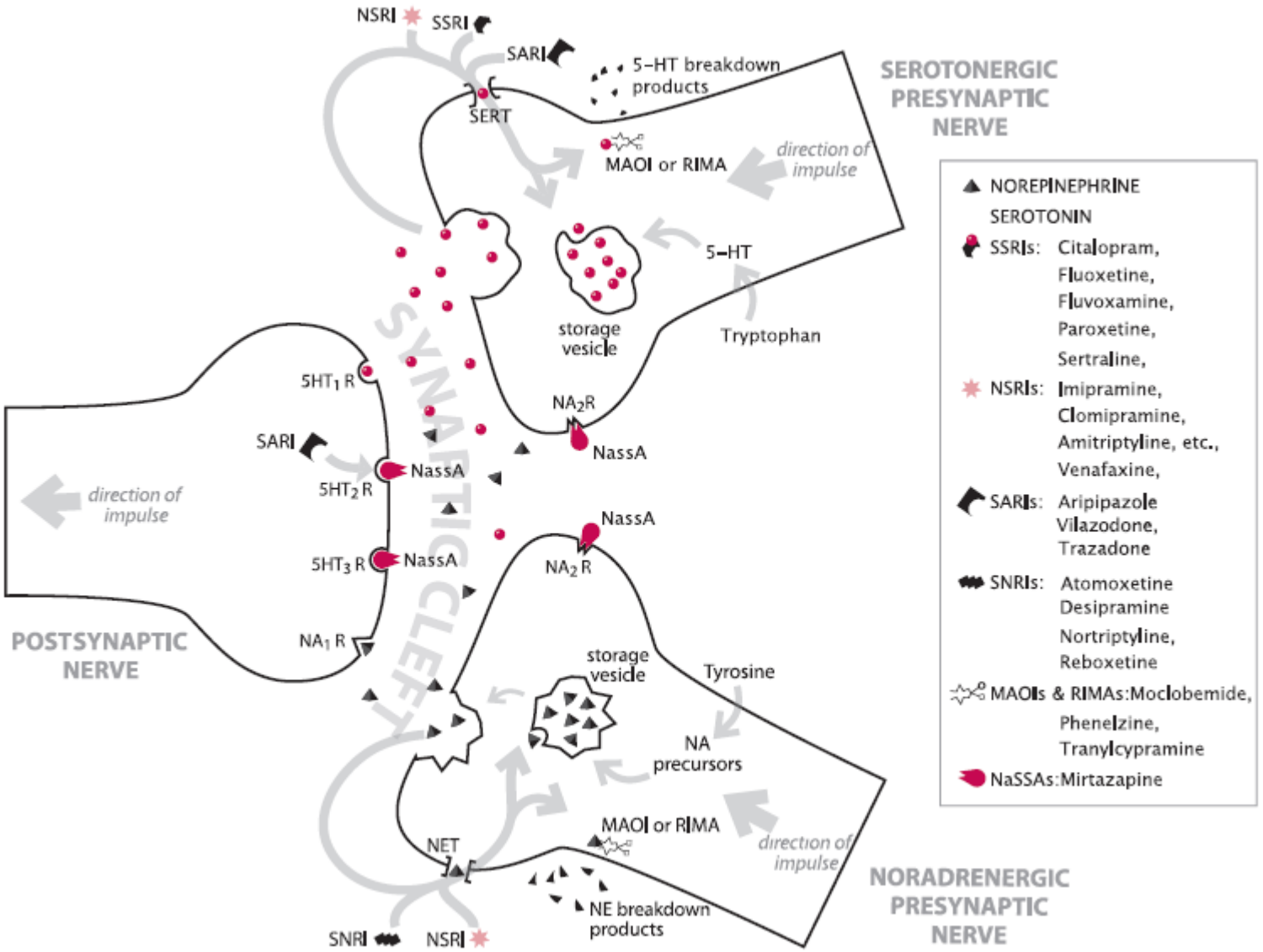

FIGURE 18.3 Sites of action of the antidepressants.

