PsychU
Improving mental health care... together

Potential Role Of Neurotransmitters & Treatment Considerations In Bipolar Disorder

Otsuka Pharmaceutical Development & Commercialization, Inc.

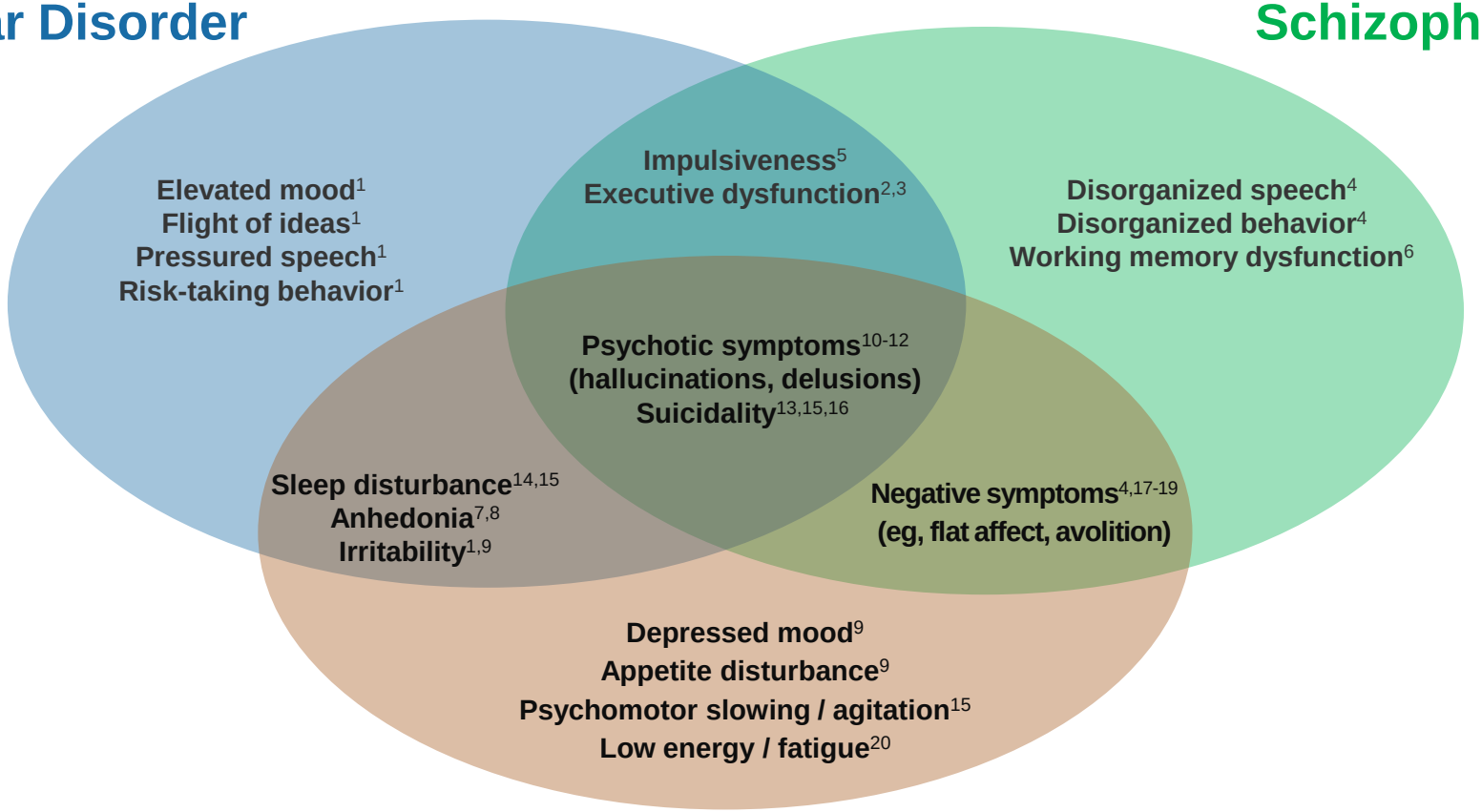
Lundbeck, LLC.

