Potential Role Of Neurotransmitters & Treatment Considerations In Bipolar Disorder
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

Bipolar Disorder
- Elevated mood
- Flight of ideas
- Pressured speech
- Risk-taking behavior

Schizophrenia
- Disorganized speech
- Disorganized behavior
- Working memory dysfunction

Major Depression
- Depressed mood
- Appetite disturbance
- Psychomotor slowing / agitation
- Low energy / fatigue

Psychotic symptoms (hallucinations, delusions)
- Suicidality

Impulsiveness
- Executive dysfunction

Sleep disturbance
- Anhedonia
- Irritability

Negative symptoms (eg, flat affect, avolition)

References:
## Proposed Anatomical Localization of Manic Symptoms

<table>
<thead>
<tr>
<th>Label</th>
<th>Region</th>
<th>Manic Symptom</th>
</tr>
</thead>
</table>
| 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

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Proposed Anatomical Localization of Depressive Symptoms

<table>
<thead>
<tr>
<th>Label</th>
<th>Region</th>
<th>Depressive Symptom</th>
</tr>
</thead>
</table>
| 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
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\(^5,6\)

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Glutamate

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GABA

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

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.

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.

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.
Potential Role of Dopamine

• In the mid-1960’s, the catecholamine hypothesis of bipolar disorder (CHBD) emerged due to pharmacological observations¹
  – Excessive DA neurotransmission involved in development of mania-like behavior²
  – Phase-related altered levels of DA and DA metabolite (HVA) found in CSF and urine³
  – Decreased DA transport (DAT) levels observed in frontal cortex of patients with bipolar disorder versus healthy control participants⁴

• Psychostimulants
  – Administration in healthy volunteers can produce a hypomanic-like state²
  – MOA of the psychostimulant amphetamine — reverses the direction of DAT⁵
  – Mood stabilizers are thought to alter DA neurotransmission²

• Catechol-O-methyltransferase (COMT, DA metabolic enzyme) — genetic variations linked to bipolar disorder⁶

MOA, mechanism of action; HVA, homovanillic acid.

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\(^4\)

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-HT2A 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-HT2A, serotonin receptor 2A; 5-HTT, serotonin transporter; 5-HTTLPR, serotonin-transporter-linked polymorphic region.

Neurotransmitter Interactions

Dopamine Neuron
Serotonin Neuron (5-HT$_{1A}$, 5-HT$_2$)
Norepinephrine Neuron (α$_2$, β$_1$)
GABA Neuron (A, B)
Glutamate Neuron

Figure adapted from Petty F. 1995

Pharmacologic Treatment of Bipolar Disorder

<table>
<thead>
<tr>
<th>US FDA-approved Therapies</th>
<th>Proposed Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mood stabilizers</strong></td>
<td>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)</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td>Blocks Na(^+) and Ca(^{2+}) channels, enhances GABA receptor functions, enhances 5-HT neurotransmission(^2,3)</td>
</tr>
<tr>
<td><strong>Atypical antipsychotics</strong></td>
<td>Antagonist and/or partial agonist activity at D(<em>2), 5-HT(</em>{2A}), 5-HT(_1A) receptors and other DA, 5-HT, and NE targets(^4,5)</td>
</tr>
</tbody>
</table>

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5-HT, serotonin; 5-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.

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