PsychU
Improving mental health care... together

Understanding The Role Of Neurotransmitters In The Treatment Of Depression

Robin Nelson, MD
Psychiatrist
DGR Behavioral Health, LLC
Wyomissing, PA

Prakash Masand, MD
Chairman and CEO
Global Medical Education
New York, NY

Otsuka America Pharmaceutical, Inc.

Lundbeck, LLC

December 2015 MRC2.CORP.D.00061

This program is paid for by Otsuka America Pharmaceutical, Inc. and Lundbeck, LLC. The speakers are paid contractors of Otsuka America Pharmaceutical, Inc.

PsychU Virtual Forum Rules of Engagement:

Otsuka America Pharmaceutical, Inc. (OAPI) and Lundbeck, LLC. have entered into collaboration with Open Minds, LLC. to explore new ways of bringing/increasing awareness around serious mental illness.

OAPI/Lundbeck's interaction with Open Minds is through PsychU, an online, non-branded portal dedicated to providing information and resources on important disease state and care delivery topics related to mental illness. One of the methods employed for the sharing of information will be the hosting of virtual fora. Virtual fora conducted by OAPI/Lundbeck are based on the following parameters:

When conducting medical dialogue, whether by presentation or debate, OAPI/Lundbeck and/or its paid consultants aim to provide the viewer with information that is accurate, not misleading, scientifically rigorous, and does not promote OAPI/Lundbeck products.

OAPI/Lundbeck and/or their paid consultants do not expect to be able to answer every question or comment during a PsychU Virtual Forum; however, they will do their best to address important topics and themes that arise.

OAPI/Lundbeck and/or their paid consultants are not able to provide clinical advice or answer questions relating to specific patient's condition.

Otsuka and Lundbeck employees and contractors should not participate in this program (e.g., submit questions or comments) unless they have received express approval to do so from Otsuka Legal Affairs.

OAPI and Lundbeck operate in a highly regulated and scrutinized industry. Therefore, we may not be able to discuss every issue or topic that you are interested in, but we will do our best to communicate openly and directly. The lack of response to certain questions or comments should not be taken as an agreement with the view posed or an admission of any kind.

Objectives

1. Explain unmet needs in the treatment of major depressive disorder (MDD)
2. Review the monoamine hypothesis in the etiology of MDD and the monoamine circuits in the brain
3. Summarize some alternative hypotheses in the etiology of MDD
4. Describe the proposed mechanisms of action of current treatment options for MDD

MDD, major depressive disorder

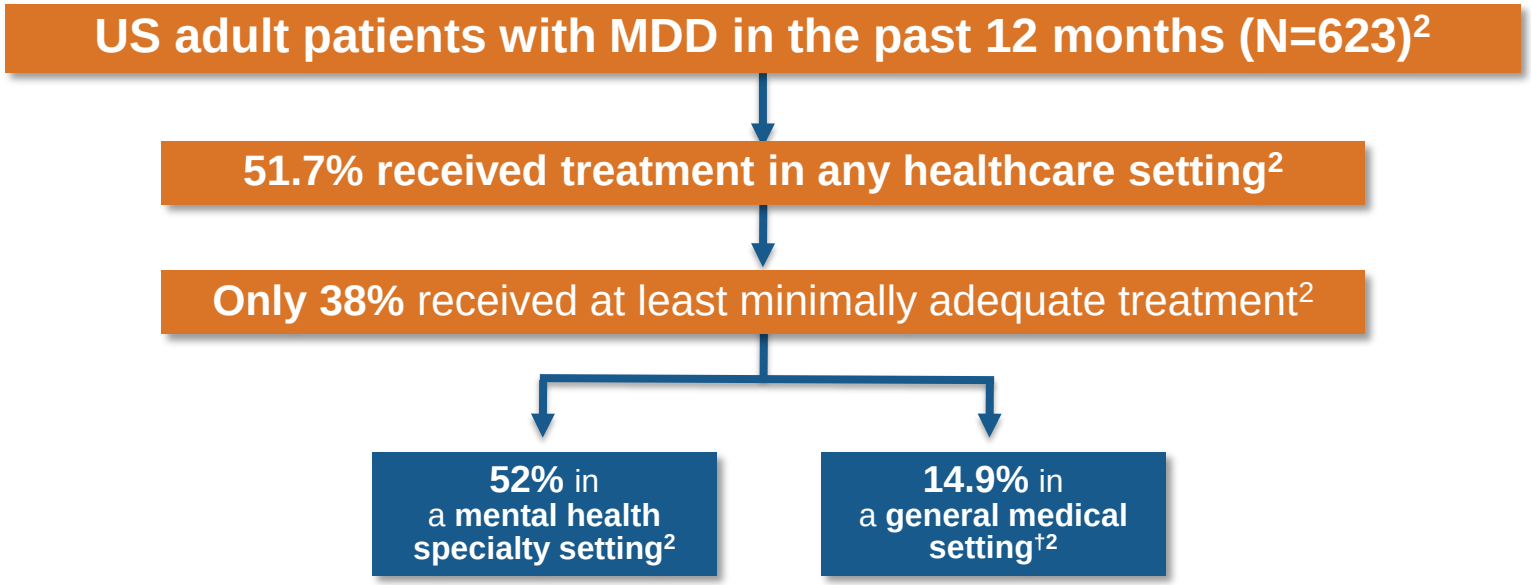
PsychU
Improving mental health care... together