March 2017 MRC2.CORP.D.00223

PsychU
Improving mental health care... together

This program was developed with the support of Otsuka Pharmaceutical Development & Commercialization, Inc. and Lundbeck, LLC. The speakers are either employees or paid contractors of Otsuka Pharmaceutical Development & Commercialization, Inc.

Clinical Overlap = Overlap of Symptoms



1. Judd LL, et al. 2012.
2. Barbosa IG, et al. 2012.
3. Brown AS, et al. 2009.
4. Kerns JG. 2006.
5. Reddy LF, et al. 2014.
6. Forbes NF, et al. 2009.
7. Pizzagalli DA, et al. 2008.
8. Berlim MT, et al. 2004.
9. Farabaugh AH, et al.. 2004.
10. Glahn DC, et al.. 2007.
11. ISC, et al. 2009.
12. Santosh SV et al. 2014.
13. MacKinnon DF, et al. 2005.
14. Harvey AG, et al. 2009.
15. Williams JM, et al. 2006.
16. Hor K, et al. 2010.
17. Foussias G, et al. 2010.
18. Pizzagalli DA, et al. 2002.
19. Bracht T, et al. 2012.
20. Stahl SM, et al. 2003.

Proposed Anatomical Localization of Manic Symptoms

Label	Region	Manic Symptom
1	Prefrontal Cortex	• Racing thoughts • Grandiosity • Distractibility • Talkative / pressured speech • Mood • Risks
2	Basal Forebrain	• Decreased sleep / arousal
3	Nucleus Accumbens	• Racing thoughts • Goal directed • Grandiosity
4	Striatum	• Motor/agitation
5	Amygdala	• Mood
6	Hypothalamus	• Decreased sleep / arousal

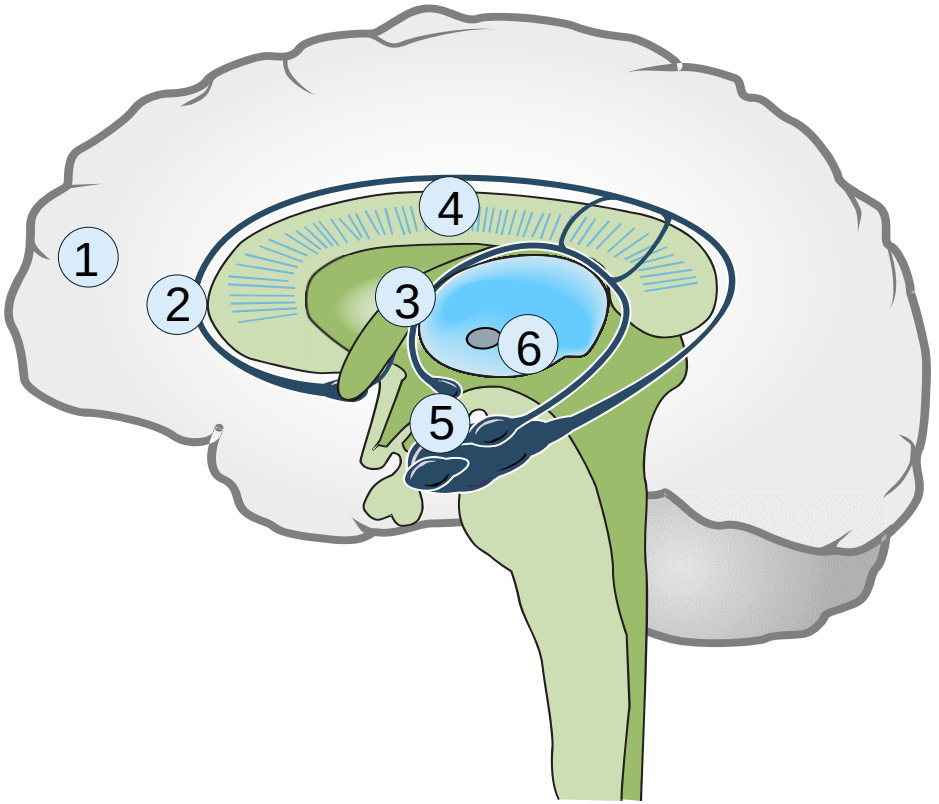


Figure adapted from Stahl SM. 2013

Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th edition. Cambridge University Press; 2013.