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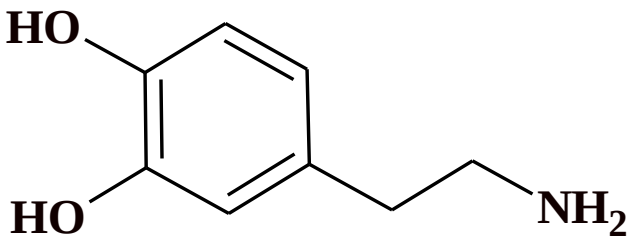
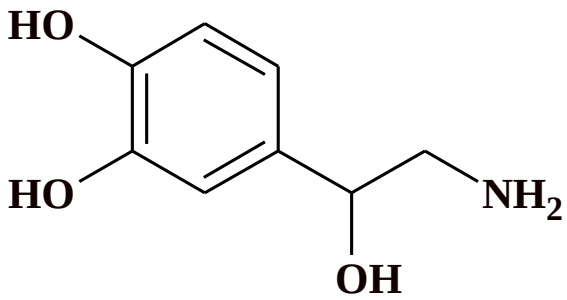
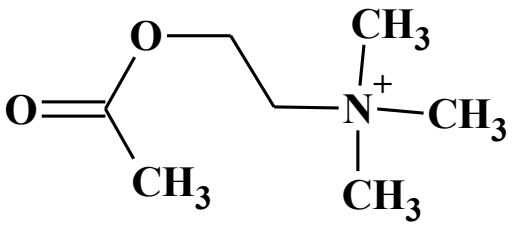
Mono-Amines Neurotransmitters (NTs) in Nervous System



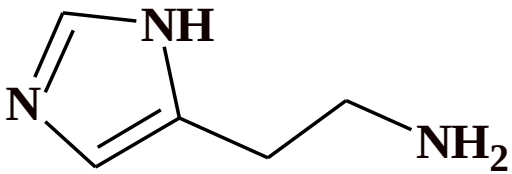
Dopamine



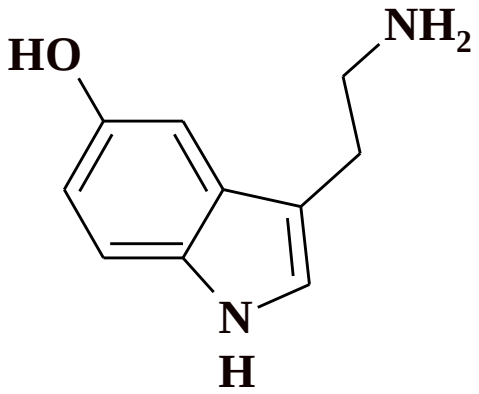
NorEpinephrine



Acetylcholine



Histamine



Serotonin

Correlation of Pharmacologic & Chemical Classification of Antidepressants

- Selective Ser Reuptake Inhibitors (SSRIs): non-TCA
- Selective NE Reuptake Inhibitors (SNRIs): non-TCA; TCA
- NE & Ser Reuptake Inhibitors (NSRIs): non-TCA; TCA
- Dop & NE Reuptake Inhibitors (DNRIs)
- Ser Receptor Modulators & Stimulators (SMSs):

✓ Noradrenergic & Specific Ser Antidepressants (NaSSAs)

✓ Ser Antagonists / Reuptake Inhibitors (SARIs)

- MonoAmine Oxidase Inhibitors (MAOIs)
- Ser precursors & providers
- Mood stabilizers
- Melatonergic agonist / Ser antagonist

TABLE 30–2 Blocking effects of some antidepressant drugs on several receptors and transporters.

Antidepressant	ACh M	α_1	H_1	5-HT_2	NET	SERT
Amitriptyline	+++	+++	++	0/+	+	++
Amoxapine	+	++	+	+++	++	+
Bupropion	0	0	0	0	0/+	0
Citalopram, escitalopram	0	0	0		0	+++
Clomipramine	+	++	+	+	+	+++
Desipramine	+	+	+	0/+	+++	+
Doxepin	++	+++	+++	0/+	+	+
Fluoxetine	0	0	0	0/+	0	+++
Fluvoxamine	0	0	0	0	0	+++
Imipramine	++	+	+	0/+	+	++
Maprotiline	+	+	++	0/+	++	0
Mirtazapine	0	0	+++	+	+	0
Nefazodone	0	+	0	++	0/+	+
Nortriptyline	+	+	+	+	++	+
Paroxetine	+	0	0	0	+	+++
Protriptyline	+++	+	+	+	+++	+
Sertraline	0	0	0	0	0	+++
Trazodone	0	++	0/+	++	0	+
Trimipramine	++	++	+++	0/+	0	0
Venlafaxine	0	0	0	0	+	++
Vortioxetine[1]	ND	ND	ND	ND	+	+++

