BEYOND MONOAMINES: NOVEL APPROACHES TO ANTIDEPRESSANT TREATMENT
Learning Objective

• Describe the molecular targets of novel agents, including adjunctive treatments, currently being investigated
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

Pharmacological modulation of downstream dysfunction in glutamatergic neurotransmission or neuroplasticity
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

Neuroplasticity: Monoamine Signaling and Brain-Derived Neurotrophic Factor Release BDNF

monoamine

CaMK: calcium/calmodulin-dependent protein kinase
PKA: protein kinase A
CREB: cAMP response element-binding protein
BDNF: brain-derived neurotrophic factor
Downstream Improvement in Neuroplasticity and Glutamatergic Neurotransmission

Genes turned on

Increased expression of AMPA receptor subunits
Downregulation of NMDA receptors
Increased proteins involved in neuroplasticity
Decreased release of glutamate

Activation of cAMP response element binding protein (CREB)

Signaling cascades

Monoamine regulation

DA  5HT  NE

MAPK  RSK  cAMP
PKC  Wnt/Frz  CaMK
GSK-3

Increased neuroplasticity and reduced glutamatergic neurotransmission

Directly targeting glutamatergic neurotransmission or neuroplasticity may lead to faster treatment response and may improve response and remission rates.
Ketamine Increases Synaptic Plasticity

mammalian Target Of Rapamycin: a critical intracellular protein that mediates neuroplasticity and neurotrophic processes

AMPARs

Increased synaptic plasticity

Ketamine’s Antidepressant Effects May Also Be Due to Activation of AMPA Receptors, not the Blocking of NMDA Receptors.
Rapid Antidepressant Effect of Ketamine in 18 Patients With Treatment-Resistant Depression

29% were considered to be in remission, with an HDRS score of 7 or below (data not shown)

Proportion With 50% Change in Score From Baseline (HDRS)

HDRS: Hamilton Depression Rating Scale

Zarate CA Jr et al. Arch Gen Psychiatry 2006;63:856-64.
Ketamine Formulations

• Ketamine intranasal administration 50 mg vs saline placebo (n=27)
  – Effective, easier to administer

• Intranasal esketamine (S-enantimer of racemic ketamine)
  – 0.20 mg/kg and 0.40 mg/kg intravenous esketamine exhibited significant reductions in MADRS scores compared with placebo (n=30)\(^2\)
  – After a 1-week period, all three intranasal esketamine treatment groups (28 mg, 56 mg, or 84 mg) changes in MADRS total scores were statistically superior to placebo on Day 8 (n=67)\(^3\)

• Efficacy and safety of intravenous, intramuscular and subcutaneous routes for treating depression with ketamine\(^4\)
  – All three had comparable antidepressant effects; Subcutaneous has fewest adverse effects

MADRS: Montgomery-Asberg Depression Rating Scale

# A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders

## Recommendations from the American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatment Recommendations for Clinical Use of Ketamine

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **Patient Selection**          | • Strongest evidence for major depressive disorder  
                                 • Less evidence in other mood disorders  
                                 • Baseline symptom assessment  
                                 • Antidepressant treatment history  
                                 • Physical and laboratory  
                                 • Informed consent including discussion of potential risks and benefits                                                                                                         |
| **Clinical Experience and Training** | • Currently no recommendations or guidelines  
                                 • Clinicians should be prepared to manage potential cardiovascular events and behavioral effects of ketamine                                                                                   |
| **Treatment Setting**           | • Setup for monitoring of cardiovascular and respiratory function                                                                                                                                                  |
| **Medication Delivery**         | • Most studies use 0.5 mg/kg of IV ketamine delivered over 40 minutes  
                                 • Dose may need to be adjusted for patients with BMI>30                                                                                                                                                    |
| **Follow-up and Assessments**  | • Use rating instruments to assess clinical response and evaluate risk:benefit ratio of continued treatment                                                                                                      |
| **Efficacy of Longer-term Repeated Administration** | • Studies suggest that repeated dosing may extend the duration of ketamine effects  
                                 • Ketamine administration 2X/week over 2-3 weeks seems as effective as 3X/week over 2-3 weeks  
                                 • Taper or discontinue treatment based on an individual patient basis                                                                                                                                             |
| **Safety Measures and Continuation of Treatment** | • Risk of cognitive impairment and cystitis are associated with chronic ketamine use  
                                 • Substance abuse liability  
                                 • Frequent ketamine administration is not recommended                                                                                                                                                        |
| **Future Directions**           | • Major knowledge gaps remain regarding long-term efficacy and safety  
                                 • Further, large-scale studies are needed  
                                 • Clinicians providing ketamine treatment are encouraged to participate in coordinated systems of data collection                                                                                      |