BACKGROUND

Prakash Masand, MD

MDD: The Burden of Inadequate Treatment

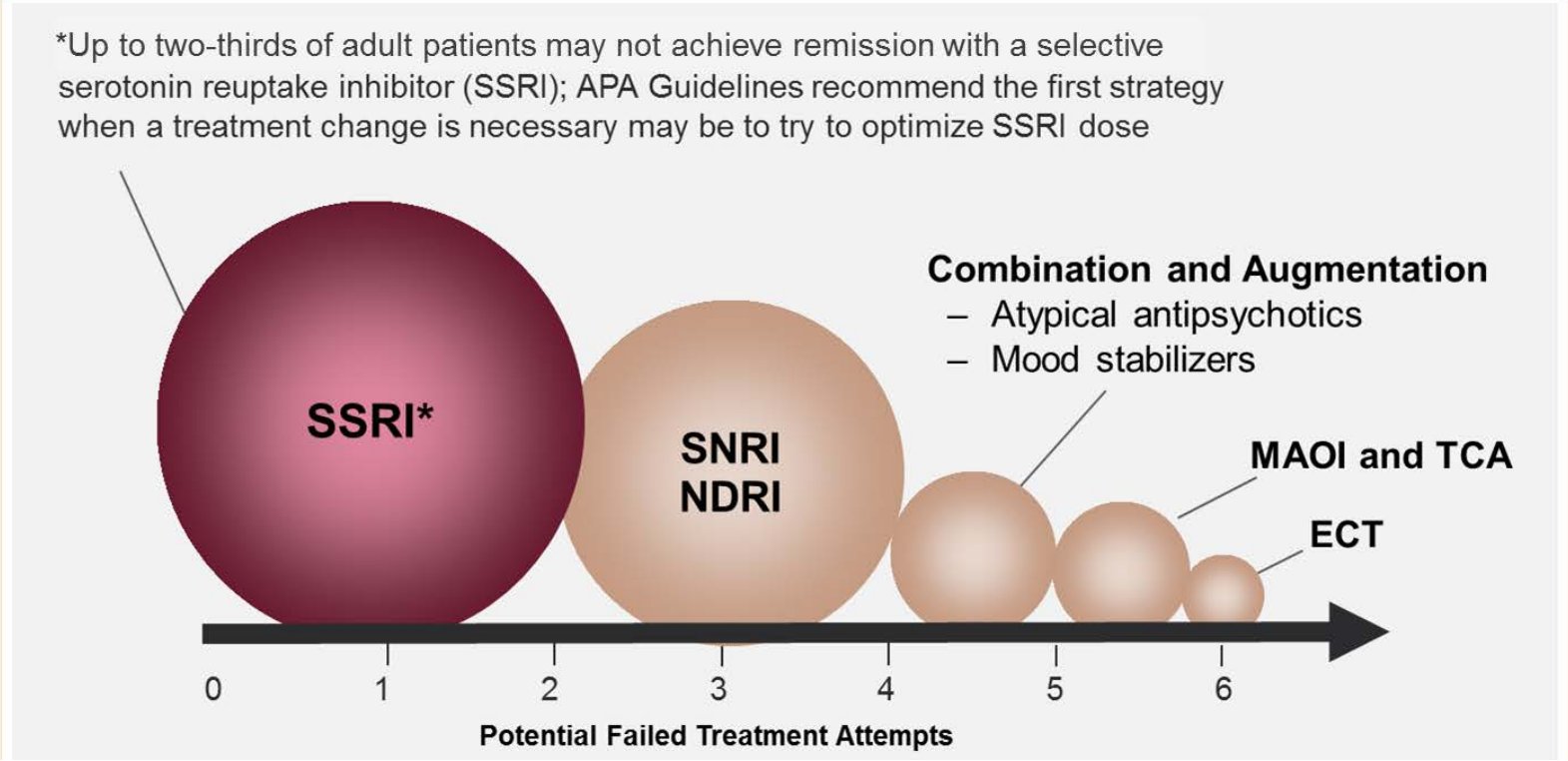
- In 2012, an estimated 16 million United States (US) adults had at least one major depressive episode in the past year, representing 6.9% of all US adults[1]
- In a 2005 analysis of the National Comorbidity Survey Replication (NCS-R), only 38% of patients treated for MDD received minimally adequate treatment*[2]



*Minimally adequate treatment was defined as receiving either pharmacotherapy (≥2 months of an appropriate medication for the focal disorder plus >4 visits to any type of physician) or psychotherapy (≥8 visits with any healthcare or human services professional lasting an average of ≥30 minutes).
†Defined as a primary care physician, other general physician, nurse, or any other health professional in non-mental health setting.
MDD, major depressive disorder

1. NIMH. Major depression among adults. Available at: http://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml. Accessed April 22, 2015. 2. Wang PS, et al. *Arch Gen Psychiatry*. 2005;62(6):629-640.