[1] Vortioxetine is an agonist or partial agonist at 5-HT_{1A} and 5-HT_{1B} receptors, an antagonist at 5-HT_3 and 5-HT_7 receptors, and an inhibitor of SERT.

ACh M, acetylcholine muscarinic receptor; α_1, alpha$_1$-adrenoceptor; H_1, histamine$_1$ receptor; 5-HT_2, serotonin 5-HT_2 receptor; ND, no data found; NET, norepinephrine transporter; SERT, serotonin transporter.

0/+, minimal affinity; +, mild affinity; ++, moderate affinity; +++, high affinity.

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Common Side Effects of Antidepressants

TABLE 33.2 Common Side Effects of Therapeutic Doses of Antidepressants

Agent	Sedation	Anticholinergic	Orthostasis	Weight Gain	Sexual Dysfunction
SSRIs	+/−	0	0	+/−	+++
TCAs	+++	+++	+++	++	++
Miscellaneous					
Trazodone	+++	0	++	++	+[a]
Bupropion	0	0	0	0	0
Nefazodone	++	0	0	0	0
Venlafaxine	+/-	0	0[b]	0	++
Mirtazapine	++	0	0	++	0
MAOIs	0	+	+++	++	+

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor.
0, no effect; +, + +, +++ indicate increasing effect.
[a]Priapism.
[b]Venlafaxine can cause a dose-dependent increase in blood pressure.

SEs:

Sedation Anticholinergic Weight gain Sexual dysfunction

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TABLE 30–1 Pharmacokinetic profiles of selected antidepressants.

Class, Drug	Bioavailability (%)	Plasma $t_{1/2}$ (hours)	Active Metabolite $t_{1/2}$ (hours)	Volume of Distribution (L/kg)	Protein Binding (%)
SSRIs					
Citalopram	80	33–38	ND	15	80
Escitalopram	80	27–32	ND	12–15	80
Fluoxetine	70	48–72	180	12–97	95
Fluvoxamine	90	14–18	14–16	25	80
Paroxetine	50	20–23	ND	28–31	94
Sertraline	45	22–27	62–104	20	98
SNRIs					
Duloxetine	50	12–15	ND	10–14	97
Milnacipran	85–90	6–8	ND	5–6	13
Venlafaxine[1]	45	8–11	9–13	4–10	27
Tricyclics					
Amitriptyline	45	31–46	20–92	5–10	90
Clomipramine	50	19–37	54–77	7–20	97
Imipramine	40	9–24	14–62	15–30	84
5-HT modulators					
Nefazodone	20	2–4	ND	0.5–1	99
Trazodone	95	3–6	ND	1–3	96
Vortioxetine	75	66	ND	ND	98
Tetracyclics and unicyclic					
Amoxapine	ND	7–12	5–30	0.9–1.2	85
Bupropion	70	11–14	15–25	20–30	85
Maprotiline	70	43–45	ND	23–27	88
Mirtazapine	50	20–40	20–40	3–7	85
Vilazodone	72	25	ND	ND	ND
MAOIs					
Phenelzine	ND	11	ND	ND	ND
Selegiline	4	8–10	9–11	8–10	99

[1]Desvenlafaxine has similar properties but is less completely metabolized.

MAOIs, monoamine oxidase inhibitors; ND, no data found; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

Katzung 2018

Common Comments in Prescribing Anti-Depressants

- Tapering start & stop
- Daily time of administration: morning, midday or night.
- Pregnancy & lactation
- Cautions for:

✓ co-administration of neurotransmitter related drugs: Ser syndrome

✓ co-administration of supplement including Trp related ingredients

✓ co-administration of nutraceuticals including valerian, ..

