Looking to the Horizon: Novel Agents in Development for the Treatment of Depression
Learning Objectives

• Explain the neurobiological rationale for potential antidepressants with novel mechanisms of action

• Describe the mechanisms of action of novel antidepressants that are currently in development
Pretest Question

One antidepressant treatment strategy currently being explored is the development of "triple reuptake inhibitors," agents that block reuptake of serotonin, norepinephrine, and dopamine. Which of the following agents currently in development is a "triple reuptake inhibitor"?

1. Amitифadine
2. Vortioxetine
3. Edivoxetine
Triple Reuptake Inhibitors

• 1 mechanism (SSRI) = good
• 2 mechanisms (SNRI) = better?
• 3 mechanisms (SERT+NET+DAT) = best?
• Attempt to capture the efficacy of MAOIs without the side effects

SERT: Serotonin reuptake transporter; NET: norepinephrine reuptake transporter; DAT: dopamine reuptake transporter

Triple Reuptake Inhibitors in Development

• Each agent differs slightly in its relative blockade of SERT, NET, and DAT
  – Too much dopamine reuptake inhibition (DRI) can lead to abuse potential; too little is not different than an SNRI
    • Ideal seems to be 10–25% inhibition of DAT

<table>
<thead>
<tr>
<th>Agent</th>
<th>Clinical Trial Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitifadine (EB-1010)</td>
<td>III</td>
</tr>
<tr>
<td>GSK-372475</td>
<td>II</td>
</tr>
<tr>
<td>BMS-820836</td>
<td>II</td>
</tr>
<tr>
<td>SEP-227162</td>
<td>II</td>
</tr>
</tbody>
</table>

Levomilnacipran

• Fetzima ® approved July 2013

• Once-daily dosing with 20-, 40-, 80-, and 120-mg extended release capsules

• Serotonin-norepinephrine reuptake inhibitor (SNRI)
  – 2-fold greater potency for NET than SERT
  – 10-fold higher selectivity for NET than SERT compared to duloxetine or venlafaxine

Levomilnacipran: Efficacy

Modified ITT population: all patients in safety population with ≥1 post-baseline MADRS total score. *P<.05 vs placebo. **P<.01 vs placebo. ***P<.001 vs placebo.


# Levomilnacipran Tolerability

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo (n=176)</th>
<th>40 mg/d (n=178)</th>
<th>80 mg/d (n=179)</th>
<th>120 mg/d (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event (AE), n(%)</td>
<td>0</td>
<td>2 (1.1)</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to discontinuation, n (%)</td>
<td>3 (1.7)</td>
<td>13 (7.3)</td>
<td>26 (14.5)</td>
<td>12 (6.7)</td>
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<tr>
<td>≥1 treatment-emergent AE</td>
<td>63.6</td>
<td>75.8</td>
<td>82.7</td>
<td>76.7</td>
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<tr>
<td>Headache</td>
<td>11.4</td>
<td>16.3</td>
<td>20.1</td>
<td>15.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3</td>
<td>10.7</td>
<td>21.8</td>
<td>12.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>4.0</td>
<td>10.7</td>
<td>10.1</td>
<td>12.8</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>9.7</td>
<td>11.2</td>
<td>6.7</td>
<td>15.0</td>
</tr>
<tr>
<td>Heart rate increased</td>
<td>1.7</td>
<td>10.1</td>
<td>6.1</td>
<td>9.4</td>
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<tr>
<td>Hyperhidrosis</td>
<td>2.3</td>
<td>5.1</td>
<td>13.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4.5</td>
<td>5.6</td>
<td>9.5</td>
<td>7.8</td>
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<tr>
<td>Upper respiratory tract infection</td>
<td>5.7</td>
<td>7.9</td>
<td>6.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5.7</td>
<td>6.2</td>
<td>5.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0.6</td>
<td>4.5</td>
<td>6.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>5.6</td>
<td>5.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.0</td>
<td>3.9</td>
<td>6.1</td>
<td>3.9</td>
</tr>
<tr>
<td>Urinary hesitancy</td>
<td>0</td>
<td>3.9</td>
<td>3.4</td>
<td>6.1</td>
</tr>
<tr>
<td>Back pain</td>
<td>4.0</td>
<td>1.1</td>
<td>5.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>2.2</td>
<td>6.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>2.9</td>
<td>5.4</td>
<td>2.9</td>
<td>9.5</td>
</tr>
<tr>
<td>Ejaculation delayed</td>
<td>0</td>
<td>0</td>
<td>5.9</td>
<td>0</td>
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Multimodal Agents