Proposed Anatomical Localization of Depressive Symptoms

Label	Region	Depressive Symptom
1	Prefrontal Cortex	• Concentration • Interest/pleasure • Psychomotor • Fatigue (mental) • Guilt • Suicidality • Worthlessness • Mood
2	Nucleus Accumbens	• Pleasure • Interests • Fatigue/energy
3	Striatum	• Psychomotor • Fatigue (physical)
4	Amygdala	• Guilt • Suicidality • Worthlessness • Mood
5	Hypothalamus	• Sleep • Appetite
6	Cerebellum	• Psychomotor
7	Spinal cord	• Fatigue (physical)

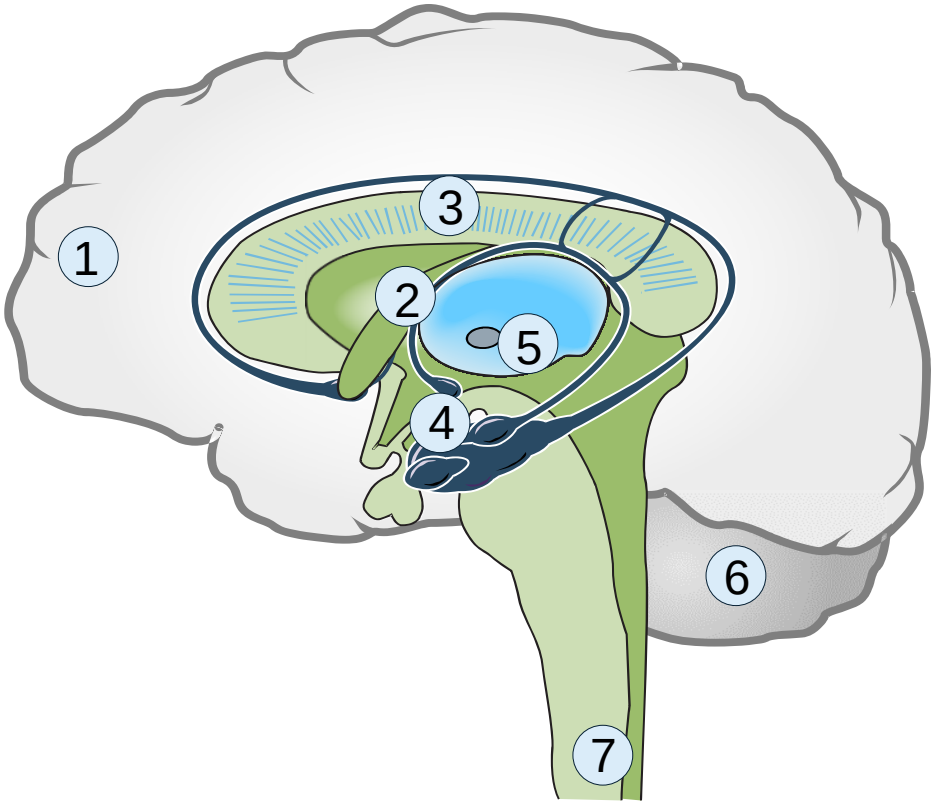


Figure adapted from Stahl SM. 2013

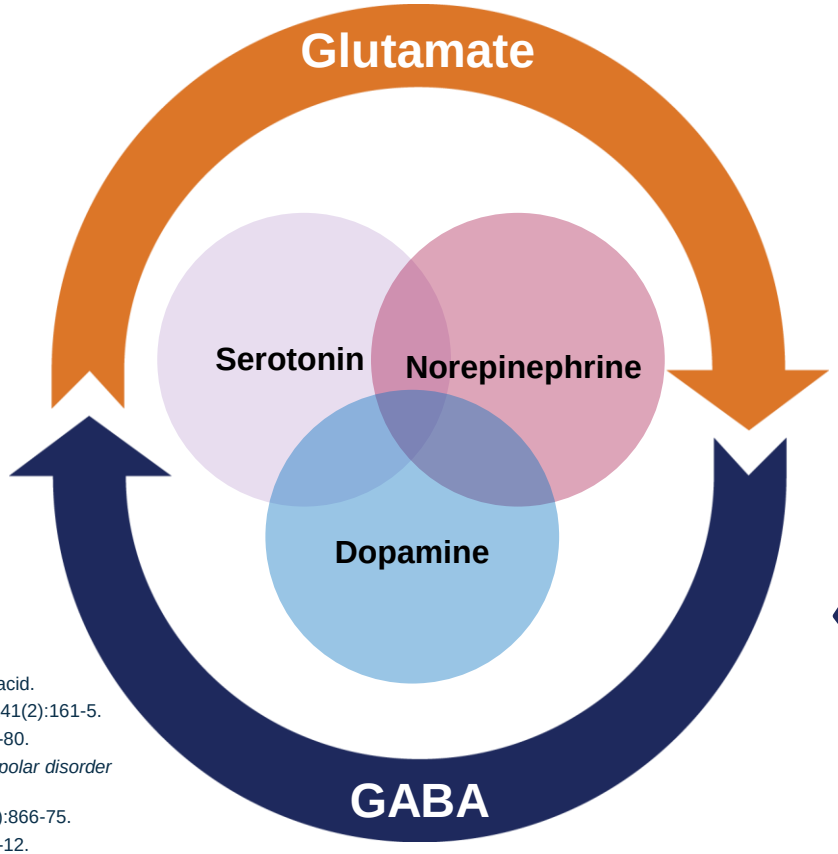
Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th edition. Cambridge University Press; 2013.

GABA and Glutamate

- The major inhibitory and excitatory neurotransmitters[1]

Glutamate

- Major excitatory neurotransmitter in the CNS[2]
- Regulates synaptogenesis and neurogenesis[2]
- Synaptic plasticity[3]



GABA

- Major inhibitory neurotransmitter in the CNS[4]
- Target of anti-anxiety drugs[4]
- Involved in sleep-wake cycle[5,6]

CNS, central nervous system; GABA, gamma-aminobutyric acid.

1. Rainesalo S, et al. *Brain Res Mol Brain Res*. 2005;141(2):161-5.
2. Boulland JL, et al. *J Comp Neurol*. 2004;480(3):264-80.
