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The Evolving Psychopharmacology of Major Depressive Disorder

Otsuka America Pharmaceutical, Inc.

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Monoamine Imbalance Theory of MDD

- One theory of depression is that it may arise from a deficit or underactivity in the brain of monoamine signaling (dopamine [DA], serotonin [5HT], and norepinephrine [NE])[1]
- Deficiency in monoaminergic neurotransmission may be in the monoamine levels themselves, or through disrupted receptor signaling[2,3]
- Evidence that supports the monoamine imbalance hypothesis is that antidepressants can, selectively or in concert, raise monoamine neurotransmission tone (5HT, NE, and/or DA) and reduce depressive symptoms[2,4]

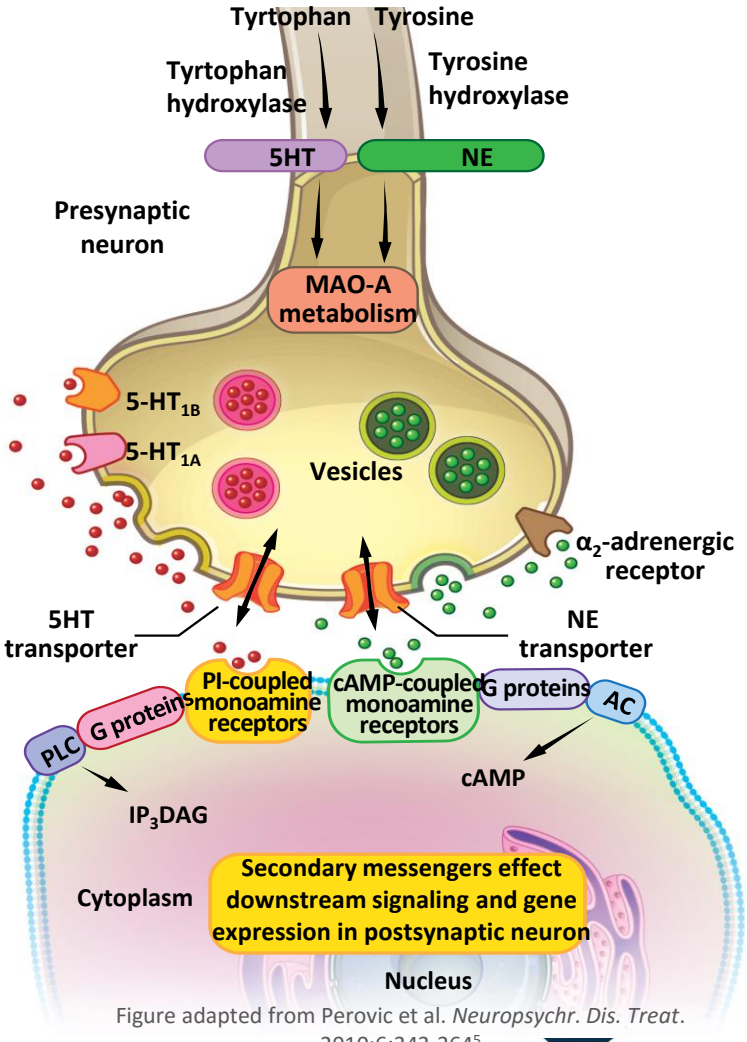
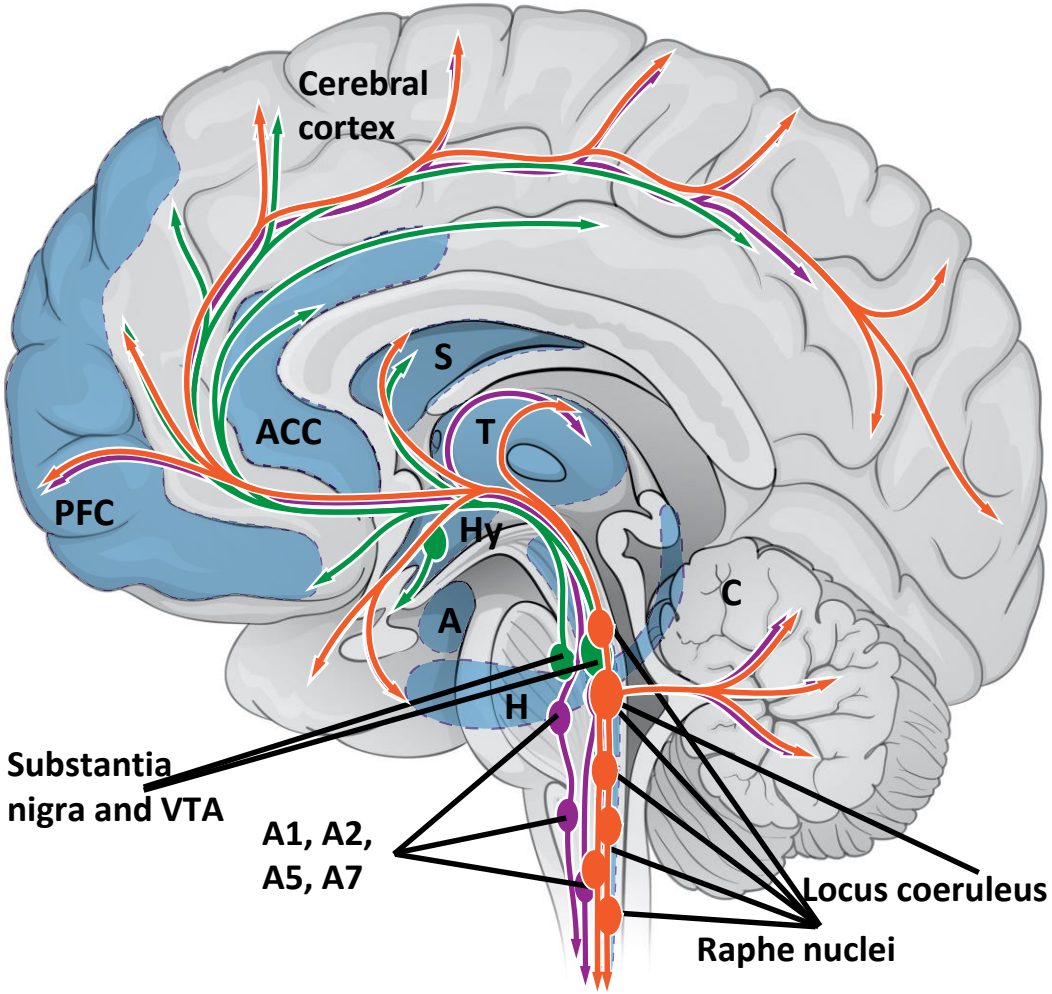


