Major Depressive Disorder: Bridging the Gap From Response to Remission
Learning Objectives

• Make evidence-based treatment adjustments to address inadequate antidepressant response
• Implement evidence-based strategies for treatment-resistant depression
• Describe the molecular targets of novel antidepressant treatments
Pre-Poll Question

I feel competent combining mechanisms for patients with depression who have inadequate response.

1. 1 (strongly disagree)
2. 2
3. 3
4. 4
5. 5 (strongly agree)
Pretest Question 1

A 25-year-old patient with first-episode major depressive disorder is being prescribed an antidepressant. The time course for therapeutic effects of antidepressants correlates with:

1. Increase in presynaptic neurotransmission
2. Increase in postsynaptic neurotransmission
3. Changes in receptor sensitivity and expression
Pretest Question 2

A 36-year-old patient with unipolar depression has only partially responded to his second monotherapy with a first-line antidepressant. Which of the following has the best evidence of efficacy in augmenting antidepressants in patients with inadequate response?

1. Adding buspirone
2. Adding lithium
3. Adding a stimulant
Pretest Question 3

The efficacy of ketamine in treatment-resistant depression is hypothesized to be due to:

1. Activation of the mTOR pathway
2. Suppression of the mTOR pathway
3. Upregulation of NMDA receptors
4. Downregulation of AMPA receptors
iSPOT: Remission Rates at 8 Weeks

Remission: HRSD17 ≤ 7
Response: ≥ 50% reduction in HRSD17

Remission: QID-SR16 ≤ 5
Response: ≥ 50% reduction in QID-SR16


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Most Common Residual Symptoms in Nonremitters

Complete remission 33%

Residual symptoms 67% most common: fatigue/pain, concentration, interest

Insomnia

Severe anxiety at baseline predicts non-remission

Present 94% of the time
Persist 44% of the time

Remission is Protective…

Remission after 1 treatment

- 33% relapse after 1 year

Response after 1 treatment

- 60% relapse after 1 year

...But It Also Matters How Fast One Gets There

...But It Also Matters How Fast One Gets There

Remission after 3 treatments

Response after 3 treatments

...But It Also Matters How Fast One Gets There

**Response after 4 treatments**

- 30% relapse
- 70% relapse

**Remission after 4 treatments**

- 0%
- 100%

THERAPEUTIC EFFECTS OF MOST ANTIDEPRESSANTS ARE DUE TO DOWNSTREAM EFFECTS
The Neuroplasticity Hypothesis

Dysregulated signaling cascades

Monoamines

DA

5HT

NE

Inactivation of cAMP response element binding protein (CREB)

Genes turned on or off

Decreased expression of AMPA receptor subunits

BDNF

Decreased proteins involved in neuroplasticity

Upregulation of NMDA receptors

Increased release of glutamate

Decreased neuroplasticity

Acting on monoaminergic systems, current antidepressants may lead to downstream improvement in neuroplasticity and glutamatergic neurotransmission.
Dysregulated signaling cascades

MAPK → RSK → cAMP → PKC → GSK-3 → CaMK

Activation of AMPA response element binding protein (CREB)

Genes turned on or off
- Decreased expression of AMPA receptor subunits
- Decreased proteins involved in neuroplasticity
- Downregulation of NMDA receptors
- Decreased release of glutamate

Increased neuroplasticity and reduced glutamatergic neurotransmission

GETTING TO REMISSION (FASTER)

Combining Mechanisms
The Brain Is a Neuronal Network—and Connectivity is Altered in Depression

The Theory of Multiple Mechanisms

• Symptoms are theoretically linked to abnormal communication in distinct brain circuits
• Multiple symptoms likely means multiple brain circuits involved
• Each circuit is regulated by multiple neurotransmitters, but not all neurotransmitters regulate all circuits
• Theoretically, it's possible that changing more than one neurotransmitter's release in more than one site can affect multiple symptoms linked to multiple circuits
Monotherapies That Target Multiple Monoamines

- bupropion
- desvenlafaxine
- duloxetine
- levomilnacipran
- milnacipran
- venlafaxine

Investigational triple reuptake inhibitors

- imipramine
- trimipramine

MAOI

Na+ channel blocker

SERT

NRI

SRI

H1

1

M1

DAT

NET

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Monotherapies That Target Multiple Receptors