- Free interval within administration of MAOIs
- Interaction to alcohol & alcoholic products

TABLE 83.1 **Selected Medical Conditions that May Mimic Depression**
CENTRAL NERVOUS SYSTEM
Alzheimer disease
Cerebrovascular accident
Epilepsy
Multiple sclerosis
Parkinson disease
CARDIOVASCULAR
Cerebral arteriosclerosis
Congestive heart failure
Myocardial infarction
ENDOCRINE
Addison disease
Diabetes mellitus (types 1 and 2)
Hypothyroidism
WOMEN'S HEALTH
Premenstrual dysphoric disorder
Antepartum/postpartum
Perimenopause
OTHER
Chronic fatigue syndrome
Chronic pain syndrome(s)
Fibromyalgia
Irritable bowel syndrome
Malignancies (various)
Migraine headaches
Rheumatoid arthritis
Systemic lupus erythematosus

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TABLE 83.2 **Selected Medications that May Induce Depression**
CARDIOVASCULAR AGENTS
β-Blockers[a] (?)
Clonidine
Methyldopa
Reserpine
CENTRAL NERVOUS SYSTEM
Barbiturates
Chloral hydrate
Ecstasy (MDMA)
Ethanol
Varenicline
HORMONAL AGENTS
Anabolic steroids
Corticosteroids
Gonadotropin-releasing hormone
Progestins
Tamoxifen
OTHERS
Efavirenz
Interferon
Isotretinoin
Mefloquine
Levetiracetam

[a]Lipophilic β-blockers (e.g., propranolol) may have higher risk but data are conflicting.

TABLE 83.7 **Complementary and Alternative Medicine Treatments for Depression**

Treatment Regimen	Efficacy	Toxicity	Dosing	Drug Interactions	Other Health Benefits
St. John's wort	Monotherapy: superior to placebo, comparable to antidepressants; best studied for mild–moderate depression Augmentation: no data available	Agitation, mania, sun sensitivity	900 mg PO daily (divided)	CYP3A4 inducer; weak evidence of 5-HT syndrome	—
S-Adenosyl-L-Methionine	Monotherapy: superior to placebo, comparable to antidepressants Augmentation: superior to placebo	Nausea, skin rashes, hypoglycemia, theoretical ↑ homocysteine levels	800–1,600 mg PO daily	One probable case of 5-HT syndrome (with clomipramine)	Osteoarthritis
Omega-3 Fatty Acids	Monotherapy: limited data available Augmentation: majority of trials positive	Fishy taste, regurgitation	1–2 g PO daily (EPA + DHA)	None	↓ CV risk; ↓ risk of obstetric complications
Folate	Monotherapy: no evidence available Augmentation: limited number of studies but positive results (especially in women); Methylfolate preferred due to superior CNS penetration (?)	Well tolerated; may mask pernicious anemia	Folic acid: 200–500 mg PO daily Methylfolate: 15–50 mg PO daily	None	Other health benefits: ↓ risk of pregnancy complications; reverse folate deficiency

5-HT, serotonin; CNS, central nervous system; CV, cardiovascular; CYP, cytochrome P-450; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PO, orally.

Source: Adapted with permission from Freeman MP et al. Complementary and alternative medicine in major depressive disorder: the American Psychiatric Association Task Report. *J Clin Psychiatry*. 2010;71:669.

Factors to Consider in Selecting an Anti-Depressant

TABLE 83.8 **Factors to Consider in Selecting an Antidepressant**

- History of prior response (personal or family member)
- Safety in overdose
- Adverse effect profiles
- Patient age
- Concurrent medical/psychiatric conditions
- Concurrent medications (e.g., potential for drug interactions)
- Convenience (e.g., minimal titration, once-daily dosing)
- Cost
- Patient preference

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TABLE 83.9 **Pharmacology of Antidepressant Medications**