MDD: Treatment Practices



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

APA, American Psychiatric Association; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant; ECT, electroconvulsive therapy; 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.

PsychU
Improving mental health care... together

DISCUSSION

MONOAMINE NEUROTRANSMITTERS AND MDD

Robin Nelson, MD

MDD Pathophysiology: Several Evolving Theories

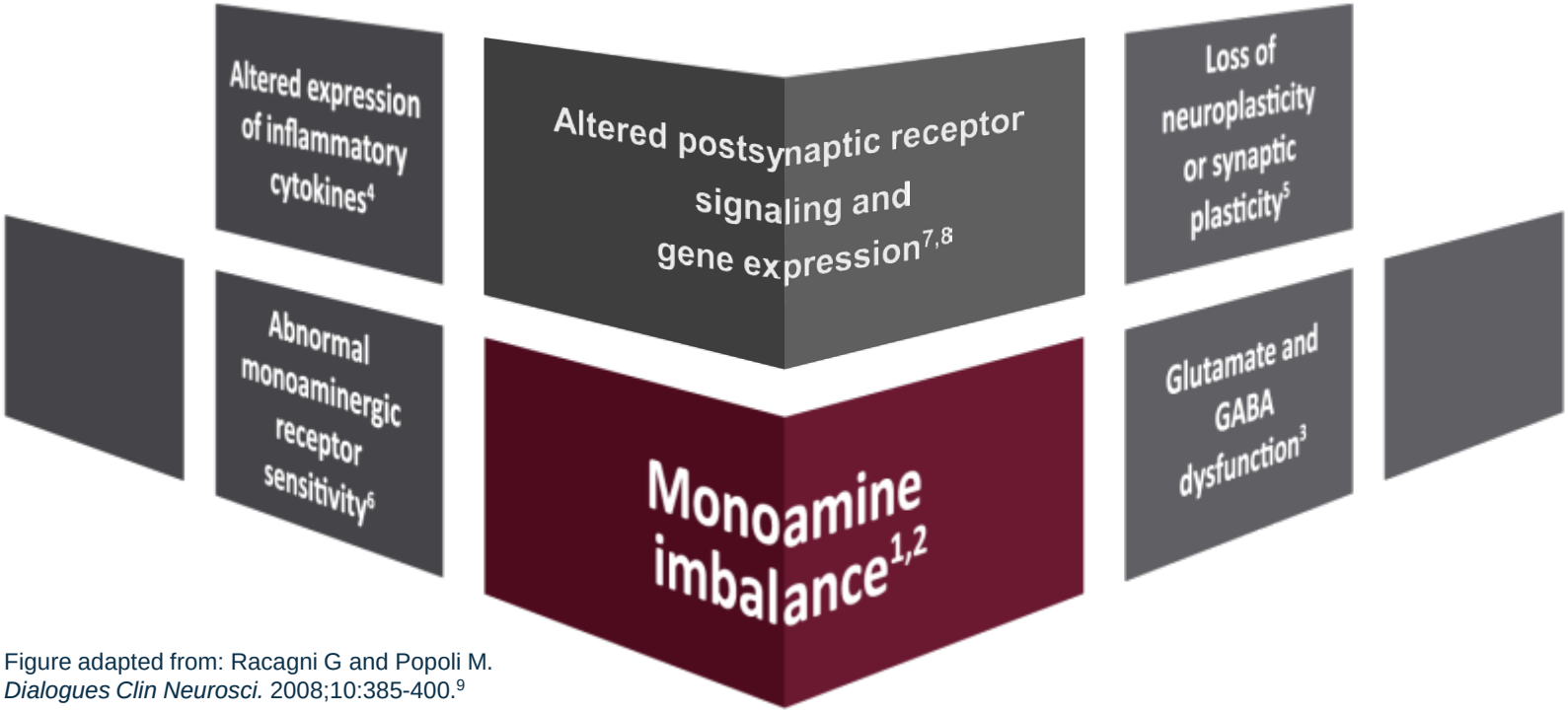


Figure adapted from: Racagni G and Popoli M. *Dialogues Clin Neurosci.* 2008;10:385-400.[9]

Monoamine depletion studies have demonstrated the importance of competent monoaminergic pathways in combating depression[1,2]

GABA, gamma-aminobutyric acid; MDD, major depressive disorder.

