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Monoamine Theory in Depression

Implications for disease and treatments

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Objectives

Identify monoamine neurobiological pathways and potential role in emotional behaviors

Review the Monoamine imbalance theory in Depression

Discuss current paradigm of treatment options and the neurobiological theories behind treatments

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Prevalence of Depression

Nearly twice as common in women than in men[1,2]

Psychiatric Comorbidities

- Obsessive compulsive disorder[3]
- Substance Abuse[2,3]

- GAD[3]
- Somatoform Disorder[3]
- Bulimia[3]

- Age of onset similar across genders[1]
  - Middle age is largest prevalence gap[1]

1. Bogren et al 2018 *Eur Arch Psychiatry Clin Neurosci* 268: 179-189.
2. Krumm et al 2017 *Psychopathology* 50: 107-124.
3. Marcus et al 2005 *J Affect Dis* 27: 141-150.
4. Brody et al 2018 *NCHS Data Brief* No 303

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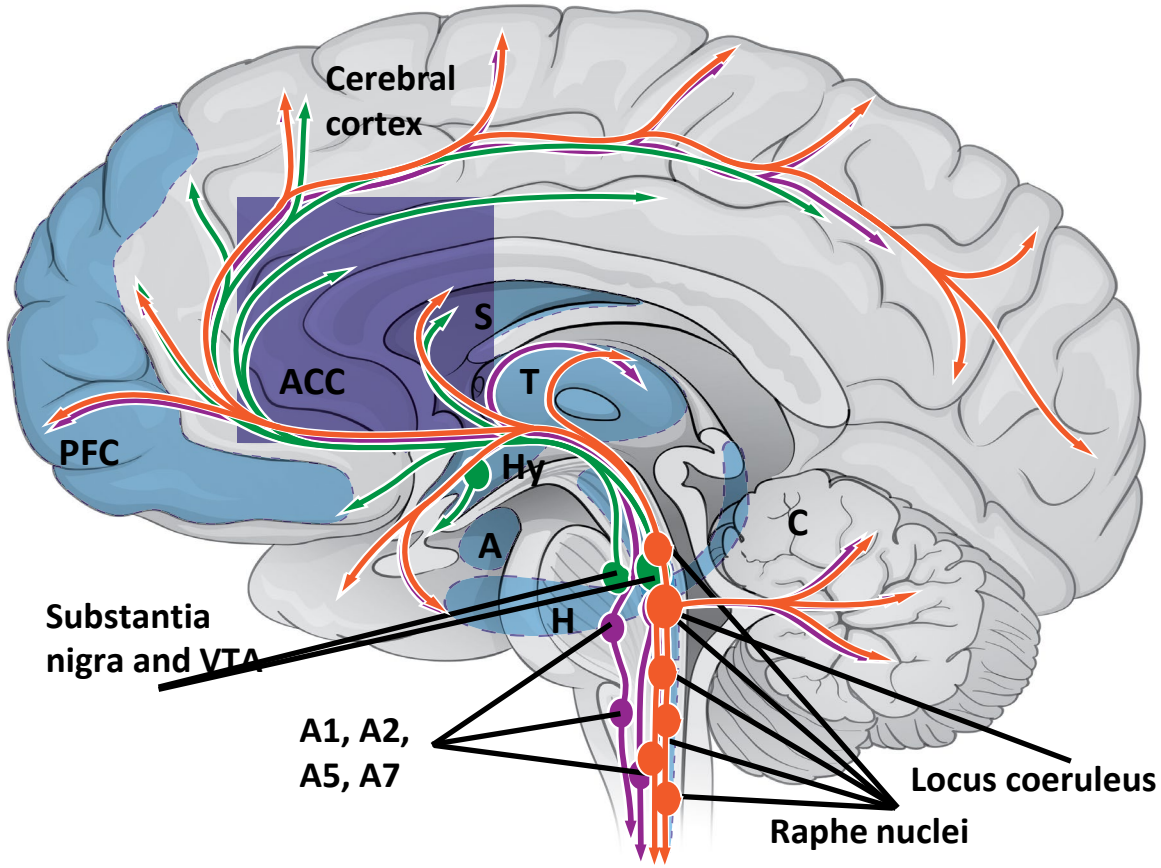
Monoamine Pathways Overlap in Several Areas of the Brain[1–8]



A = amygdala
ACC = anterior cingulate cortex
C = cerebellum
H = hippocampus
Hy = hypothalamus
NA = nucleus accumbens
PFC = prefrontal cortex
S = striatum
T = thalamus
VTA = ventral tegmental area