Medication	Serotonin	Norepinephrine	Dopamine	Bioavailability (Oral)	Protein Binding	Half-Life (hours) (Active Metabolite)
SELECTIVE SEROTONIN REUPTAKE INHIBITORS						
Fluoxetine	++++	0/+	0	80%	95%	24–72 (146)
Sertraline	++++	0/+	+	>44%	95%	26 (66)
Paroxetine	++++	+	0	64%	99%	24
Citalopram	++++	0	0	80%	<80%	33
Escitalopram	++++	0	0	80%	56%	27–32
SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS						
Venlafaxine	++++	+++	0	92%	25%–29%	4 (10)
Desvenlafaxine	+++	+++	0	80%	30%	11 (0)
Duloxetine	++++	++++	0	50%	>90%	12 (8–17)
NOREPINEPHRINE REUPTAKE INHIBITORS						
Bupropion	0/+	+	+	>90%	85%	10–21
TRICYCLIC ANTIDEPRESSANTS						
Desipramine	+	++++	0/+	51%	90%	12–28
Nortriptyline	++	+++	0	46%–56%	92%	18–56
Amitriptyline	++++	++++	0	37%–49%	95%	9–46 (18–56)
Imipramine	+++	++	0/+	19%–35%	95%	6–28 (12–28)
Doxepin	+++	+	0	17%–37%	68%–85%	11–23
OTHERS						
Mirtazapine	+++	++++	0	50%	85%	20–40

0, negligible; +, very low; ++, low; +++, moderate; ++++, high.

TABLE 83.11 **Adverse Effects of Antidepressant Medications**

Medication	Sedation	Agitation/ Insomnia	Anticholinergic Effects	Orthostasis	GI Effects (Nausea/ Diarrhea)	Sexual Dysfunction	Weight Gain
SELECTIVE SEROTONIN REUPTAKE INHIBITORS							
Fluoxetine	+	++++	0/+	0/+	++++	++++	+
Sertraline	+	+++	0/+	0	+++	+++	+
Paroxetine	+++	++	++	0	+++	++++	+++
Citalopram	++	++	0/+	0	+++	+++	+
Escitalopram	+	++	0/+	0	+++	+++	+
SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS							
Venlafaxine (Effexor)	++	++	+	0	+++	+++	+
Desvenlafaxine (Pristiq)	++	++	+	+	+++	++	0/+
Duloxetine (Cymbalta)	++	++	+	0	+++	++	0/+
NOREPINEPHRINE REUPTAKE INHIBITORS							
Bupropion (Wellbutrin)	0	+++	+	0	+	0/+	0
TRICYCLIC ANTIDEPRESSANTS							
Desipramine (Norpramin)	++	+	++	+++	0/+	+	++
Nortriptyline (Pamelor)	++	+	++	++	0/+	+	++
Amitriptyline (Elavil)	++++	0/+	++++	++++	0/+	++	+++
Imipramine (Tofranil)	+++	0/+	+++	++++	0/+	++	++
Doxepin (Sinequan)	++++	0/+	++++	++++	0/+	++	++
OTHERS							
Mirtazapine (Remeron)	++++	0	++	0/+	+	0/+	+++

Management of SSRI-Induced Sexual Dysfunction

TABLE 83.14 **Management of SSRI-Induced Sexual Dysfunction**

- Patience (may improve after 2–4 weeks)
- Reduced dosage (if possible)
- Drug holidays (sertraline, paroxetine, citalopram, escitalopram only)
- Antidotes
  - Bupropion SR 150 mg daily to BID
  - Sildenafil 50–100 mg daily PRN
  - Mirtazapine 7.5–15 mg at bedtime
  - Cyproheptadine 4–12 mg PRN (1 hour prior)
  - Methylphenidate 2.5–5.0 mg daily
  - Others: yohimbine, amantadine, buspirone, gingko
- Change of antidepressants (e.g., bupropion, mirtazapine)

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TABLE 83.16 **Drug Interactions of the Cytochrome P-450 System**