1. Millan MJ. *Eur J Pharmacol*. 2004;500(1-3):371-384. 2. Delgado PL. *Primary Psychiatry*. 2004;11:28-30. 3. Lee TS, et al. *AJNR Am J Neuroradiol*. 2014;35(6 Suppl):S44-54. 4. Miller AH, et al. *Depress Anxiety*. 2013;30(4):297-306. 5. Sanacora G, et al. *Neuropharmacology*. 2012;62(1):63-77. 6. Perovic B, et al. *Neuropsychiatr Dis Treat*. 2010;6:343-364. 7. Goswami DB, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;43:126-133. 8. Feyissa AM, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33(1):70-75. 9. Racagni G and Popoli M. *Dialogues Clin Neurosci.* 2008;10:385-400.

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]

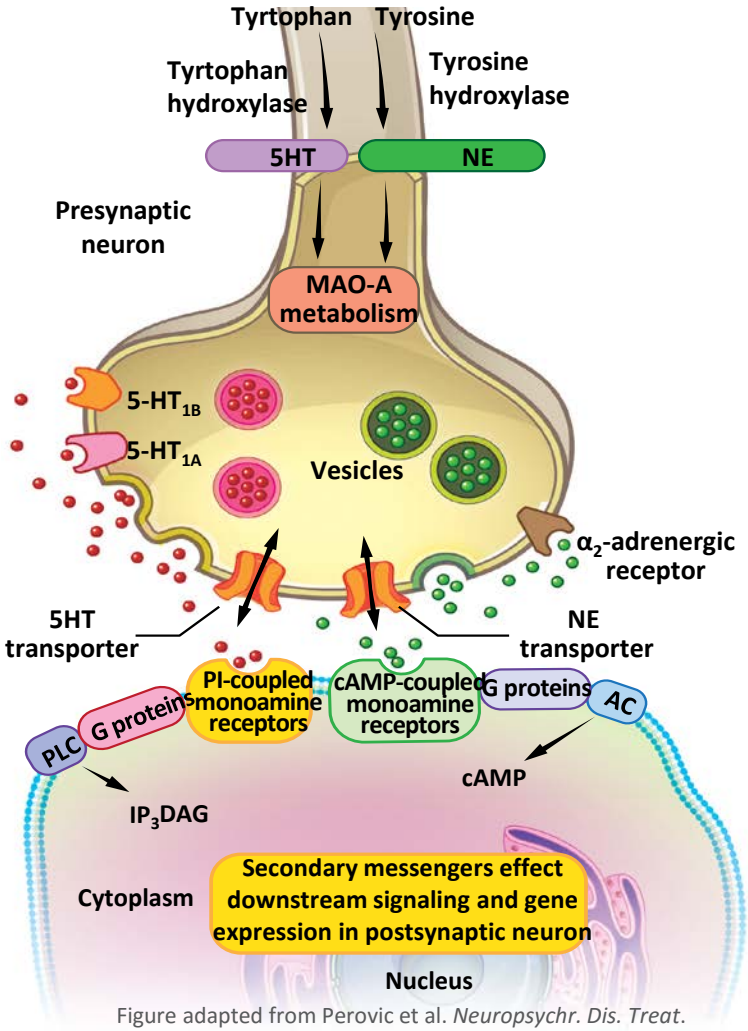


Figure adapted from Perovic et al. *Neuropsychr. Dis. Treat*. 2010;6:343-364[5]

5HT, serotonin; AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; DA, dopamine; MAO-A, monoamine oxidase A; MDD, major depressive disorder; NE, norepinephrine; PLC, phospholipase-C; PI, phosphoinositide.