- Combine multiple modes of monoaminergic action
- Vortioxetine (LuAA21004)
  - Transporter mode: SERT inhibitor
  - Ion channel mode: 5HT3 antagonist
  - G protein receptor mode:
    - 5HT1A partial agonist
    - 5HT1B/D partial agonist
    - 5HT7 antagonist
  - Raises 5 neurotransmitters in preclinical models
    - 5HT, NA, DA
    - Plus histamine and acetylcholine

<table>
<thead>
<tr>
<th>SERT inhibition</th>
<th>5HT1A partial agonism</th>
<th>5HT1B partial agonism</th>
<th>5HT7 antagonism</th>
<th>5HT3 antagonism</th>
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</thead>
<tbody>
<tr>
<td>5HT</td>
<td><img src="image" alt="5HT1A partial agonism" /></td>
<td><img src="image" alt="5HT1B partial agonism" /></td>
<td><img src="image" alt="5HT7 antagonism" /></td>
<td><img src="image" alt="5HT3 antagonism" /></td>
</tr>
</tbody>
</table>

5HT, NE, DA, ACh, HA

Vortioxetine

<table>
<thead>
<tr>
<th>SERT inhibition</th>
<th>5HT1A partial agonism</th>
<th>5HT1B partial agonism</th>
<th>5HT7 antagonism</th>
<th>5HT3 antagonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant</td>
<td>Antidepressant</td>
<td>Antidepressant?</td>
<td>Antidepressant</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Reduce sexual dysfunction?</td>
<td></td>
<td></td>
<td>Pro-cognitive</td>
<td>Pro-cognitive?</td>
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</table>

Beyond Monoamines: The Neuroplasticity Hypothesis of Depression

Duration of antidepressant treatment (days)

- Monoamine levels
- Changes in neuroplasticity and glutamatergic neurotransmission
- Depressive symptoms
Beyond Monoamines: The Neuroplasticity Hypothesis of Depression

• The depressed brain shows signs of inadequate neuroplasticity and excessive glutamate

• Acting on monoaminergic systems, currently available antidepressants may lead to downstream improvement in neuroplasticity and glutamatergic neurotransmission

• Directly targeting glutamatergic neurotransmission or neuroplasticity may:
  – Lead to faster treatment response (e.g., ketamine)
  – Improve response and remission rates

Activation of cAMP response element binding protein (CREB)

Various signaling cascades
- MAPK - RSK - cAMP - PKC
- Wnt/Frz - GSK-3 - CaMK

Genes turned on or off
- Increased expression of AMPA receptor subunits
- Increased proteins involved in neuroplasticity (e.g., BDNF)
- Downregulation of NMDA receptors
- Decreased release of glutamate

Increased neuroplasticity and reduced glutamatergic neurotransmission
50% of Patients Respond to Monoaminergic Antidepressants

Deficiency in monoamines

Increase monoamine levels with an antidepressant
50% of Patients DO NOT Respond to Monoaminergic Antidepressants

Adequate monoamines

Increase monoamine levels with an antidepressant

Downstream dysfunction in glutamatergic neurotransmission or neuroplasticity
50% of Patients DO NOT Respond to Monoaminergic Antidepressants

Adequate monoamines

Pharmacological modulation of downstream dysfunction in glutamatergic neurotransmission or neuroplasticity
## Novel Treatments to Address Excess Glutamate in Depression


<table>
<thead>
<tr>
<th>Agent</th>
<th>Clinical Trial Phase</th>
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<tbody>
<tr>
<td>Lamotrigine/Riluzole</td>
<td>IV/II</td>
</tr>
<tr>
<td>Memantine/Amantadine</td>
<td>III</td>
</tr>
<tr>
<td>Ketamine/Dextromethorphan</td>
<td>IV</td>
</tr>
</tbody>
</table>
NMDA Receptor

Glutamate

Glycine

Mg$^{2+}$

Ca$^{2+}$

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Possible Sites of Action of Lamotrigine and Riluzole on Glutamate Release

Memantine and Amantadine

- Bind to magnesium site only when NMDA channel is open

Memantine
- Mild to moderate Alzheimer's disease

Amantadine
- Parkinson's disease
- Also increases dopamine release via an unknown mechanism
Memantine Actions
Ketamine

• Ketamine (anesthetic)
  – Blocks NMDA receptors, evokes glutamate release
  – Like phencyclidine, induces schizophrenia-like symptoms in normal volunteers and exacerbates them in patients
  – Short-term, low-dose intravenous ketamine does not induce full range of psychotic symptoms in experimental setting
Site of Action of Ketamine: Binds to Open Channel at PCP Site to Block NMDA Receptor

Site of Action of Ketamine: Binds to Open Channel at PCP Site to Block NMDA Receptor
PCP-Ketamine: Model of Schizophrenia or Novel Antidepressant?