- Trazodone
  - 5HT2A
  - 5HT2C
  - SERT

- Mirtazapine
  - 5HT3
  - 5HT2A
  - 5HT2C

- Vilazodone
  - 1A
  - SERT

- Vortioxetine
  - 1A
  - 1B
  - 1D
  - 3
  - 7
  - SERT

- Amitriptyline
- Amoxapine (minimal SRI)
- Clomipramine
- Doxepin
- Nortriptyline (minimal SRI)
Combining Reuptake Inhibitors

At Last Visit

Dual vs. bupropion: HAM-D 17: $\chi^2=4.39$, df =1, p<.04; HAM-D 29: $\chi^2=4.39$, df =1, p<.04.

Combining Reuptake Inhibitors

At Week 2

<table>
<thead>
<tr>
<th>Measure</th>
<th>Escitalopram (N=84)</th>
<th>Bupropion (N=83)</th>
<th>Dual therapy (N=78)</th>
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<tbody>
<tr>
<td>HAM-D 17</td>
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Dual vs. escitalopram: HAM-D 29: $\chi^2=5.26$, df =1, p<.02; MADRS: $\chi^2=3.66$, df =1, p<.06.
Dual vs. bupropion: HAM-D 17: $\chi^2=4.21$, df =1, p<.04; HAM-D 29: $\chi^2=6.74$, df =1, p<.01; MADRS: $\chi^2=3.56$, df =1, p<.07.

Combining Reuptake Inhibition With Receptor Actions: Positive Study

**FIGURE 1.** Mean Scores on the Hamilton Depression Rating Scale (HAM-D), by Visit, for All Patients Treated (Last Observation Carried Forward) in a Randomized Trial of Antidepressant Monotherapy or Combination Treatment.\(^a\)

- Fluoxytine (N=28)
- Venlafaxine + mirtazapine (N=26)
- Fluoxytine + mirtazapine (N=25)
- Bupropion + mirtazapine (N=26)

\(^a\) Statistically significant difference between fluoxetine monotherapy and all combination treatment groups (F=3.87; df=3, 101, p=0.011).

Combining Reuptake Inhibition With Receptor Actions (CO-MED): Negative Study

## Atypical Antipsychotics in Depression: Proposed Mechanisms

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<thead>
<tr>
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<th>5HT2A</th>
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<th>5HT1B/D</th>
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*Approved (olanzapine in combination with fluoxetine; quetiapine only for XR).


Atypical Antipsychotic Augmentation

• Adjunct olanzapine, quetiapine, aripiprazole, or risperidone to SSRI/SNRI
  – Meta-analysis¹
    • Significant benefit vs. placebo for remission rates; NNT=7
    • Significantly higher discontinuation rate due to adverse effects
  – Meta-analysis²
    • Greater effect sizes in patients with higher degree of treatment resistance (response)

Combining Mechanisms: Adjunct Lithium

neurotrophin

GSK-3

promotes neuroprotection
long-term plasticity

Chiu CT, Chuang DM. Pharmacol Ther 2010;128:281-304;

= lithium
Lithium Augmentation

• Augmenting response (meta-analysis)$^1$
  – 10 studies (7 TCAs, 3 SSRIs)
  – Significant benefit vs. placebo; NNT = 4

• Augmenting remission (STAR*D)$^2$
  – Benefit not confirmed

• Accelerating response (meta-analysis)$^1$
  – 5 studies, TCAs
  – No benefit (trend)

• Overall: evidence strongest for augmenting TCAs

Combining Mechanisms: Adjunct Triiodothyronine (T3)

blood-brain barrier

T3/T4

T3 Augmentation

• Augmenting remission (STAR*D)\(^1\)
  – Trend favoring T3 over lithium (methodological factors?)