1. Delgado PL. *Primary Psychiatry*. 2004;11:28-30. 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.

PsychU
Improving mental health care... together

DISCUSSION

PsychU
Improving mental health care... together

THE ROLE OF MONOAMINE NEUROTRANSMITTERS IN DEPRESSION

Prakash Masand, MD

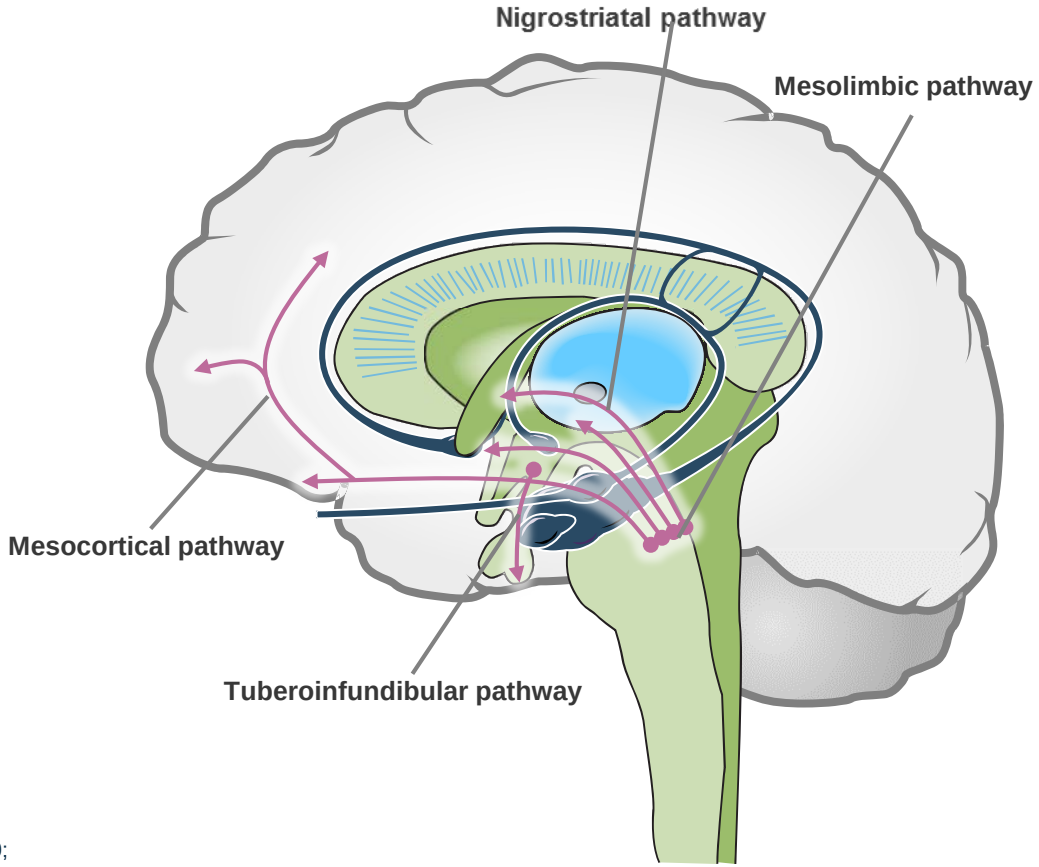
Dopamine (DA)

- Neurotransmitter implicated in schizophrenia as well as depression.[1,2]

Proposed Actions

- Utilized in multiple neural circuits in the brain related to reward, cognition, and executive functioning.[3,4]
- Related to positive and negative symptoms of schizophrenia and major side-effects of treatment.[5,6]
- Effects in schizophrenia mediated largely via D_2-receptor type.[5]
- Dysregulation can lead to loss of motivation, interest, and ability to experience pleasure in MDD.[7]

Dopamine projections in the brain[6]



D/DA, dopamine; MDD, major depressive disorder.

1. Brisch et al. *Front Psychiatry*. 2014;5:47;
2. aan het Rot M, Mathew SJ, Charney DS. CMAJ. 2009;180(3):305-13;
3. Kandel ER et al (eds). *Principles of neural science*. 4th Edition. McGraw-Hill, 2000;
4. Purves D et al (eds). *Neuroscience*. 2nd Edition. Sinauer Associates, 2001;
5. Lieberman JA. *CNS Drug*s. 2004;18(4):251-267;
6. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th Edition. New York, NY: Cambridge University Press; 2013; (Image based on Stahl)
7. Gorwood P. *Dialogues Clin Neurosci*. 2008;10(3):291-9.

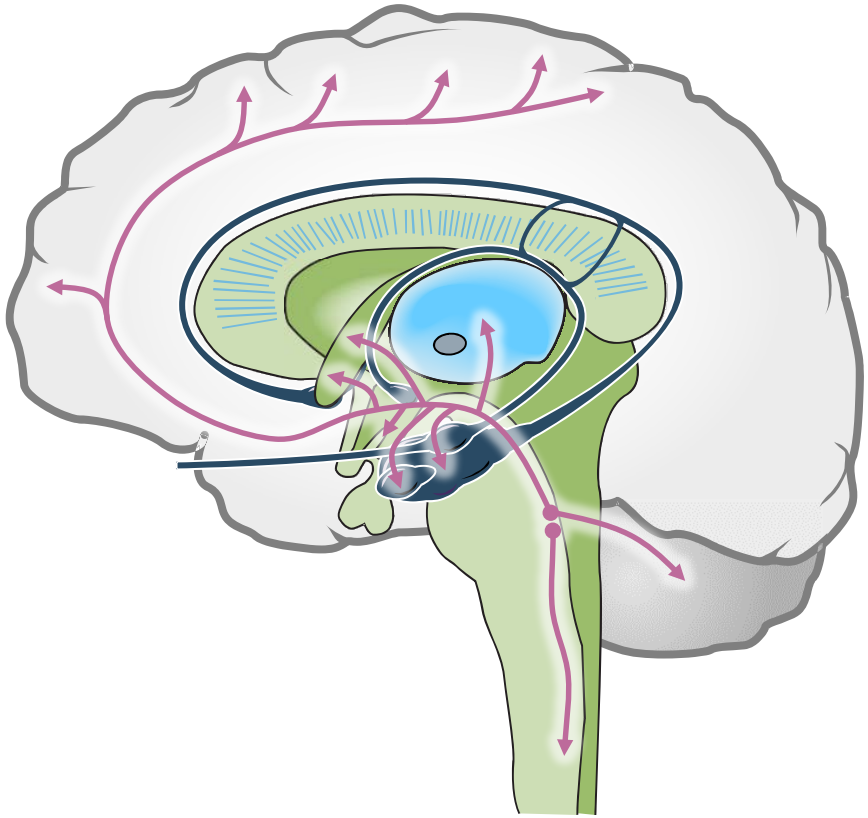
Serotonin (5HT)