3. Manji, HK, et al (eds). *Behavioral neurobiology of bipolar disorder and its treatment*. Springer, 2011
4. D'Hulst C, et al. *Drug Discov Today*. 2009;14(17-18):866-75.
5. Nitz D, et al. *Am J Physiol*. 1996;271(6 Pt 2):R1707-12.
6. Murillo-Rodríguez E, et al. *CNS Neurol Disord Drug Targets*. 2009;8(4):245-53.

Potential Role of GABA

- In 1980, Emrich and colleagues proposed the GABA hypothesis for mood disorders, in which a potential GABAergic deficiency underlies mood disorders[1]
- Cerebrospinal fluid (CSF), plasma, and metabolite levels of GABA are altered (often decreased) in bipolar disorder (alterations may be dependent on current episode)[1]
- GABA system changes occur in specific brain regions: hippocampus, prefrontal cortex, and anterior cingulate cortex[1]
- Neuroimaging techniques assessing specific chemicals in certain brain regions (including GABA-related enzymes) may provide a means to differentiate between bipolar and unipolar depression[1,2]
- Drugs effective in the treatment of bipolar disorder have direct effects on the GABA system including increasing GABA levels in specific brain regions and altering several key metabolic enzymes[1]

GABA, gamma-aminobutyric acid.

1. Brambilla P, et al. *Mol Psychiatry*. 2003;8(8):721-37, 715.
2. Maletic V, Raison C. *Front Psychiatry*. 2014;5(98):1-24.