• Augmenting response (meta-analysis)\(^2\)
  – 8 studies, TCAs
  – Significantly increased response rate; NNT = 5

• Augmenting response to SSRIs (various studies)\(^3\)
  – Mixed results, placebo-controlled study showed no benefit

• Overall: evidence strongest for augmenting TCAs

Meta-analysis
Across Augmentation Options

• 48 trials (6,654 participants)
• Significantly more effective than placebo
  – Quetiapine (OR=1.92; 95%CI 1.39–3.13)
  – Aripiprazole (OR=1.85; 95%CI 1.27–2.27)
  – Thyroid (OR=1.84; 95%CI 1.06–3.56)
  – Lithium (OR=1.56; 95%CI 1.05–2.55)
• Aripiprazole and quetiapine efficacy estimates were more robust than thyroid and lithium
• Quetiapine, olanzapine, aripiprazole, and lithium were significantly less well tolerated than placebo

Recommended Adjunct Doses in Unipolar Depression

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
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<tbody>
<tr>
<td>lithium</td>
<td>0.6–1.0 mEq/L (bipolar depression)*</td>
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<tr>
<td>T3</td>
<td>25–50 mcg</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>2–10 mg</td>
</tr>
<tr>
<td>brexpiprazole</td>
<td>2 mg</td>
</tr>
<tr>
<td>olanzapine</td>
<td>5–20 mg</td>
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<tr>
<td>olanzapine-fluoxetine combination</td>
<td>3/25 mg–12/50 mg</td>
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<tr>
<td>quetiapine</td>
<td>150–300 mg</td>
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*Blood level listed due to narrow therapeutic index
## Adjunct Medications: Side Effects

<table>
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<th>LI</th>
<th>T3</th>
<th>ARIP</th>
<th>BRX</th>
<th>OLZ</th>
<th>QUET</th>
<th>Other</th>
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<td>hyperthyroidism</td>
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<td>Acne</td>
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<td>nausea, akathisia</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>akathisia</td>
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## Adjunct Medications: Monitoring Guidelines

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<th>Parameter</th>
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<th>6 Months</th>
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<td>Thyroid*</td>
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<td>Calcium</td>
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<td>Li</td>
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<td>Serum levels**</td>
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<td>Weight</td>
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<td>Fasting lipids</td>
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<td>Fasting glucose</td>
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AAP: atypical antipsychotic  
Li: lithium

*Periodic for T3  
**Stable patients  
†For first 3 months of treatment  
‡For first year of treatment

Combining Mechanisms: Transcranial Magnetic Stimulation (TMS)

1. Electromagnetic coil on scalp: magnetic field penetrates skull by a few cm
2. Depolarizes neurons in superficial cortex
3. Through neural pathways, this local stimulation causes functional changes in other brain regions

TMS Augmentation

Change From Baseline in HAMD Scores

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
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<tbody>
<tr>
<td>Bakim 2012</td>
<td>1.09 [0.34, 1.84]</td>
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<tr>
<td>Bretlau 2008</td>
<td>0.98 [0.36, 1.60]</td>
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<tr>
<td>Chen 2013</td>
<td>0.91 [-0.02, 1.84]</td>
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<tr>
<td>Garcia-Toro 2001</td>
<td>1.08 [0.36, 1.79]</td>
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<tr>
<td>Garcia-Toro 2006</td>
<td>0.78 [-0.00, 1.57]</td>
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<tr>
<td>Martinot 2010</td>
<td>0.43 [-0.19, 1.06]</td>
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<tr>
<td>Total (95% CI)</td>
<td>0.86 [0.57, 1.15]</td>
<td></td>
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</table>

Heterogeneity: Tau² = 0.00; Chi² = 2.67, df = 5 (P = 0.75); I² = 0%
Test for overall effect: Z = 5.75 (P < 0.00001)

TMS: The Procedure

- Generally done on an outpatient basis
- No anesthesia, no loss of consciousness
- Pulses of magnetic field are delivered in 30-s intervals
  - 4 s each, 26-s rest intervals, 10 pulses/s
  - Feels/sounds like light tapping on the scalp (patient and staff should wear protective earplugs)
- Session length: typically 30–50 min
- Treatment duration: usually 5 treatments/week, 4–6 weeks
- Therapeutic dose: 90–120% of motor threshold*

*Motor threshold: magnetic field strength that results in movement of right thumb
TMS: Clinical Considerations

