KEEPING UP WITH THE CLINICAL ADVANCES: DEPRESSION
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

- Increase monoamine levels with an antidepressant
- Downstream dysfunction in glutamatergic neurotransmission or neuroplasticity
- Adequate monoamines
- 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, rapastinel, SAGE-547, SAGE-217)
  • Improve response and remission rates

Neuroplasticity: Monoamine Signaling and Brain-Derived Neurotrophic Factor Release


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

Monoamine regulation

- DA
- 5HT
- NE

Signaling cascades

- MAPK
- RSK
- cAMP
- PKC
- Wnt/Frz
- GSK-3
- CaMK

Activation of cAMP response element binding protein (CREB)

Genes turned on

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

Increased neuroplasticity and reduced glutamatergic neurotransmission

The Three G's
Glutamate, GABA, and Glycine
Impaired Neuroplasticity Due to Imbalanced GABA and Glutamate signaling

- Abnormalities in glutamatergic neurotransmission via the N-methyl-D-aspartate receptor (NMDA-R) have a key role in the pathophysiology of depression

Hashimoto K et al. Transl Psychiatry. 2016;6:e744.
Dysfunction of Glutamate Signaling

• Glutamate is an excitatory neurotransmitter involved in many functions, including synaptic plasticity, learning, and memory.

• Studies have shown regional changes in glutamate receptors, as well as elevated levels of glutamate in the brains of patients with MDD.

• Normal glutamatergic activity is thought to be involved in maintaining normal neuroplasticity.

• Under conditions of stress or depression, glutamate signaling is impaired, leading to a reduction of neuroplasticity.

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

Ketamine

• Ketamine (anesthetic)
  • Blocks NMDA receptors, evokes glutamate release
  • 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
Ketamine Increases Synaptic Plasticity

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

Ketamine’s Antidepressant Effects May Also Be Due to Activation of AMPA Receptors, not the Blocking of NMDA Receptors

Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism

Recent study showed that ketamine may work to treat depression, at least in part, by activating opioid receptors.

- **Ketamine** + **Placebo**
  - Reduction in symptoms of depression

- **Ketamine** + **Naltrexone** (opioid-blocking drug)
  - Almost no effect on symptoms of depression

Utility of (2R,6R)-Hydroxynorketamine via Direct AMPA Activation

(2R,6R)-Hydroxynorketamine (HNK)—a metabolite of ketamine

- Underlying antidepressant mechanism for ketamine may be due to the metabolite (2R,6R)-HNK acting through activation of AMPA receptors, instead of blocking NMDA receptors
  - More effective at reducing depression-like symptoms, even though the (S)-form is about 3–4 times more potent at blocking NMDA receptors
  - Lacks the negative side effects and potential for abuse that ketamine has
- Future research aims to test the effectiveness of (2R,6R)-HNK for the treatment of depression in humans.

Antidepressant Effect of Ketamine Within Hours in Patients With Treatment-Resistant Depression

Dose of intravenous ketamine consistently decreases symptoms of depression in patients with treatment-resistant depression in a rapid (within hours), robust (across many symptoms of depression), and relatively sustained (typically 7-14 days) manner.
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)

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

HDRS: Hamilton Depression Rating Scale
Safety and Efficacy of Repeated-Dose Intravenous Ketamine

- Repeated doses (six infusions over the course of several weeks) have shown promise from an efficacy and safety standpoint
  - Even when dose is escalated

- No advantage in efficacy in sustaining the initial antidepressant effects for two times versus three times a week intravenous ketamine in patients (n=67)

Ketamine Formulations

• Ketamine intranasal administration 50 mg vs saline placebo (n=27)
  – Effective, easier to administer\(^1\)

• 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

| **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-perform placebo on mean MADRS$^{1,05}$</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>
<tr>
<td>AVP-923</td>
<td>NMDA receptor, Sigma-1 receptor, SERT, NET</td>
<td>Alzheimers, no TRD efficacy</td>
</tr>
<tr>
<td>AVP-786</td>
<td>NMDA receptor, Sigma-1 receptor, SERT, NET</td>
<td>Alzheimers, no TRD efficacy</td>
</tr>
</tbody>
</table>


### Still in Development

<table>
<thead>
<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>AXS 05</td>
<td>dextromethorphan + bupropion</td>
<td>Currently in Phase III; Moderate evidence</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