Figure adapted from Perovic et al. *Neuropsychr. Dis. Treat*. 2010;6:343-364[5]

MAO-A=monoamine oxidase A; PLC=phospholipase-C; PI=phosphoinositide; cAMP=cyclic adenosine monophosphate; AC=adenylate cyclase

1. Delgado PL. *Primary Psychiatry*. 2004;11:28-30
2. 2. Svenningsson P, et al. *Science.* 2006;311(5757):77-80
3. Savitz JB, Drevets WC. *Neurobiol Dis.* 2013;52:49-65.
4. Tran P, et al. *J of Psychiatric Research*. 2012;46:64-71.
5. Perovic B, et al. *Neuropsychiatr Dis Treat.* 2010;6:343-364.

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.

Alternative Hypotheses

Current research is focusing on potential factors related to MDD aside from monoamine activity

Hypothesis	Details/Evidence
Non-monoamine neurotransmitters	• Possible role of glutamate, GABA, or acetylcholine dysregulation[1-3]
Genetics	• Family studies suggest genetic risk for MDD[4] • Many candidate genes related to factors associated with MDD[5]
Hormone activity	• HPA axis dysregulation and early life adversity linked to MDD[4] • Possible role for thyroid and growth hormones, estrogen/progesterone[6]
Psychoneuroimmunology	• Neuroinflammation, microglial activation, cytokine production, and other immune processes observed in disease[7,8]
Neurotrophic factors	• MDD and stress may result in neuronal degeneration[9] • Antidepressant treatment may stimulate neuronal growth via BDNF[10] • Monoaminergic neurotransmitters stimulate astrocytic NT-3 production[11]
Circuit dysfunction	• Neuroimaging suggests changes in blood flow and glucose metabolism in brain areas involved in emotional processing[12]

BDNF, brain-derived neurotrophic factor; MDD, major depressive disorder.

1. Zhao et al. *J Affect Disord*. 2012;138(3):494-502
2. Witkin JM et al. *J Pharmacol Exp Ther*. 2014;351(2):448-56
3. Mineur YS and Picciotto MR. *Trends Pharmacol Sci*. 2010;31(12):580-6;
4. Hasler G. *World Psychiatry.* 2010;9(3):155-61
5. Laje G et al. *Psychiatr Serv*. 2009;60(11):1446-57
6. Bondy B. *Dialogues Clin Neurosci*. 2002;4(1):7-20
7. Haroon E et al. *Neuropsychopharmacology*. 2012;37(1):137-62
8. Moylan S et al. *Neurosci Biobehav Rev*. 2014;45:46-62
9. Lee AL et al. *Bipolar Disord*. 2002;4(20):117-28
10. Pittenger C et al. *Neuropsychopharmacology.* 2008;33(1):88-109
11. Mele T et al. *Int J Dev Neurosci.* 2010;28(1):13-9
12. Palazidou E. *Br Med Bull*. 2012;101:127-45.