Ketamine blockade of NMDA receptors
PCP-Ketamine: Model of Schizophrenia or Novel Antidepressant?

Ketamine blockade of NMDA receptors
Ketamine Increases Synaptic Plasticity

Ketamine Rapidly Increases the Density and Function of the Dendritic Spines of Layer V Pyramidal Neurons in the Prefrontal Cortex

Bottom slide shows regeneration of synaptic connections in group receiving ketamine compared to control group (Courtesy of Yale University)
Dextromethorphan

- Oral ketamine?
- Approved for cough, pseudobulbar affect
  - Potent $\sigma$-1 receptor agonist
    - Modulates NMDA signaling, inhibiting presynaptic release of glutamate in cortex
    - Modulates postsynaptic intracellular $\text{Ca}^{2+}$ mobilization
  - Uncompetitive NMDA receptor antagonist
    - Limits glutamatergic signaling and potentiates dopaminergic signaling
  - Serotonin reuptake transporter (SERT) inhibitor
  - Norepinephrine reuptake transporter (NET) inhibitor
Other Glutamatergic Strategies: NMDA Receptor Subtypes
### Other Glutamatergic Strategies: NR2B Selective NMDA Antagonists

<table>
<thead>
<tr>
<th>Agent</th>
<th>Clinical Trial Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traxoprodil (CP101,606)</td>
<td>II</td>
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<tr>
<td>AZD6765</td>
<td>II</td>
</tr>
<tr>
<td>EVT101/103</td>
<td>II</td>
</tr>
<tr>
<td>Radiprodil (RGH 896)</td>
<td>II</td>
</tr>
<tr>
<td>MK 0657</td>
<td>II</td>
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</tbody>
</table>

## Additional Treatment Strategies In Development

<table>
<thead>
<tr>
<th>Agent (Mechanism)</th>
<th>Clinical Trial Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin (MAOI)</td>
<td>IV</td>
</tr>
<tr>
<td>Infliximab (TNF-alpha antagonist)</td>
<td>IV</td>
</tr>
<tr>
<td>Rellidep (From chicken eggs/unknown)</td>
<td>III</td>
</tr>
<tr>
<td>ALKS 5461 (Buprenorphine + opiate antagonist)</td>
<td>III</td>
</tr>
<tr>
<td>Cimicoxib (COX-2 inhibitor)</td>
<td>II</td>
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</table>

# Additional Treatment Strategies In Development: Augmentation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Clinical Trial Phase</th>
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<tbody>
<tr>
<td>Folate</td>
<td>IV</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>IV</td>
</tr>
<tr>
<td>Cariprazine and brexpiprazole (atypical antipsychotics)</td>
<td>III</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>III</td>
</tr>
<tr>
<td>Edivoxetine (NET inhibitor)</td>
<td>III</td>
</tr>
<tr>
<td>Omega-3</td>
<td>III</td>
</tr>
<tr>
<td>S-adenosylmethionine (SAMe)</td>
<td>III</td>
</tr>
<tr>
<td>St. John's Wort</td>
<td>III</td>
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</tbody>
</table>

Cariprazine

• D2 partial agonist
  – More of an antagonist than aripiprazole

• In late-stage clinical testing for schizophrenia, acute bipolar mania, bipolar depression, and treatment-resistant depression
  – Higher doses for schizophrenia and mania (antagonist actions)
  – Lower doses for depression (agonist actions)

• Stronger affinity for D3 than D2 receptors

• Few metabolic side effects and low risk of EPS identified thus far

• Long-lasting metabolites have potential for long-acting formulations

- D2 partial agonist
  - More of an antagonist than aripiprazole

- Very low risk of EPS and rare akathisia identified thus far despite strong affinity for D2 receptors
  - Possibly due to potent 5HT2A antagonism, 5HT1A agonism, and α1 antagonism

- Potential treatment for agitation and psychosis in dementia

Summary

• There are several investigational drugs in development for the treatment of depression.

• Some of the novel antidepressants in development target impaired monoaminergic neurotransmission in accordance with the monoamine hypothesis of depression.

• Additionally, a number of novel agents in development target components of the neuroplasticity hypothesis of depression, including hypothetically overactive glutamatergic neurotransmission and dysfunctional HPA axis functioning.