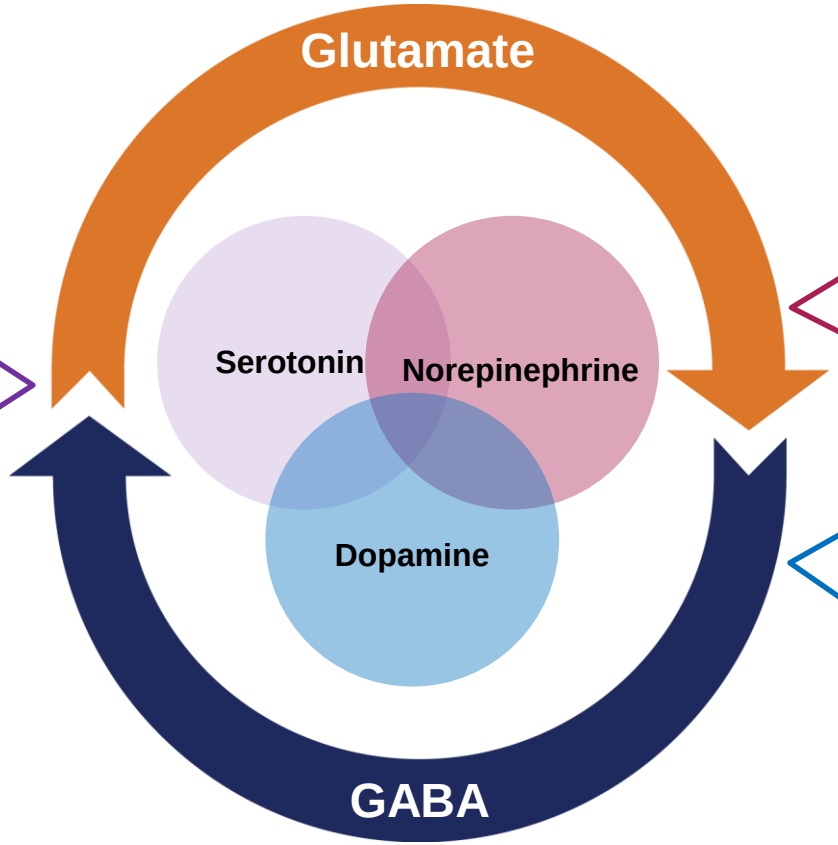
Potential Role of Glutamate

- Evidence from genetic, postmortem, biochemical, and imaging studies points to a principal role of glutamatergic dysregulation in the etiopathogenesis of bipolar disorder[1]
- Studies show an increase in glutamatergic transmission in the frontal cortex and hippocampus of bipolar subjects relative to control groups[1]
- Studies reveal elevation of various glutamate/GABA metabolites in the anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (DLPFC), parieto-occipital cortex, insula, and hippocampus across bipolar mood states and euthymic individuals[1]
- Drugs effective in bipolar disorder impact glutamatergic neurotransmission[2]
- An increased understanding of glutamate-dopamine (DA) interactions may enhance drug development efforts[3]

GABA, gamma-aminobutyric acid.

1. Muneer A. *Psychiatry Investig*. 2016;13(1):18-33.
2. Soares JC. *Bipolar Disorders: Basic Mechanisms and Therapeutic Implications*. 3rd edition. Cambridge University Press; 2016.
3. de Bartolomeis A, et al. *J Psychopharmacol*. 2014;28(6):505-26.

Serotonin, Norepinephrine, and Dopamine



Serotonin

- Impulsive behavior
- Anxiety, irritability
- Sex, appetite, aggressive behavior
- Mood, emotion, cognitive function

Norepinephrine

- Energy, interest
- Anxiety, irritability
- Motivation
- Mood, emotion, cognitive function

Dopamine

- Drive
- Sex, appetite, aggressive behavior
- Motivation
- Mood, emotion, cognitive function

GABA, gamma-aminobutyric acid.

Zajecka J, et al. *J Clin Psychiatry*. 2013;74:407-414.

Potential Role of Dopamine

- In the mid-1960's, the catecholamine hypothesis of bipolar disorder (CHBD) emerged due to pharmacological observations[1]
  - Excessive DA neurotransmission involved in development of mania-like behavior[2]
  - Phase-related altered levels of DA and DA metabolite (HVA) found in CSF and urine[3]
  - Decreased DA transport (DAT) levels observed in frontal cortex of patients with bipolar disorder versus healthy control participants[4]
- Psychostimulants
  - Administration in healthy volunteers can produce a hypomanic-like state[2]
  - MOA of the psychostimulant amphetamine — reverses the direction of DAT[5]
  - Mood stabilizers are thought to alter DA neurotransmission[2]
- Catechol-O-methyltransferase (COMT, DA metabolic enzyme) — genetic variations linked to bipolar disorder[6]

MOA, mechanism of action; HVA, homovanillic acid.