Other Glutamatergic Modulators

### Failed to Show Efficacy or No Longer in Development

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riluzole</td>
<td>Voltage-gated sodium channels</td>
<td>Did not out-preform placebo on mean MADRS$^{10.05}$</td>
</tr>
<tr>
<td>Memantine</td>
<td>NMDA receptor</td>
<td>Trials for depression unsuccessful$^{2,3}$</td>
</tr>
<tr>
<td>Lanicemine</td>
<td>NMDA receptor</td>
<td>Failed to show superior efficacy$^4$</td>
</tr>
<tr>
<td>CP-101,606</td>
<td>NMDA-NR2B subunit</td>
<td>Ceased due to association with cardiac conduction abnormalities$^5$</td>
</tr>
<tr>
<td>EVT-101</td>
<td>NR2B selective antagonist</td>
<td>Clinical hold issued by the FDA</td>
</tr>
<tr>
<td>MK-0657</td>
<td>NMDA-NR2B subunit</td>
<td>Weak evidence of efficacy</td>
</tr>
<tr>
<td>AZD-6423</td>
<td>NMDA receptor</td>
<td>Weak evidence of efficacy</td>
</tr>
</tbody>
</table>

### Still in Early Development

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<tr>
<th>Agent</th>
<th>Target</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-Cycloserine</td>
<td>NMDA receptor</td>
<td>Moderate evidence$^6$</td>
</tr>
<tr>
<td>GLYX-13 (rapastinel)</td>
<td>NMDA receptor</td>
<td>Currently in Phase III; Moderate evidence$^7$</td>
</tr>
<tr>
<td>AVP-786</td>
<td>NMDA receptor, Sigma-1 receptor, SERT, NET</td>
<td>Phase II clinical trial in MDD) as adjunct</td>
</tr>
<tr>
<td>AVP-923</td>
<td>NMDA receptor, Sigma-1 receptor, SERT, NET</td>
<td>Phase II clinical trial in MDD</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>NMDA receptor</td>
<td>Preliminary evidence of efficacy for MDD$^8$</td>
</tr>
</tbody>
</table>

Rapastinel: An NMDA Receptor Glycine-Site Functional Partial Agonist vs Positive Allosteric Modulator

- Produces rapid antidepressant effects
  - Single Dose Study Phase IIA (n=116): Single IV dose of rapastinel dose of 1, 5, 10, or 30 mg, or placebo
    - At 1-week post-infusion, 5 and 10 mg of rapastinel showed significant antidepressant response
  - Repeated Dose Study Phase IIB (n=116): Weekly infusions of IV rapastinel (at doses of 1, 5, or 10 mg) or placebo, with follow-up on days 3, 7, and 14
    - IV rapastinel 5 or 10 mg showed a reduction in HAM-D scores on days 1 through 7, but no effects were observed thereafter

- No ketamine-like side effects

- Currently in large phase III trials for MDD

Endogenous Opioid Receptors

**Opioid Peptides**
- β-endorphin
- enkephalin
- dynorphin

**Opioid Receptors**
- Mu (μ)
- Delta (δ)
- Kappa (κ)

**Endogenous Opioid Receptors**

<table>
<thead>
<tr>
<th>Opioid Receptor</th>
<th>Main Endogenous Agonists</th>
<th>Reward Mechanisms</th>
<th>Effect on Pain</th>
<th>Agonism Effects on Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu (μ)</td>
<td>β-Endorphin Met-enkephalin</td>
<td>Facilitates</td>
<td>Analgesia (spinal)</td>
<td>Improved mood, reward and dependence, euphoria, <strong>antidepressant</strong>-like behavior, sedation</td>
</tr>
<tr>
<td>Delta (δ)</td>
<td>Enkephalins</td>
<td>Facilitates</td>
<td>Analgesia (supraspinal &amp; spinal analgesia)</td>
<td>Improved mood; <strong>antidepressant</strong> and antianxiety-like behavior, sedation</td>
</tr>
<tr>
<td>Kappa (κ)</td>
<td>Dynorphin A</td>
<td>Inhibits</td>
<td>Analgesia (spinal)</td>
<td>Worsened mood; dysphoria, anti-reward, sedation</td>
</tr>
</tbody>
</table>