Relative Rank	CYP1A2	CYP2C9/19	CYP2D6	CYP3A4
OFFENDING AGENT (INHIBITS ENZYME)				
High	Fluvoxamine	*CYP2C9*	Paroxetine	Fluoxetine (norfluoxetine)
		Fluoxetine	Fluoxetine	Fluvoxamine
		Fluvoxamine	Duloxetine	
		CYP2C19	Bupropion	
		Fluvoxamine		
Moderate	Fluoxetine	*CYP2C19*	Citalopram	
	Paroxetine	Fluoxetine	Escitalopram	
		Sertraline	Sertraline	
Low	Citalopram	*CYP2C9/19*	Venlafaxine	Citalopram
	Escitalopram	Citalopram	Mirtazapine	Escitalopram
	Sertraline	Escitalopram		Paroxetine
	Venlafaxine	Paroxetine		Sertraline
	Duloxetine	Sertraline		Venlafaxine
				Desvenlafaxine
	Bupropion	Venlafaxine		Duloxetine
OTHER INHIBITORS				
	Quinolones (ciprofloxacin, enoxacin, etc.)	Modafinil (2C9, 2C19)	Fenfluramine	Macrolides (erythromycin, clarithromycin)
	Macrolides (erythromycin, clarithromycin)	Cimetidine (2C19)	Yohimbine	Cimetidine
	Grapefruit juice	Omeprazole (2C19)	Methadone	CCB (verapamil, diltiazem)
		Imidazoles (2C9, 2C19) (ketoconazole, fluconazole)	Quinidine	Imidazoles (ketoconazole, fluconazole)
			Celecoxib	Protease inhibitors
				Grapefruit juice

Continued on following page

TABLE 83.16 **Drug Interactions of the Cytochrome P-450 System (Continued)**

Relative Rank	CYP1A2	CYP2C9/19	CYP2D6	CYP3A4
OTHER INDUCERS				
	Cigarettes Caffeine St. John's wort	St. John's wort	Modafinil Phenytoin and phenobarbital Carbamazepine Rifampin Prednisone Testosterone	St. John's wort
AFFECTED AGENT (INCREASED CONCENTRATION)				
	TCA-tertiary amines (imipramine, amitriptyline) Phenothiazines (chlorpromazine) Thiothixene Haloperidol Clozapine Olanzapine Caffeine Theophylline Propranolol Tacrine	CYP2C9 Phenytoin Tolbutamide Warfarin NSAIDs CYP2C19 TCA-tertiary amines (imipramine, amitriptyline) Citalopram Barbiturates Propranolol Omeprazole	TCA-secondary amines (desipramine, nortriptyline) Fluoxetine Paroxetine Venlafaxine Duloxetine Amphetamines Atomoxetine Risperidone Donepezil Codeine Hydrocodone Tramadol Dextromethorphan Chlorpheniramine β-Blockers (propranolol, metoprolol)	Fluoxetine Sertraline Venlafaxine Modafinil Quetiapine Ziprasidone Aripiprazole Buspirone Benzodiazepines (triazolam, alprazolam) Zolpidem Carbamazepine Donepezil CCB (verapamil, diltiazem, nifedipine) Sex hormones (estrogen) Corticosteroids Statins (lovastatin, simvastatin) Protease inhibitors Sildenafil

CCB, calcium-channel blockers; NSAIDs, nonsteroidal anti-inflammatory drugs; TCA, tricyclic antidepressant.

TABLE 83.17 **Medications Associated with Serotonin Syndrome**
MOST COMMONLY ASSOCIATED[a]
Monoamine oxidase inhibitors (selegiline, phenelzine, tranylcypromine)
COMMONLY ASSOCIATED[a]
SSRI (all) SNRI (all) Clomipramine Sibutramine
OCCASIONALLY ASSOCIATED[a]
Tramadol Meperidine Linezolid Dextromethorphan (high dose)

[a]The combination of any two medications from these categories should be strongly discouraged.

TABLE 83.18 **Foods Containing Tyramine**
HIGH AMOUNTS OF TYRAMINE[a]
Smoked, aged, or pickled meat or fish
Sauerkraut
Aged cheeses (e.g., Stilton, blue cheese)
Yeast extracts (e.g., marmite)
Fava beans
MODERATE AMOUNTS OF TYRAMINE[b]
Beer (microbrewed > commercial)
Avocados
Meat extracts
Red wines such as Chianti
LOW AMOUNTS OF TYRAMINE[c]
Caffeine-containing beverages
Distilled spirits
Chocolate
Soy sauce
Cottage and cream cheese
Yogurt and sour cream

[a]May not consume.
[b]May consume in moderation.
[c]May consume.
Source: Adapted with permission from Shulman KI et al. Dietary restriction, tyramine, and the use of monoamine oxidase inhibitors. *J Clin Psychopharmacol.* 1989;9:397.

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