1. Soares JC. *Bipolar Disorders: Basic Mechanisms and Therapeutic Implications*. 3rd edition. Cambridge University Press; 2016.
2. Berk M, et al. *Acta Psychiatr Scand Suppl*. 2007;(434):41-9.
3. Cousins DA, et al. *Bipolar Disord*. 2009;11(8):787-806.
4. Rao JS, et al. *J Affect Disord*. 2012;136(1-2):63-71.
5. Berman SM, et al. *Mol Psychiatry*. 2009;14(2):123-42.
6. Andreazza AC, et al. *Int J Neuropsychopharmacol*. 2014;17(7):1039-52.

Potential Role of Norepinephrine

- Plasma and urine norepinephrine (NE) levels and NE metabolite levels are lower in patients with bipolar depression compared with those with unipolar depression, and is higher in the manic phase versus the depressed phase[1]
- Plasma NE levels are lower in response to orthostatic challenge in bipolar depression versus unipolar depression[2,3]
- Elevated NE metabolite levels are observed in postmortem bipolar brains[4]

1. Manji HK, et al. *World Psychiatry*. 2003;2(3):136-46.
2. Roy A, et al. *Arch Gen Psychiatry*. 1985;42(12):1181-5.
3. Rudorfer MV, et al. Arch Gen Psychiatry. 1985;42(12):1186-92.
4. Young LT, et al. *Biol Psychiatry*. 1994;35(2):121-7.

Potential Role of Serotonin

- No simple model for serotonergic involvement in bipolar exists
  - Deficient serotonin (5-HT) signaling seems to contribute to both depressive and manic symptoms
    - Low energy, anhedonia, altered sleep, and appetite
    - Impulsivity, interpersonal aggression
  - Increased 5-HT signaling implicated in some symptoms of mania
    - Increased hedonic behavior, decreased need for sleep, increased energy
- Postmortem studies show reduced levels of 5-HIAA
- Neuroimaging research implications:
  - Reduced 5-HT transporter binding in midbrain of depressed bipolar patients has been shown, extent of alterations correlates with aggressive symptoms in patients with bipolar II
  - One study reveals reduced 5-HT_{2A} receptor binding in manic patients
- Genetics: Two gene variants in 5-HTT have modest associations with bipolar
  - Short allele of 5-HTTLPR & intron two variable number of tandem repeats (VNTR)

5-HIAA, 5-hydroxyindoleacetic acid; 5-HT_{2A}, serotonin receptor 2A; 5-HTT, serotonin transporter; 5-HTTLPR, serotonin-transporter-linked polymorphic region.

Soares JC. *Bipolar Disorders: Basic Mechanisms and Therapeutic Implications*. 3rd edition. Cambridge University Press; 2016.