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 5HT receptors, NE receptors, and a variety of other receptor types

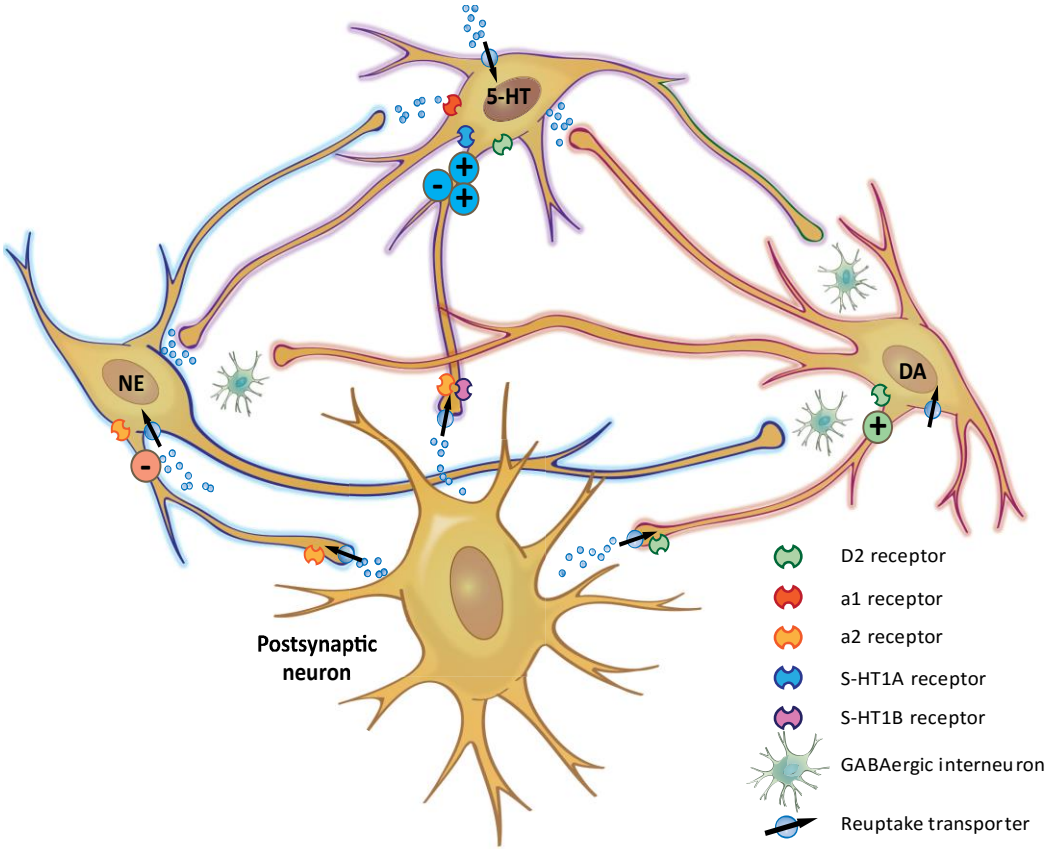


Figure adapted from:Blier P, El Mansari M. *Philos Trans R Soc Lond B Biol Sci.* 2013;368(1615):20120536.

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.

Theoretical Receptor-mediated Physiological Effects of Pharmacological Agents: Monoamine Neurotransmitters [1-7]

Neurotransmitter	Receptor Target(s)	Intrinsic Activity	Clinical/Safety Implications
Dopamine	**D_{1-3}**	**Antagonist or partial agonist**	**Antipsychotic; antidepressant; anti-manic**
Serotonin	**$5HT_{2A}$**	Agonist or inverse agonist	Reduce motor side effects; improve mood and cognition; sleep regulation
	$5HT_{1A}$, $5HT_{1B/D}$, $5HT_{2C}$, $5HT_{6}$, $5HT_{7}$	Antagonist or partial agonist	Possibly contribute to efficacy and tolerability
	$5HT_{1A}$	Partial agonist	Anxiolytic; booster of antidepressant action
Norepinephrine	**$\alpha_{2A, 2B, 2C}$**	Agonist or Antagonist	Antidepressant; anxiolytic; effects on emotional memories[7]
	$\alpha_{1A, 1B, 1C}$	Agonist	Improve cognition and reduce behavioral disturbance in ADHD, depression and OCD; cardiac effects. reduce orthostatic hypotension and sedation[1,6]

1. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th Edition. New York, NY: Cambridge University Press; 2013;
2. Cottingham C et al. *J Biol Chem*. 2011;286(41):36063-75;
3. Gibbs AA et al. *J Neurosci*. 2013;33(43):17023-8;
4. Neumeister A et al. *Neuropsychopharmacology*. 2006;31(8):1750-6;
5. O'Connell TD et al. *J Clin Invest*. 2003;111(11):1783-91;
6. Doze VA et al. *Mol Pharmacol*. 2011;80(4):747-58;
7. Schramm NL et al. *J Neurosci*. 2001;21(13):4875-82.