← Norepinephrine
← Dopamine
← Serotonin

1. Fuchs E, Flugge G. *Dialogues Clin Neurosci.* 2004;6(2):171-183.
2. Stahl SM. Chapter 7. In: Stahl SM, ed. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application*. 4th ed; 2013:284-369.
3. Jacobs BL, Azmitia EC. *Physiol Rev.* 1992;72(1):165-229.
4. Abercrombie ED, et al. *J Neurochem.* 1989;52(5):1655-1658.
5. Stanford SC. *Pharmacol Ther.* 1995;68(2):297-242.
6. Meana JJ, et al. *Biol Psychiatry*. 1992;31:471-490.
7. Garcia-Sevilla JA, et al. *J Neurochem.* 1999;72(1):282-291.
8. Roiser JP, Sahakian BJ. *CNS Spectr.* 2013;18(3):139-149.

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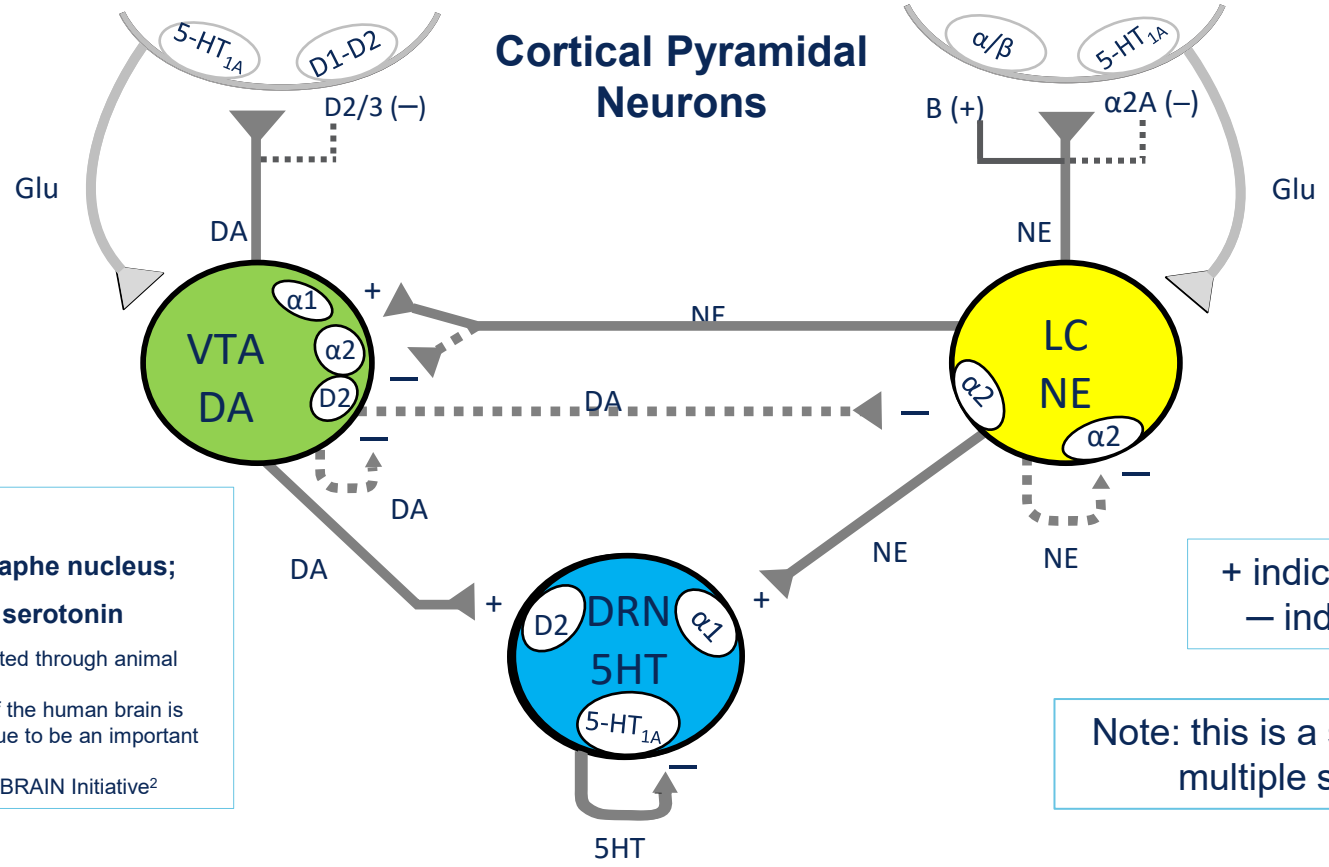
Neural Circuitry Of Monoamines Overlap