- Neurotransmitter implicated in the pathophysiology of MDD.[1]

Proposed Actions

- Impacts multiple functions like mood regulation, anxiety, irritability, feeding, sleep, and sexual behavior.[2,3]
- Altering 5HT system can affect positive or negative symptoms and cognition in schizophrenia[4]:
  - Modulates DA release through $5HT_{2A}$ and $5HT_{1A}$ receptors.

Serotonin projections in the brain[3]



5HT, serotonin; DA, dopamine; MDD, major depressive disorder.

1. Nemeroff CB, Owens MJ. *Clin Chem*. 2009;55(8):1578-9;
2. Maejima T et al. *Front Integr Neurosci*. 2013;7:40;
3. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th Edition. New York, NY: Cambridge University Press; 2013; (Image based on Stahl);
4. Roth & Meltzer. 2000. Available at: www.acnp.org/g4/GN401000117. Accessed Sept 1, 2015.

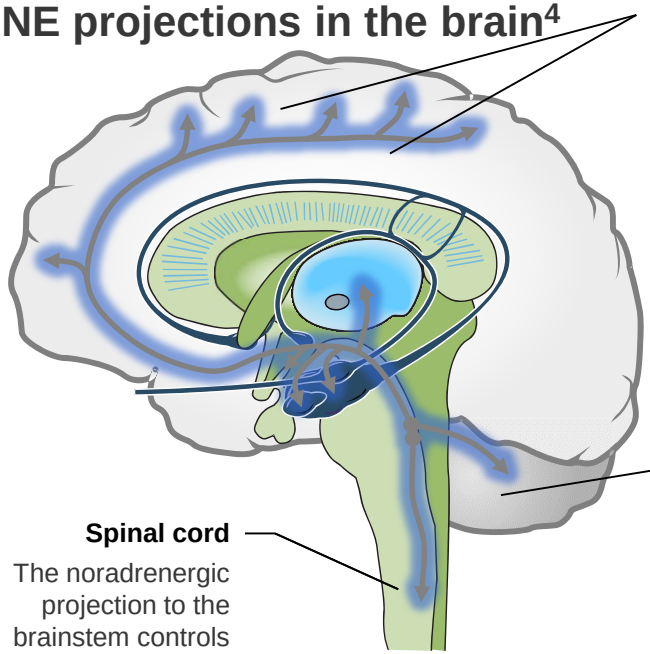
Noradrenaline (Norepinephrine – NE)

- Stored in the locus coeruleus (a nucleus extending from the brainstem into the midbrain that projects diffusely to a variety of forebrain targets).[1]
- The principal function of the locus coeruleus is to prioritize competing incoming stimuli, whether external (eg, a threat from the environment) or internal (eg, pain), and to focus attention.[2]

Proposed Actions

- Influences sleep and wakefulness, attention, stress response, and feeding behavior).[1,3]
- α_1 and α_2 receptors are believed to modulate serotonin release.[4]
- In schizophrenia - α_1 receptor suppression may reduce positive symptoms[5]; α_2 suppression may improve dopaminergic signaling; Enhances antipsychotic effects of DA antagonists.[5,6]

NE projections in the brain[4]



Prefrontal cortex

Some noradrenergic projections to the frontal cortex are thought to help regulate mood; others are thought to mediate attention

The noradrenergic projection to the limbic cortex is thought to mediate emotions, energy, fatigue, and psychomotor agitation/retardation[2]

Cerebellum

The noradrenergic projection to the cerebellum is thought to mediate motor movements, especially tremor[2]

Spinal cord

The noradrenergic projection to the brainstem controls blood pressure[2]

DA, dopamine; MDD, major depressive disorder; NE, norepinephrine.