😊 Side Effects

Headache, discomfort at stimulation site
Rare risk of generalized seizure

🚫 Contraindications

Patients with ferromagnetic metal within 30 cm of the coil

⚠️ Caution

Patients with an implantable device controlled by physiological signs

<table>
<thead>
<tr>
<th>Option</th>
<th>Data summary</th>
<th>References</th>
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<tbody>
<tr>
<td>Buspirone</td>
<td>Makes sense mechanistically but data are mixed/weak</td>
<td>Connolly and Thase, 2011; Trivedi et al., 2006; Appelberg et al., 2001</td>
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<tr>
<td>Stimulants</td>
<td>Limited data show trend of benefit</td>
<td>Trivedi et al., 2013</td>
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<tr>
<td>DA agonists</td>
<td>Best evidence for modafinil/armodafinil</td>
<td>Goss et al., 2013; Aiken, 2007; Cassano et al., 2005; Calabrese et al., 2010; Fava et al., 2005</td>
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<td>L-methylfolate</td>
<td>Positive controlled studies</td>
<td>Bottiglieri, 2013</td>
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<tr>
<td>Option</td>
<td>Data summary</td>
<td>References</td>
</tr>
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<td>----------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
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<tr>
<td>Bright light therapy</td>
<td>Meta-analysis in non-seasonal depression suggests possible efficacy</td>
<td>Golden et al., 2005; Pail et al., 2011</td>
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<td>SAMe</td>
<td>Positive controlled study; dosed 800–1600 mg/day oral or 200–400 mg/day IM; best absorbed if taken 20 min before a meal; not recommended in first trimester</td>
<td>Papakostas et al., 2010</td>
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<tr>
<td>Omega-3</td>
<td>Multiple meta-analyses suggest modest efficacy; 60% EPA (of total EPA+DHA) needed; 1–3 g/day is generally safe (including dietary intake)</td>
<td>Lin et al., 2012; Martins et al., 2012; Freeman et al., 2006; McNamara and Shawn, 2013; Grosso et al., 2014</td>
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<tr>
<td>Exercise</td>
<td>5 times/wk, 45–59 min/session was best in studies</td>
<td>Rethorst et al., 2009; Rimer et al., 2012; Josefsson et al., 2015</td>
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</table>
GETTING TO REMISSION (FASTER)

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

Ketamine Increases Synaptic Plasticity

Bunney BG, Bunney WE. *Int J Neuropsychopharmacol* 2012;15:695-713.
AMPA receptor

NMDA receptor blocked by ketamine

ERK, AKT

mTOR

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)
Prospects for Glutamatergic Strategies

• Alternative delivery for ketamine
  – Preliminary case studies and open-label trials for:
    • Oral (20% bioavailability)
    • Intramuscular (similar bioavailability)
    • Sublingual (~30% bioavailability)
  – Double-blind trial
    • Intranasal
• Other promising glutamatergic strategies?
  – Not yet...

GETTING TO REMISSION (FASTER)

Personalized Treatment
Evolving Disease Models in Depression

Can collections of biomarkers help stratify patients based on their underlying pathogenesis?
Plasma Biomarkers Involved in L-methylfolate Treatment Response

- SAM/SAH ratio
- hsCRP (mg/L)
- 4-HNE (ug/mL)

Effect Size (HDRS-28 Change from Baseline)
- Favors L-methylfolate
- ≥2.71
- ≥2.25 < 2.25
- ≥3.28 < 3.28

Preliminary Data: CRP Level Affects Differential Treatment Response

Targeting "Inflammatory Depression"

• Several studies and meta-analysis show that NSAIDs and cytokine inhibitors can reduce depressive symptoms, BUT...
  – With few exceptions, the studies have not pre-selected or stratified patients based on baseline inflammation
  – Drugs studied (e.g., celecoxib) have additional, non-inflammatory effects

• Standardized subset of inflammatory markers is needed
  – C-reactive protein, tumor necrosis factor, and interleukin-6

Other Potential Biomarkers

• Growth factors: BDNF, insulin-like growth factor 1, vascular endothelial growth factor, interferon regulatory factor 7
• Endocrine factors: dexamethasone (dex) suppression test, CRF stimulation test, Dex-CRF test, sleep EEG (CRF)
• Genetic: serotonin transporter, 5HT2A, COMT, MTHFR
• Metabolic: BMI, leptin, ghrelin, others?
• Gene expression: histone deacetylase 5, CREB, histone deacetylase 2

Summary

- Depression is likely a result of several underlying pathogeneses that lead to overlapping symptoms.
- Likely due to their downstream effects, monoaminergic agents are effective for many patients.
- Goal of treatment is to get patients to remission as fast as possible—and keep them there.
- Theoretical strategies to enhance/hasten remission:
  - Combining mechanisms
  - Directly targeting glutamate and neuroplasticity
  - Personalized strategies