Glu = glutamate; LC = locus coeruleus;

VTA = ventral tegmental area; DRN = dorsal raphe nucleus;

NE = Norepinephrine; DA = dopamine; 5HT = serotonin

Hypothetical model of brain neural circuitry, primarily supported through animal models*[1]
*Although the exact cellular taxonomy and neural circuitry of the human brain is still being determined, animal models have been and continue to be an important contributing
factor to this effort, as discussed by members of the human BRAIN Initiative[2]

\+ indicates stimulatory effect
— indicates inhibitory effect

Note: this is a synthesis of data from multiple studies across species

1. El Mansari et al. *CNS Neurosci Ther.* 2010;16(3):e1-17.
2. Jorgenson et al. *Philos Trans R Soc Lond B Biol Sci.* 2015;370(1668):1-12.

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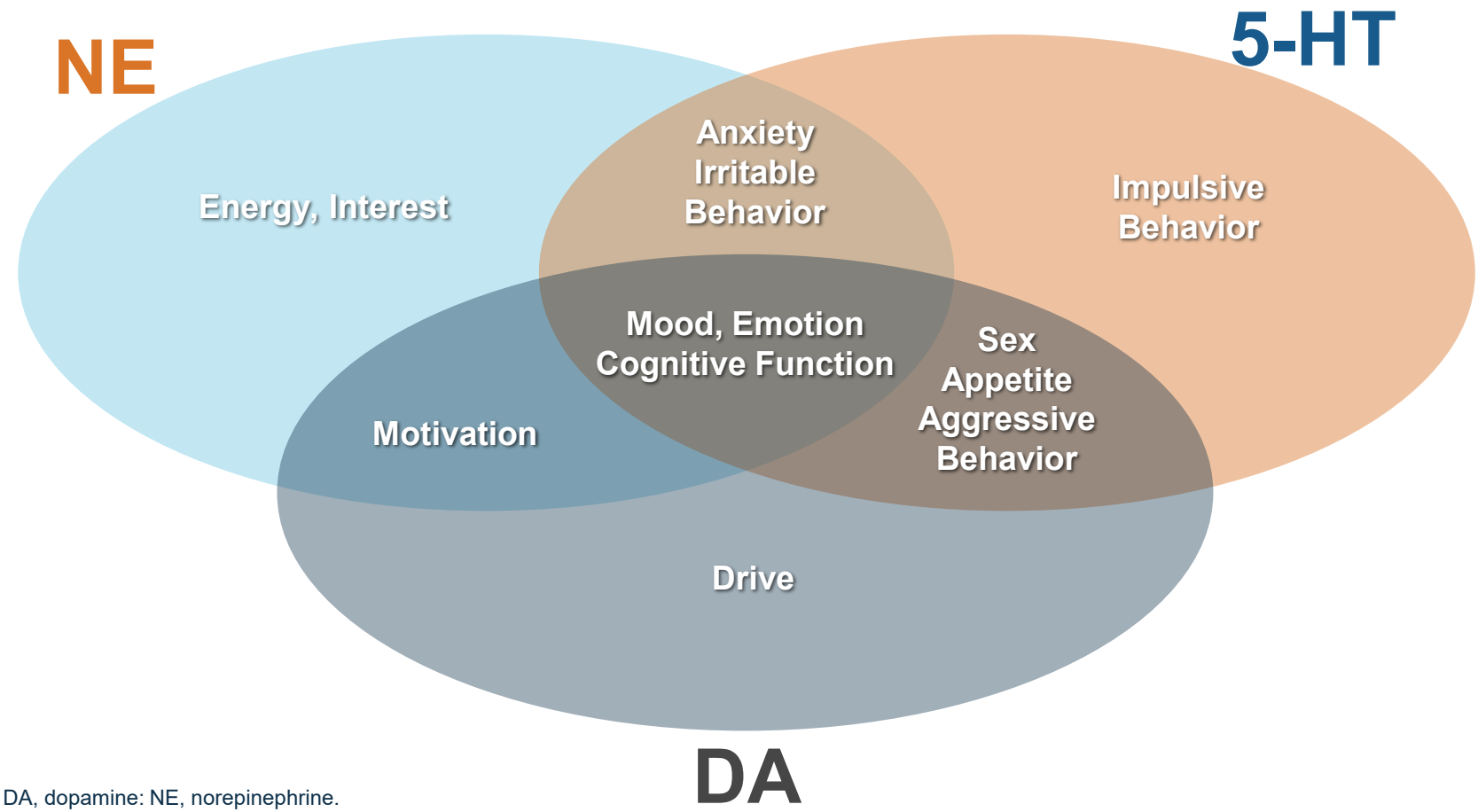
Overlap Between Monoamine Neurotransmitter Systems Plays a Role in Emotional Behavior



