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
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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
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\(^2\)

\[\begin{align*}
\text{US adult patients with MDD in the past 12 months (N=623)}^2 & \\
\text{51.7% received treatment in any healthcare setting}^2 & \\
\text{Only 38% received at least minimally adequate treatment}^2 & \\
52\% \text{ in a mental health specialty setting}^2 & \\
14.9\% \text{ in a general medical setting}^2 & \\
\end{align*}\]

*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

MDD: Treatment Practices

*Up to two-thirds of adult patients may 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.

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.

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MONOAMINE NEUROTRANSMITTERS AND MDD

Robin Nelson, MD
MDD Pathophysiology: Several Evolving Theories


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

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

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\(^2,4\)

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DISCUSSION
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 D₂-receptor type.⁵
- Dysregulation can lead to loss of motivation, interest, and ability to experience pleasure in MDD.⁷

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

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 schizophrenia4:
  - Modulates DA release through 5HT$_{2A}$ and 5HT$_{1A}$ receptors.

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

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).
- The principal function of the locus coeruleus is to prioritize competing incoming stimuli, whether external (e.g., a threat from the environment) or internal (e.g., pain), and to focus attention.

Proposed Actions
- Influences sleep and wakefulness, attention, stress response, and feeding behavior.
- $\alpha_1$ and $\alpha_2$ receptors are believed to modulate serotonin release.
- In schizophrenia, $\alpha_1$ receptor suppression may reduce positive symptoms; $\alpha_2$ suppression may improve dopaminergic signaling; Enhances antipsychotic effects of DA antagonists.

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

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 schizophrenia¹:
  - Receptor genes associated with increased risk of schizophrenia
  - Signaling components reduced in people with schizophrenia
  - Glutamatergic neurons regulate DA neurons.

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

Interaction Between 5-HT and NE Neurons

5-HT, serotonin; NE, norepinephrine.


The potential inhibitory effect of 5-HT projections to NE neurons is still under investigation.

NE neurons send excitatory projections to 5-HT neurons mediated by α₁ adrenergic receptors on 5-HT neurons.
DISCUSSION
TREATMENT APPROACHES FOR MDD

Robin Nelson, MD
# Theoretical Receptor-mediated Physiological Effects of Pharmacological Agents: Monoamine Neurotransmitters

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Receptor Target(s)</th>
<th>Intrinsic Activity</th>
<th>Clinical/Safety Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>D&lt;sub&gt;1-3&lt;/sub&gt;</td>
<td>Antagonist or partial agonist</td>
<td>Antipsychotic; antidepressant; anti-manic</td>
</tr>
<tr>
<td>Serotonin</td>
<td>5HT&lt;sub&gt;2A&lt;/sub&gt;</td>
<td>Agonist or inverse agonist</td>
<td>Reduce motor side effects; improve mood and cognition; sleep regulation</td>
</tr>
<tr>
<td>Serotonin</td>
<td>5HT&lt;sub&gt;1A&lt;/sub&gt;, 5HT&lt;sub&gt;1B/D&lt;/sub&gt;, 5HT&lt;sub&gt;2C&lt;/sub&gt;, 5HT&lt;sub&gt;6&lt;/sub&gt;, 5HT&lt;sub&gt;7&lt;/sub&gt;</td>
<td>Antagonist or partial agonist</td>
<td>Possibly contribute to efficacy and tolerability</td>
</tr>
<tr>
<td>Serotonin</td>
<td>5HT&lt;sub&gt;1A&lt;/sub&gt;</td>
<td>Partial agonist</td>
<td>Anxiolytic; booster of antidepressant action</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>α&lt;sub&gt;2A, 2B, 2C&lt;/sub&gt;</td>
<td>Agonist or Antagonist</td>
<td>Antidepressant; anxiolytic; effects on emotional memories&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>α&lt;sub&gt;1A, 1B, 1C&lt;/sub&gt;</td>
<td>Agonist</td>
<td>Improve cognition and reduce behavioral disturbance in ADHD, depression and OCD; cardiac effects. reduce orthostatic hypotension and sedation&lt;sup&gt;1,6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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

# Theoretical Receptor-mediated Physiological Effects of Pharmacological Agents: Non-monoamine Neurotransmitters

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Receptor Target(s)</th>
<th>Intrinsic Activity</th>
<th>Clinical/Safety Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA</td>
<td>GABA&lt;sub&gt;B&lt;/sub&gt;</td>
<td>Agonist</td>
<td>Sleep modification; pain reduction; anxiolytic&lt;sup&gt;2&lt;/sup&gt;; anti-epileptic&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Histamine</td>
<td>H&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Antagonist</td>
<td>Alleviate anxiety and insomnia; may cause sedation and weight gain</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>M&lt;sub&gt;1&lt;/sub&gt;, M&lt;sub&gt;3&lt;/sub&gt;/M&lt;sub&gt;5&lt;/sub&gt;</td>
<td>Antagonist</td>
<td>May contribute to metabolic dysregulation</td>
</tr>
<tr>
<td>Glutamate</td>
<td>NMDAR, mGluR</td>
<td>Agonist or antagonist</td>
<td>Antidepressant, antipsychotic, anxiolytic, pain control</td>
</tr>
</tbody>
</table>

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

Effective Pharmacologic Treatments for Depression

<table>
<thead>
<tr>
<th>Class</th>
<th>Proposed Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US Food and Drug Administration-Approved Therapies for Depression</strong></td>
<td></td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)¹</td>
<td>Increase synaptic serotonin levels and possibly postsynaptic serotonin receptor activation</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitors (SNRIs)¹</td>
<td>Increase synaptic levels and possibly receptor activation of both serotonin and norepinephrine</td>
</tr>
<tr>
<td>Selective norepinephrine reuptake inhibitors (NRIs)²</td>
<td>Increases synaptic norepinephrine and postsynaptic adrenergic receptor activation</td>
</tr>
<tr>
<td>Tricyclic antidepressants (TCAs)³</td>
<td>Inhibit serotonin and norepinephrine reuptake</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors (MAOIs)⁴</td>
<td>Inhibits an enzyme that degrades synaptic monoamines</td>
</tr>
<tr>
<td>Atypical/multimodal antidepressants &amp; antipsychotics⁵⁻⁷</td>
<td>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)</td>
</tr>
</tbody>
</table>

| Other Potential Therapies for Depression                  |
|---------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Amphetamines⁸                                             | Increase extracellular dopamine levels through multiple mechanisms                         |
| Mood stabilizers⁹,¹⁰                                       | Unknown                                                                                  |
| Other¹¹⁻¹³                                               | Variable                                                                                 |

¹, ², ³, ⁴, ⁵, ⁶, ⁷, ⁸, ⁹, ¹⁰, ¹¹, ¹², ¹³: References are provided at the end of the page.

References:
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

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

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

QUESTIONS