Pharmacologic Treatments In Major Depressive 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.
MDD: Treatment Practices

*Up to two-thirds of adult patients will 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.

**Combination and Augmentation**
- Atypical antipsychotics
- Mood stabilizers

**SSRI**

**SNRI NDRI**

**MAOI and TCA**

**ECT**

**Potential Failed Treatment Attempts**


- VNS may be an additional option for individuals who have not responded to at least 4 adequate trials of antidepressant treatment, including ECT.
Proposed Mechanisms for Antidepressant Activity\textsuperscript{1-7}

Antidepressants

- Reuptake inhibitors
  - SSRIs, SNRIs, NDRIs
  - TCAs
- MAOIs

Mood Stabilizers

- Evidence suggests some may enhance serotonergic neurotransmission

Antipsychotics

- All alter D\textsubscript{2} neurotransmission
- Some atypical antipsychotics also target 5-HT receptors, NE receptors, and a variety of other receptor types

GABA=gamma aminobutyric acid; MAOI=monoamine oxidase inhibitor; NDRI=norepinephrine-dopamine reuptake inhibitor; NE=norepinephrine; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant.

In general, most antidepressants function by increasing the availability of monoamines (serotonin, norepinephrine, and/or dopamine) in the synapse, which is thought to be depleted in depression¹:

- **SSRIs, SNRIs and TCAs** increase monoamines by blocking one or more of the monoamine transporters thus preventing the neurotransmitters from being taken back into the axon terminal for recycling or degradation¹
- **MAOIs** increase monoamines by inhibiting the activity of the monoamine oxidase enzyme (acting as an ‘enzyme inhibitor’), and thus preventing the breakdown of neurotransmitters¹

Effective Pharmacologic Treatments for Depression

<table>
<thead>
<tr>
<th>Class</th>
<th>Proposed Mechanism of Action</th>
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<tbody>
<tr>
<td><strong>US Food and Drug Administration-Approved Therapies for Depression</strong></td>
<td></td>
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<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>
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</tbody>
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<table>
<thead>
<tr>
<th>Other Potential Therapies for Depression</th>
<th></th>
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<tbody>
<tr>
<td>Amphetamines⁸</td>
<td>Increase extracellular dopamine levels through multiple mechanisms</td>
</tr>
<tr>
<td>Mood stabilizers⁹,¹⁰</td>
<td>Unknown</td>
</tr>
<tr>
<td>Other¹¹-¹³</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Differential Actions of Antidepressant Agents on Positive and Negative Affect

Loss of Positive Affect

Depression With Loss of Interest and Energy

Loss of Pleasure/Enjoyment

Loss of Motivation

Loss of Interest

Low mood

Sadness

Fear

Irritability

Anxiety

Guilt

Depression With Anxiety

Negative Affect

Dopamine/Norepinephrine Agents

Norepinephrine/Serotonin Agents

### 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>
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</thead>
<tbody>
<tr>
<td><strong>Dopamine</strong></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><strong>Serotonin</strong></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>
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<tr>
<td></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></td>
<td>5HT&lt;sub&gt;1A&lt;/sub&gt;</td>
<td>Partial agonist</td>
<td>Anxiolytic; booster of antidepressant action</td>
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<tr>
<td><strong>Norepinephrine</strong></td>
<td>α&lt;sub&gt;2A&lt;/sub&gt;, α&lt;sub&gt;2B&lt;/sub&gt;, α&lt;sub&gt;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></td>
<td>α&lt;sub&gt;1A&lt;/sub&gt;, α&lt;sub&gt;1B&lt;/sub&gt;, α&lt;sub&gt;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>
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