1. 5-HT, serotonin; DA, dopamine: NE, norepinephrine.
2. Zajecka J, et al. *J Clin Psychiatry*. 2013;74:407-414.

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Monoamine Imbalance Theory of Major Depressive Disorder (MDD)

- Imbalance theory describes patients with depression having deficient[1]:
  - Dopamine (DA),
  - Serotonin (5-HT),
  - Norepinephrine (NE)
- Monoaminergic deficiencies may be caused by depleted or dysregulated[2]:
  - Monoamine synthesis
  - Monoamine receptor signaling
- The efficacy of SSRIs, SNRIs, and dopamine agonists as antidepressants supports this theory[3]

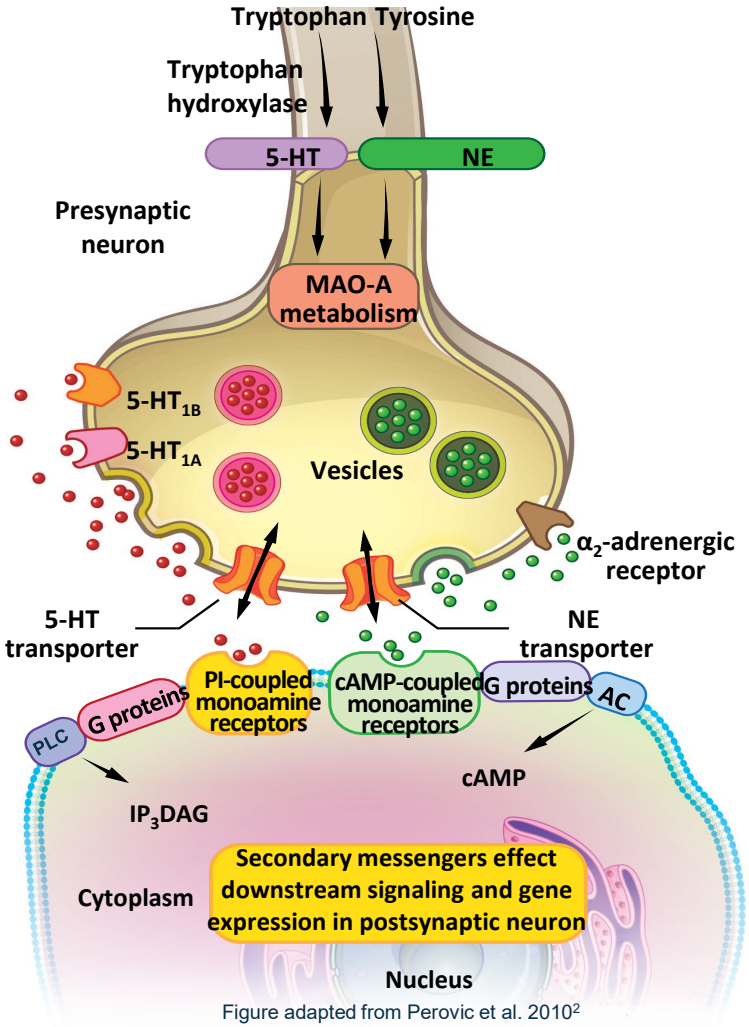

Figure adapted from Perovic et al. 2010[2]

AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; MAO-A, monoamine oxidase A; PLC, phospholipase-C; PI, phosphoinositide; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

1. Delgado PL. *J Clin Psychiatry*. 2006;67 Suppl 4:22-6.
2. Perovic B, et al. *Neuropsychiatr Dis Treat.* 2010;6:343-364.
3. Tran P, et al. *J of Psychiatric Research*. 2012;46:64-71.