- δ-opioid receptor agonists and κ-opioid receptor antagonists have antidepressant potential
- Likely to be implicated in mood regulation
- All 3 opioid receptors modulate BDNF activity and neurogenesis in the hippocampus

Buprenorphine

- Partial mu opioid agonist
- Kappa antagonist
- Currently used in addiction treatment
- Open label, positive data in refractory depression
- Low Dose Buprenorphine Reduces Suicidal Ideation
  - Double-blind, placebo-controlled trial 88 patients received either 0.1-0.8 mg/day (mean dose 0.44 mg/day) or placebo for 4 weeks
  - Very low dosages of buprenorphine were associated with decreased suicidal ideation in a group of severely suicidal patients without substance abuse

ALKS 5461: Buprenorphine & Samidorphan

- Combination of buprenorphine (partial μ-opioid agonist, kappa antagonist) and samidorphan (μ antagonist)

- Samidorphan added to counteract the μ-opioid agonist activity of buprenorphine & reduce its addictive potential

- Kappa antagonism has shown antidepressant activity in animal models

Study 205

- Ph III Double-blind, placebo controlled
- 11 week trial in AD non-responders (n=814)
- Doses of buprenorphine/ samidorphan
  - 0.5/0.5 mg
  - 2/2 mg
- Both doses not statistically superior to placebo on primary endpoint (MADRS at week 5)
  - Post hoc analysis showed significance for the 2/2 mg dose at other time points

Study 207

• Ph III Multicenter, randomized, double-blind, pbo-controlled (n=407)
• Doses of buprenorphine/samidorphan
  – 1/1 mg
  – 2/2 mg
• Evidence of antidepressant activity in both groups
• Statistically significant for the 2/2mg group only

2/2mg Superior to Placebo
- Improving core symptoms of depression (MADRS-6, p=0.018)
- Overall symptoms of depression (MADRS-10, p=0.026)

The most common AEs:
- Nausea
- Dizziness
- Fatigue

No pattern of AEs indicative of abuse potential

ALKS 5461 as Adjunct in MDD

- **Study 208**: ongoing long-term phase 3b will evaluate the efficacy, safety, and tolerability of ALKS 5461 as adjunctive treatment in patients with MDD

- Agonist-antagonist opioid modulation represents a novel approach to the treatment of MDD

- May be an alternative to adjunct treatment with antipsychotics

Onabotulinumtoxin A

- Acetylcholine (Ach) release inhibitor and neuromuscular blocking agent
- 2 positive randomized-controlled trials in MDD
- Effects of one injection last up to 16 weeks
- Treatment in the glabellar (forehead) region can treat MDD
- 3 groups (n=101)
  - Statistically significant reduction in depressive symptoms in those who received botulinum toxin A versus placebo injections in the frown muscles.

Increased Cholinergic Activity Associated with Depression

• Depression may be associated with hyperactivation of the cholinergic system and, as a consequence, decreased activity in the noradrenergic system

• Anticholinergic agents have been associated with antidepressant effects
  - These antidepressant effects are thought to be mediated through downstream increase in neuroplasticity

• Typical anticholinergic adverse side effects, such as dry mouth, blurred vision, and drowsiness may imply limitation to its broad clinical use

Rapid Antidepressant Actions of Scopolamine

• Acetylcholine muscarinic (AChM) receptor antagonist

• Double-blind, placebo-controlled, crossover clinical trial (n=18)
  – Scopolamine infused at 4.0 μg/kg intravenously produced robust antidepressant effects versus placebo, which were evident within 3 days after the initial infusion

• Scopolamine may exert antidepressant effects by acting on the MTORC1 complex via the mTOR pathway and thereby inducing synaptogenesis

Emerging Somatic Treatments

• Deep Transcranial Magnetic Stimulation (DTMS)
• Repetitive Transcranial Magnetic Stimulation (rTMS)
• Synchronized Transcranial Magnetic Stimulation (sTMS)
• Low Field Magnetic Stimulation (LFMS)
Summary

• Neurobiological substrates of depression may go beyond monoaminergic circuits

• Glutamatergic targets like ketamine, esketamine, and rapastinel have shown promise in treatment of MDD

• Opioid agents like buprenorphine and ALKS 5461 have shown efficacy in treatment of MDD

• Additional research is needed to validate these targets