1. Purves D, et al (eds). *Neuroscience*. 4th Edition. Sinauer Associates, 2007;
2. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 2nd Edition. New York, NY: Cambridge University Press; 2000;
3. Dunn & Swiergiel. *Eur J Pharmacol*. 2008;583:186–193.
4. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th Edition. New York, NY: Cambridge University Press; 2013; (Image also based on this reference);
5. Svensson TH. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003 Oct;27(7):1145-1158;
6. Hensler et al. *Adv Pharmacol*. 2013;68:167-97.

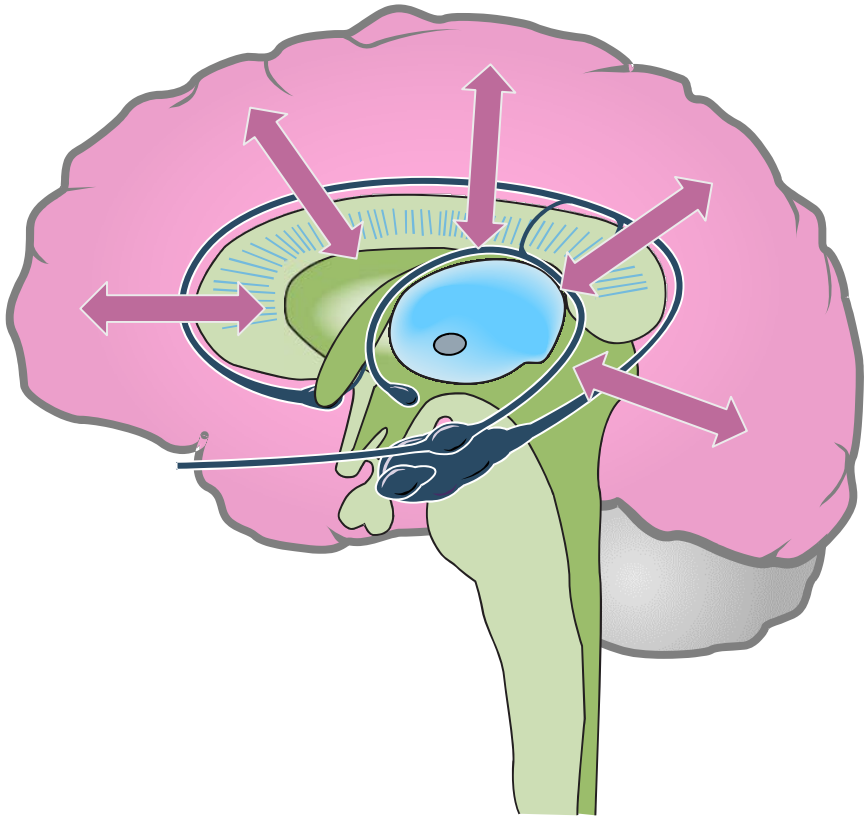
Glutamate (Glu)

- Major excitatory neurotransmitter of the brain.[1]

Proposed Actions

- Implicated in cognition and emotion in MDD.[2]
- Strong evidence for NMDA receptor activity in schizophrenia.[1]
- Proposed links to schizophrenia[1]:
  - Receptor genes associated with increased risk of schizophrenia
  - Signaling components reduced in people with schizophrenia
  - Glutamatergic neurons regulate DA neurons.