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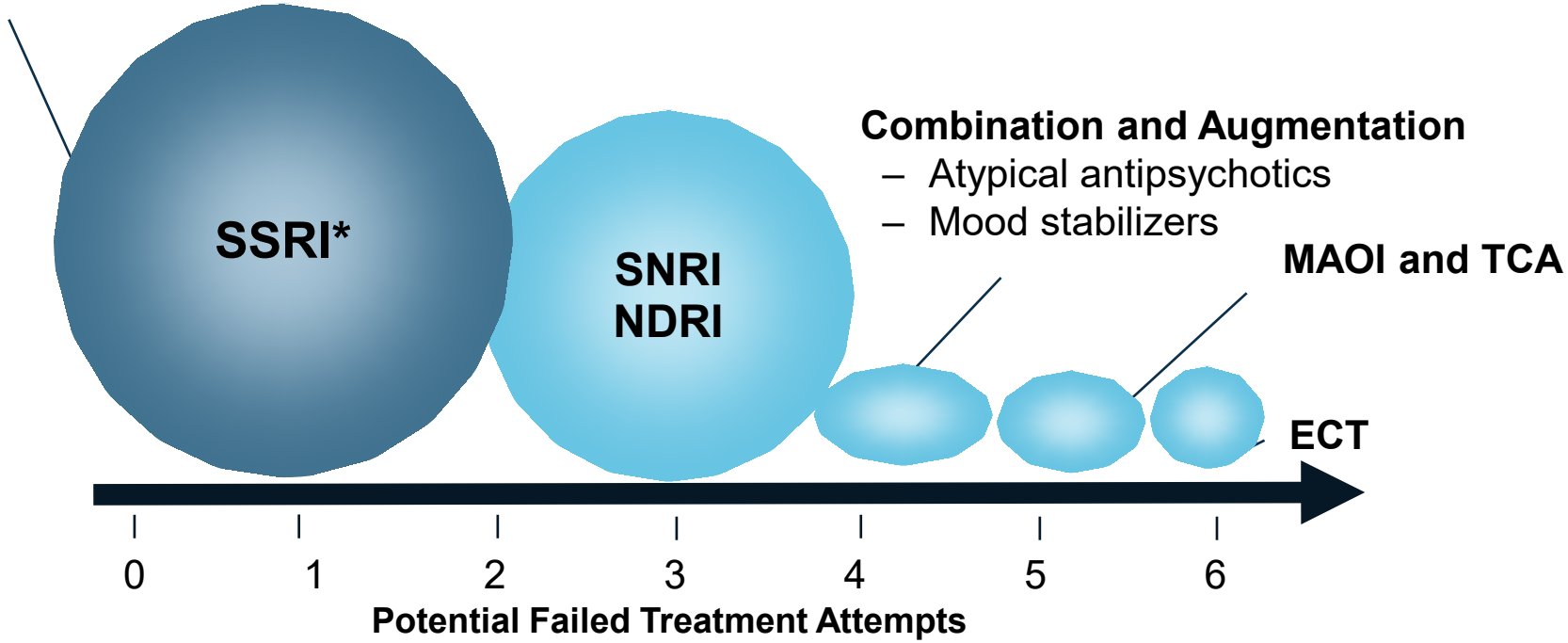
MDD: Treatment Practices

*Up to two-thirds of adult patients will not achieve remission with a selective serotonin reuptake inhibitor (SSRI); APA Guidelines recommend the first strategy when a treatment change is necessary may be to try to optimize SSRI dose

- VNS may be an additional option for individuals who have not responded to at least 4 adequate trials of antidepressant treatment, including ECT



APA=American Psychiatric Association; ECT=electroconvulsive therapy; MAOI=monoamine oxidase inhibitor; NDRI=norepinephrine-dopamine reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; VNS=vagus nerve stimulations.

1. Gelenberg AJ, et al; on behalf of the Work Group on Major Depressive Disorder. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder.* Third Edition. 2010.
2. Al-Harbi KS. *Patient Prefer Adherence.* 2012;6:369-388. 3. Nemeroff CB. *J Clin Psychiatry.* 2007;68 Suppl 8:17-25. 4. Mojtabai R, Olfson M. *J Clin Psychiatry.* 2008;69(7):1064-1074.