Theoretical Receptor-mediated Physiological Effects of Pharmacological Agents: Non-monoamine Neurotransmitters[1-3]

Neurotransmitter	Receptor Target(s)	Intrinsic Activity	Clinical/Safety Implications
GABA	$GABA_B$	Agonist	Sleep modification; pain reduction; anxiolytic[2]; anti-epileptic[3]
Histamine	H_1	Antagonist	Alleviate anxiety and insomnia; may cause sedation and weight gain
Acetylcholine	M_1, M_3/M_5	Antagonist	May contribute to metabolic dysregulation
Glutamate	NMDAR, mGluR	Agonist or antagonist	Antidepressant, antipsychotic, anxiolytic, pain control

1. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th Edition. New York, NY: Cambridge University Press; 2013.; Javitt DC et al. *Sci Transl Med*. 2011 Sep 28;3(102):102mr2;
2. Chen X et al. *Adv Pharmacologic Sci*. 2012;ID134523;
3. Cavanna AE et al. *Discov Med*. 2010;9(45);138-44.

Effective Pharmacologic Treatments for Depression

Class	Proposed Mechanism of Action
US Food and Drug Administration-Approved Therapies for Depression	
Selective serotonin reuptake inhibitors (SSRIs)[1]	Increase synaptic serotonin levels and possibly postsynaptic serotonin receptor activation
Serotonin-norepinephrine reuptake inhibitors (SNRIs)[1]	Increase synaptic levels and possibly receptor activation of both serotonin and norepinephrine
Selective norepinephrine reuptake inhibitors (NRIs)[2]	Increases synaptic norepinephrine and postsynaptic adrenergic receptor activation
Tricyclic antidepressants (TCAs)[3]	Inhibit serotonin and norepinephrine reuptake
Monoamine oxidase inhibitors (MAOIs)[4]	Inhibits an enzyme that degrades synaptic monoamines
Atypical/multimodal antidepressants & antipsychotics[5-7]	Variable MOAs to increase synaptic monoamine levels. Includes norepinephrine-dopamine reuptake inhibitors (NDRIs) serotonin antagonist/reuptake inhibitors (SARIs), and serotonin partial agonist/reuptake inhibitors (SPARIs)
Other Potential Therapies for Depression	
Amphetamines[8]	Increase extracellular dopamine levels through multiple mechanisms
Mood stabilizers[9,10]	Unknown
Other[11-13]	Variable

1. Gartlehner G et al. 2007. Available at: http://www.ncbi.nlm.nih.gov/books/NBK83442/; 2. Szabo ST et al. *Neuropsychopharmacology*. 2001;25(6):845-57; 3. Gillman PK. *Br J Pharmacol*. 2007;151(6):737-48; 4. Remick RA et al. *Can Fam Physician.* 1990;36:1151-5; 5. Stahl SM. Stahl's Essential Psychopharmacology. 4th Edition. 2013; 6. Graves SM et al. *Brain Res*. 2012;1472:45-53; 7. Katonia CL et al. *Neuropsychiatr Dis Treat*. 2014;10:349-54; 8. Calipari ES et al. *J Neurosci*. 2013;33(21):8923-5; 9. Hantouche EG et al. *J Affect Disord*. 2005;84(2-3):243-9; 10. Schloesser RJ et al. *Trends Neurosci*. 2011;35(1):36-46; 11. Nemeroff CB. *Focus*. 2008; 6(1):3-14; 12. Wellbutrin PI 2014; 13. Oleptro PI 2010.

Nonpharmacological Treatments for Depression[1-3]

- Electroconvulsive therapy[1]
- Bright light therapy[1]
- Psychotherapy[1]
- Meditation[2]
- Exercise[1]
- Transcranial magnetic stimulation[1]
- Vagus nerve stimulation[1]
- Nutraceuticals[3]
- Acupuncture[1]

1. Gelenberg AJ et al. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Available at http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed May 29, 2015
2. Sarris J et al. *BMC Psychiatry*. 2014;14:107
3. Nahas R and Sheikh O. *Clin Rev*. 2011;57:659-663.

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