• Allosteric modulator of both glutamate and glycine at novel binding site
  • Functional partial agonist of the glycine site of the NMDA receptor

• In preclinical studies, rapastinel showed robust antidepressant effects with rapid onset and appeared to increase neuroplasticity and enhance synaptic function

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\(^1\)
    - At 1-week post-infusion, 5 and 10 mg of rapastinel showed significant antidepressant response
  - **Repeated Dose Study Phase IIB (n=116):** Weekly infusion of IV rapastinel (at doses of 1, 5, or 10 mg) or placebo, with follow-up on days 3, 7, and 14\(^2\)
    - 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

Novel Positive Allosteric Modulators

- **SAGE-547** (brexanolone), is a intravenous (IV) formulation of allopregnanolone, a naturally occurring neuroactive steroid that acts as a positive allosteric modulator of GABA-A receptors, including both synaptic and extrasynaptic populations.

- **SAGE-217**, a novel, oral neuroactive steroid that, like SAGE-547, is a positive allosteric modulator of GABAA receptors, targeting both synaptic and extrasynaptic GABA-A receptors.
Extrasynaptic Benzodiazepine-Insensitive GABA-A Receptor

GABA-A Complex Receptor contain δ subunit

GABA binding site
Neurosteroid binding site
Two Types of GABA-A Mediated Inhibition

GABA neuron

GABA
Benzodiazepine-sensitive GABA-A receptor
postsynaptic

Benzodiazepine-insensitive GABA-A receptor
extrasynaptic

Phasic Inhibition

Tonic Inhibition

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. 2013
Allosteric Modulation of Extrasynaptic GABA-A Receptors

Positive Allosteric Modulation (PAM) can increase receptor efficiency and/or potency

SAGE-547: Positive Allosteric Modulator of GABA-A Receptors for PPD

Two Double-Blind, Placebo-Controlled, Phase-III Studies

• Women (age 18 – 45) with severe postpartum depression (PPD) for ≤ 6 months

• 3 groups administered a continuous inpatient infusion for 60 hours
  • (brexanolone IV 90 g/kg/hour; brexanolone IV 60 g/kg/hour; and placebo)

• **Results**: Both brexanolone groups experienced a greater mean reduction in HAM-D score compared with placebo after 60 hours
  
  – brexanolone IV 90 g/kg/hour: 17.7 points; P = 0.0252
  – brexanolone IV 60 g/kg/hour: 19.9 points; P = 0.0013

• Effects observed at 60 hours was maintained at the 30-day follow-up

• Brexanolone was well-tolerated overall, and the most common adverse events were headache, dizziness and somnolence.

SAGE-217: Positive Allosteric Modulator of GABA-A Receptors for MDD

• Phase II Clinical Trial: randomized, double blind, placebo controlled clinical trial
  – 89 subjects with moderate-to-severe major depressive disorder (MDD); ages 18-65

• Onset of action is within 24 hours after first dose

• At the end of 14 days patients receiving 30mg of SAGE-217 had a 17.6-point reduction from baseline in HAM-D scale vs. 10.7 point on placebo (p<0.0001)

• Most common adverse events were headache, dizziness, nausea, somnolence
  – AE rates were 53% on SAGE-217 and 46% on placebo

The Endogenous Opioid System
# Identified Phases of Reward Processing

<table>
<thead>
<tr>
<th>Reward Phase</th>
<th>Associated Symptom</th>
<th>Translational Term</th>
<th>Example Experimental Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediction</td>
<td>Anticipatory anhedonia</td>
<td>Reward/loss anticipation</td>
<td>Monetary incentive delay task</td>
</tr>
<tr>
<td>Decision</td>
<td>Impaired decision making</td>
<td>Choice</td>
<td>Iowa gambling task</td>
</tr>
<tr>
<td>Action</td>
<td>Low energy</td>
<td>Effort expenditure</td>
<td>Effort expenditure for rewards task</td>
</tr>
<tr>
<td>Experience</td>
<td>Consummatory anhedonia</td>
<td>Reward/loss feedback</td>
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</table>
Neural Aberrations During Reward Processing in Depression

- Meta-analyses of 38 fMRI and 12 EEG studies
- fMRI studies revealed significantly reduced striatal activation in depressed compared with healthy individuals during reward feedback.
  - When region-of-interest analyses were included, reduced activation was also observed in reward anticipation, effect stronger in individuals <18
- EEG studies involved mainly the FRN event-related potential
  - FRN was also significantly reduced in depression, with pronounced effects in individuals under age 18. In longitudinal studies, reduced striatal activation in fMRI and blunted FRN in EEG were found to precede the onset of depression in adolescents.