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Proposed Mechanisms for Antidepressant Activity[1-7]

Antidepressants

- Reuptake inhibitors
  - SSRIs, SNRIs, NDRIs
  - TCAs
- MAOIs

Mood Stabilizers

- Evidence suggests some may enhance serotonergic neurotransmission

Antipsychotics

- All alter D_2 neurotransmission
- Some atypical antipsychotics also target 5-HT receptors, NE receptors, and a variety of other receptor types

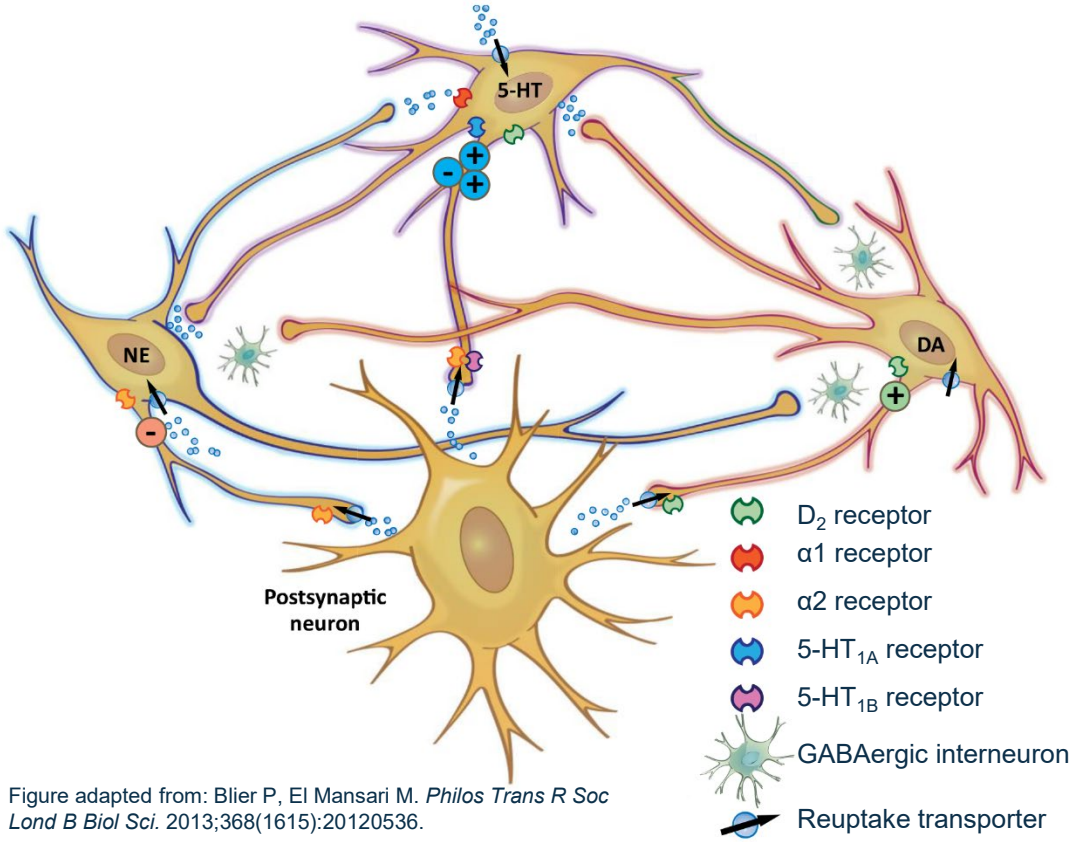

Figure adapted from: Blier P, El Mansari M. *Philos Trans R Soc Lond B Biol Sci.* 2013;368(1615):20120536.

1. Stahl SM. Chapter 5. In: Stahl SM, ed. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application*. 4th ed; 2013:129-236.
2. Stahl SM. Chapter 7. In: Stahl SM, ed. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application*. 4th ed; 2013:284-369.
3. Blier P, El Mansari M. *Philos Trans R Soc Lond B Biol Sci.* 2013;368(1615):20120536.
4. Rang HP, Dale MM. In. *Rang and Dale's Pharmacology*. 7th ed; 2012:564-583.
5. Nugent AC, et al. *J Psychopharmacol.* 2013;27(10):894-902.
6. Andrews PW, et al. *Front Psychol.* 2011;2(159).
7. Artigas F. *Pharmacol Ther.* 2013;137(1):119-131.

GABA=gamma aminobutyric acid; MAOI=monoamine oxidase inhibitor; NDRI=norepinephrine-dopamine reuptake inhibitor; NE=norepinephrine; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant.

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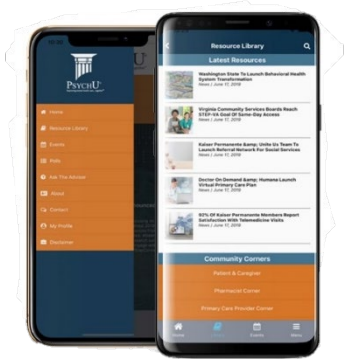

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