Neurotransmitter Interactions

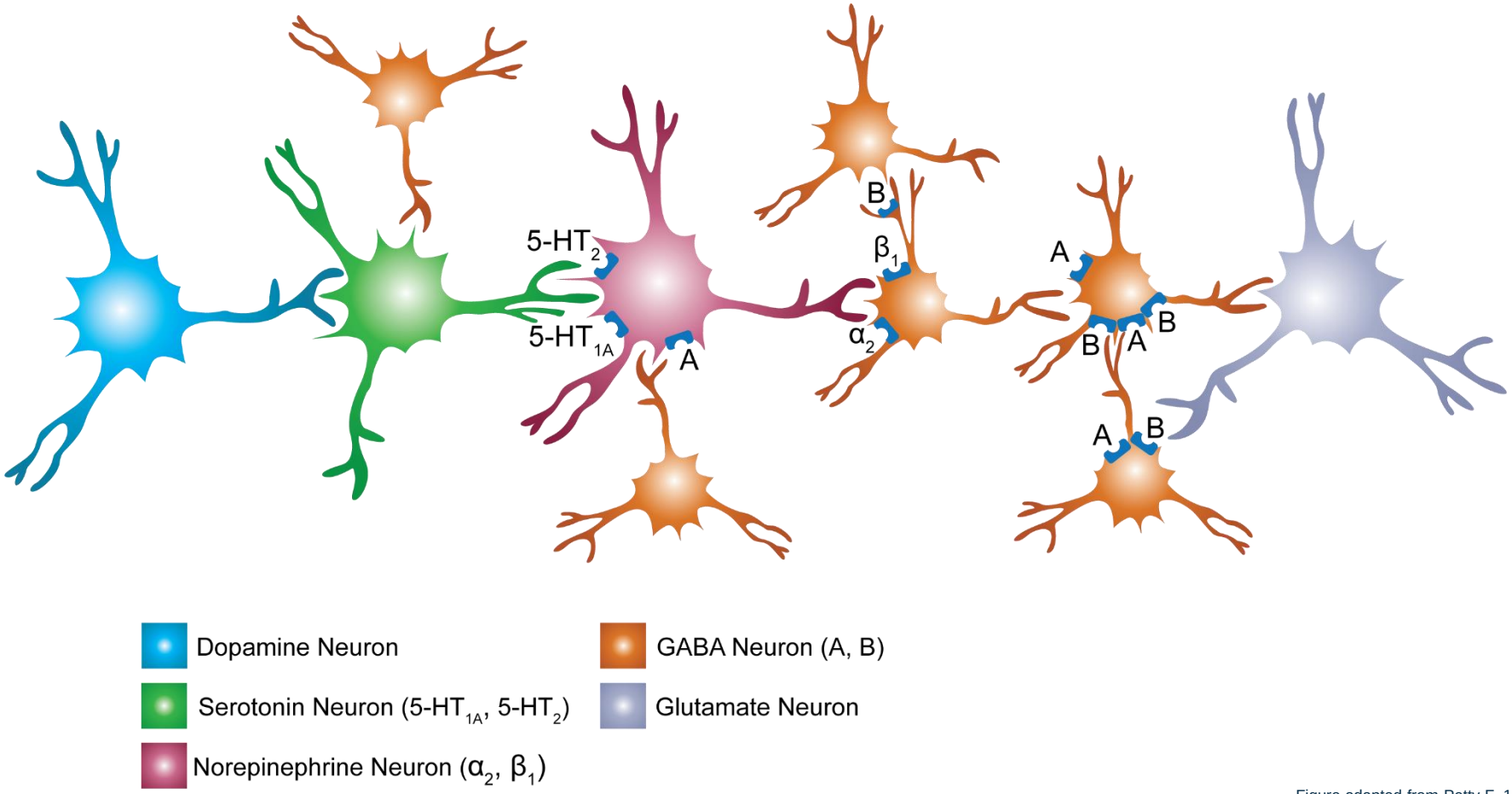


Figure adapted from Petty F. 1995

Petty F. *J Affect Disord*. 1995;34(4):275-81.

Pharmacologic Treatment of Bipolar Disorder

US FDA-approved Therapies	Proposed Mechanism of Action
Mood stabilizers	Mechanism of action is complex and not fully understood.[1] Suppresses formation of secondary messengers (eg, IP_3, by inhibiting IMPase).[1] Reduces DA and Glu neurotransmission, enhances 5-HT and GABA neurotransmission[1]
Anticonvulsants	Blocks Na^+ and Ca^{2+} channels, enhances GABA receptor functions, enhances 5-HT neurotransmission[2,3]
Atypical antipsychotics	Antagonist and/or partial agonist activity at D_2, $5\text{-}HT_{2A}$, $5\text{-}HT_{1A}$ receptors and other DA, 5-HT, and NE targets[4,5]

5-HT, serotonin; $5\text{-}HT_X$, serotonin receptor X; Ca, calcium; D_x, dopamine receptor X; DA, dopamine; FDA, Food and Drug Administration: GABA, gamma-aminobutyric acid; Glu, glutamate; IMPase; inositol monophosphatase; IP_3, inositol triphosphate; Na, sodium; NE, norepinephrine; US, United States.

1. Malhi GS, et al. *CNS Drugs*. 2013;27(2):135-53.
2. Schloesser RJ, et al. *Trends Neurosci*. 2012;35(1):36-46.
3. Nugent AC, et al. *J Psychopharmacol*. 2013;27(10):894-902.
4. Li X, et al. *Neuropsychopharmacology*. 2012;37(1):77-101.
5. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th edition. Cambridge University Press; 2013.

Potential Role Of Neurotransmitters & Treatment Considerations In Bipolar Disorder

Otsuka Pharmaceutical Development & Commercialization, Inc.

Lundbeck, LLC.

March 2017 MRC2.CORP.D.00223