EEG: electroencephalogram; fMRI: functional magnetic resonance imaging; FRN: feedback-related negativity
Endogenous Opioid Receptors

<table>
<thead>
<tr>
<th>Opioid Receptors</th>
<th>Opioid Peptides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu (μ)</td>
<td>β-endorphin</td>
</tr>
<tr>
<td>Delta (δ)</td>
<td>enkephalin</td>
</tr>
<tr>
<td>Kappa (κ)</td>
<td>dynorphin</td>
</tr>
</tbody>
</table>

Location of Opioid Receptors

Location of Mu-Receptors in the Brain

Overlap of human emotion circuit

Partial agonist binds to the opioid receptor and causes it to open more frequently than the resting state but less frequently than with a full agonist.
<table>
<thead>
<tr>
<th>Opioid Receptor</th>
<th>Main Endogenous Agonists</th>
<th>Effect on Pain</th>
<th>Effects on Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu (μ)</td>
<td>β-Endorphin</td>
<td>analgesia (spinal)</td>
<td>• antidepressant-like behavior</td>
</tr>
<tr>
<td></td>
<td>Metenkephalin</td>
<td></td>
<td>• euphoria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• reward and physical dependence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• improved mood</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• respiration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• sedation</td>
</tr>
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Mu-opioid receptor agonists may also have antidepressant potential
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<td>Delta (δ)</td>
<td>Enkephalins</td>
<td>Analgesia</td>
<td>• sedation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(supraspinal &amp; spinal analgesia)</td>
<td>• inhibition of dopamine release</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• modulation of mu-opioid receptors</td>
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</tbody>
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Delta-opioid receptors may have antidepressant and anti-anxiety actions.
Kappa neurons may interact to block Mu neurons and thus, kappa agonists worsen depression and cause dysphoria in animal models.

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<tbody>
<tr>
<td>Kappa (κ)</td>
<td>Dynorphin A</td>
<td>Analgesia (spinal)</td>
<td>• worsened mood</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• diuresis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• dysphoria</td>
</tr>
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</table>
Kappa antagonist, especially if combined with a small degree of mu agonist, will potentiate possible antidepressant effects by a novel non monoaminergic mechanism.

Currently being studied for their potential antidepressant actions.
## Endogenous Opioid Receptors

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<th>Opioid Receptor</th>
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<th>Reward Mechanisms</th>
<th>Effect on Pain</th>
<th>Agonism Effects on Behavior</th>
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<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>
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<tr>
<td>Delta (δ)</td>
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- 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

Mu and Kappa Systems Appear to Counteract, Especially in the Mesolimbic Dopaminergic System

In contrast, the activation of kappa ($\kappa$) receptors located presynaptically in the nucleus accumbens inhibits dopamine release.

Activation mu ($\mu$) receptors located on GABA interneurons leads to a disinhibition of dopaminergic neurons projecting the nucleus accumbens.

This leads to an increase in dopamine release in nucleus accumbens.

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
- Possible adjunct to ongoing antidepressant

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
- Neither dose was 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

ALKS 5461: Buprenorphine & Samidorphan

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.

Other Targets in Depression Treatments

Acetylcholine (Ach) Release Inhibitor and Neuromuscular Blocking Agent
- Onabotulinumtoxin A - treatment in the glabellar (forehead) region can treat MDD
  - Effects of one injection last up to 16 weeks

Acetylcholine Muscarinic (AChM) Receptor Antagonist
- Scopolamine may exert antidepressant effects by acting on the MTORC1 complex via the mTOR pathway and thereby inducing synaptogenesis

Glucocorticoid Receptor Antagonists
- Mifepristone (III)
- Metyrapone (III)
- Org-34517 (II)

Emerging Somatic Treatments
- Deep Transcranial Magnetic Stimulation (DTMS)
- Repetitive Transcranial Magnetic Stimulation (rTMS)
- Synchronized Transcranial Magnetic Stimulation (sTMS)
- Low Field Magnetic Stimulation (LFMS)

References:
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