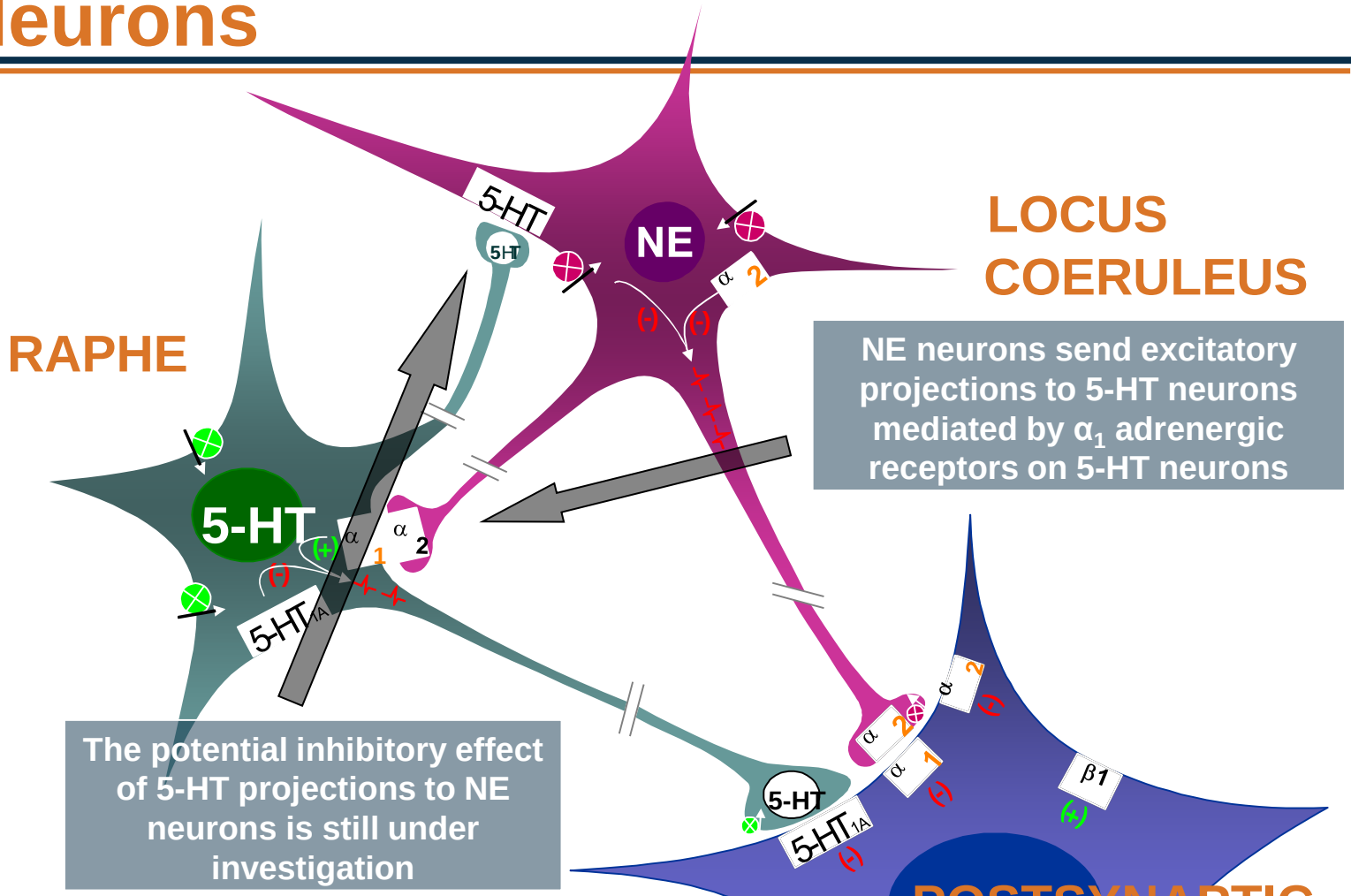
Glutamate pathways in the brain[3]



DA, dopamine; Glu, glutamate; MDD, major depressive disorder; NMDA, N-methyl D-aspartate.

1. Nasrallah HA, Smeltzer DJ. Contemporary Diagnosis and Management of Schizophrenia. 2nd Edition. Newtown, PA: Handbooks in Health Care Company; 2011.
2. Sanacora G, Treccani G, Popoli M. *Neuropharmacology*. 2012;62(1):63-77.
3. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th Edition. New York, NY: Cambridge University Press; 2013; (Image adapted based on Stahl)

Interaction Between 5-HT and NE Neurons



5-HT, serotonin; NE, norepinephrine.

1. Baraban JM et al. *Brain Res*. 1981;204:1-11.
2. Pineyro G et al. *Pharmacol Rev*. 1999;51:533-91.

PsychU
Improving mental health care... together

DISCUSSION

PsychU
Improving mental health care... together

TREATMENT APPROACHES FOR MDD

Robin Nelson, MD

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]

5HT, serotonin; ADHD, attention deficit hyperactivity disorder; OCD, obsessive compulsive disorder.

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

GABA, gamma-aminobutyric acid; NMDAR, N-methyl-D-aspartate receptor; mGluR, metabotropic glutamate receptor.

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.

PsychU
Improving mental health care... together

DISCUSSION

PsychU
Improving mental health care... together

What pharmacologic considerations do you make when deciding on an appropriate treatment strategy for your patients with MDD?

What other alternative hypotheses exist in the pathophysiology of depression?

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

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. Bondy B. *Dialogues Clin Neurosci*. 2002;4(1):7-20; 6. Haroon E et al. *Neuropsychopharmacology*. 2012;37(1):137-62; 7. Moylan S et al. *Neurosci Biobehav Rev*. 2014;45:46-62; 8. Lee AL et al. *Bipolar Disord*. 2002;4(20):117-28; 9. Pittenger C et al. *Neuropsychopharmacology.* 2008;33(1):88-109; 10. Mele T et al. *Int J Dev Neurosci.* 2010;28(1):13-9; 11. Palazidou E. *Br Med Bull*. 2012;101:127-45.

PsychU™
Improving mental health care... together

QUESTIONS

PsychU
Improving mental health care... together

PsychU™
Improving mental health care... together

CLOSING

PsychU
Improving mental health care... together