Novel Treatments for Major Depression

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Consultant in Psychiatry, Massachusetts General Hospital
My spouse and I have the following relevant financial relationships with a commercial interest to disclose:

<table>
<thead>
<tr>
<th>Consultant (Honoraria)</th>
<th>Axsome, CNS Response, Lundbeck, Sunovion</th>
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<tbody>
<tr>
<td>Research Funding (though the Icahn School of Medicine at Mount Sinai)</td>
<td>Alkermes, Brainsway</td>
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</table>
STAR*D: Current Antidepressant Medications Have Modest Efficacy

% remission

Meta-Analysis on the Comparative Efficacy of 12 New-Generation Antidepressants

117 RCTs (25,928 patients)

Odds Ratio – Fluoxetine as Reference

Favors fluoxetine

Favors comparator

Efficacy (response rate) drug vs. fluoxetine

Bupropion, Citalopram, Duloxetine, Escitalopram, Fluvoxamine, Miniprazapram, Mirtazapine, Paroxetine, Reboxetine, Sertraline, Venlafaxine

*p<0.05

Cipriani et al., Lancet 2009
FDA-Approved Antidepressants in the Last Five Years

- Vilazodone (2011)

- Levomilnacipran ER (2013)

- Vortioxetine (2013)
Vilazodone Blocks Serotonin Transporters and is a Partial Agonist of 5HT$_{1A}$ Receptors

1. Selective inhibition of serotonin reuptake
2. Partial agonist at 5-HT$_{1A}$ receptors

Only serotonergic neurotransmission is depicted here.
Vilazodone – Clinical Efficacy

Lower Rates of Sexual AEs than SSRIs, similar to BUP

- Whether the statistically significant differences observed at time points earlier than 8 or 10 weeks represent clinically relevant treatment effects is unknown.
- VIIBRYD should be taken with food. Taking VIIBRYD on an empty stomach can reduce plasma concentrations by approximately 50% and may diminish effectiveness.

Levomilnacipran-ER

- SNRI
- Two-fold greater selectivity for NE vs. 5-HT
- Starting dose = 20 mg/day
- Effective Dose = 40-120 mg/day

<table>
<thead>
<tr>
<th></th>
<th>5-HT</th>
<th>NE</th>
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<tr>
<td>IC_{50}, ng/mL</td>
<td>4.7</td>
<td>2.5</td>
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<td>IC_{80}, ng/mL</td>
<td>22.4</td>
<td>10.1</td>
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<td>IC_{90}, ng/mL</td>
<td>58.3</td>
<td>22.6</td>
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</table>

Inhibition of 5-HT and NE Transporters by Levomilnacipran
Levomilnacipran ER – Clinical Efficacy

Safety and Efficacy of Levomilnacipran

Number Needed to Treat or Harm vs. Placebo

Efficacy - NNT

Tolerability - NNH


NNT for response/remission, NNH for adverse events where incidence with levomilnacipran ≥ 5% and ≥ 2 times the rate for placebo as identified in product labelling (3), and NNH for discontinuation because of an adverse event, with 95% CIs, for pooled short-term studies comparing levomilnacipran vs. placebo. AE, adverse event; D/C, discontinuation; NNH, number needed to harm; NNT, number needed to treat.
Levomilnacipran ER: Impact on Functional Disability

- Improved functional outcomes (Sheehan Disability Scale) vs. placebo in 4/5 studies
- Only antidepressant with FDA approval for functional improvement

Vortioxetine - Serotonin Receptor Modulator at Clinically Relevant Doses

Clinical dose range gives 50-90% SERT occupancy

<table>
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<th>Receptor</th>
<th>Affinity (nM)</th>
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<td>5-HT&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>5-HT&lt;sub&gt;1B&lt;/sub&gt;</td>
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<td>SERT</td>
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Pehrson AL et al. Eur Neuropsychopharmacol 2012;
Vortioxetine – Clinical Efficacy

7/11 placebo-controlled trials were positive

Relative Efficacy/Safety of Vortioxetine

Number Needed to Treat or Harm vs. Placebo

Efficacy - NNT

Tolerability - NNH

Vortioxetine Effects on Cognition
Meta-Analysis of 3 RCTs

Efficacy on the DSST (Digit Symbol Substitution Test)

Also positive on the self-report PDQ (Perceived Deficits Questionnaire)

Treatment-Resistant Depression

• Failure to respond to 2+ antidepressant trials of adequate dose and duration
• Constitutes ~1/3 of patients with MDD
• Remission rates in TRD<<20%
• Contributes significant costs, morbidity, mortality
• Important Steps in Evaluation:
  – Diagnostic reassessment (unipolar vs. bipolar)
  – Psychiatric and medical comorbidities
  – Previous trials adequate in dose and duration?
  – Pharmacokinetic factors (metabolic inducers; rapid/fast metabolizers)
Promising Next-Generation Pharmacological Strategies for TRD

- Glutamatergic receptors modulators
- Opioid receptors modulators
- Scopolamine
- Anti-inflammatory agents
The Glutamate Synapse

Sanacora et al. 
Nat Rev Drug Discovery 2008
Glutamate Signaling is Abnormal in Depression

- Acute stress increases glutamate signaling in cortex
- Chronic stress leads to alterations in glutamate receptors and synapses
- Glial cell loss in human postmortem cortex in MDD is related to glutamate toxicity
- Altered glutamate in MDD detected by brain H¹-MRS
- **Ketamine**: a dissociative anesthetic agent
  - Glutamate NMDA receptor antagonist
  - Rapid antidepressant effects
  - Abuse liability

RCT IV Ketamine vs. Saline (N=18)

Rapid Antidepressant Effect

Robust, rapid, and relatively sustained antidepressant effect of low dose ketamine, and response rates to ketamine in a double-blind placebo crossover trial in patients with treatment-resistant major depression.

Zarate et al. Arch Gen Psych 2006
RCT IV Ketamine vs. Midazolam (N=72)

Rapid Antidepressant Effect

Mean diff = 7.95 points
[95%CI: 3.2, 12.7]  
P = 0.002

KET RR = 64%
MID RR = 28%

OR = 2.18, P = 0.006

Meta-Analysis of Ketamine Efficacy in TRD

Newport DJ et al. *Am J Psychiatry. 2015*

### At 1 day

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
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### At 1 week

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<td>Murrough et al. (87)</td>
<td>3.937</td>
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<td>13.492</td>
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Odds Ratio and 95% CI
Acute Behavioral and Hemodynamic Effects of Ketamine in TRD

Review of 205 IV ketamine infusions:

- No significant increase in psychotic symptoms
- Measurable small and transient increase in dissociative symptoms
- Transient increase in blood pressure

Next steps: Repeated IV Ketamine and Intranasal Ketamine

- Repeated dose IV ketamine – effective, but mean duration of improvement is 18 days
- Intranasal ketamine – effective, easier to administer
- Janssen is developing IN esketamine for TRD (currently in phase 3 studies)

Lanicemine (AZ6765) - a Novel NMDA Receptor Antagonist
Positive Phase II Results, Development Terminated in Phase III

Failed to Show Efficacy
• Memantine
• Lamotrigine
• Lanicemine (AZ 6765)
• MK 0657 (NR2B Antag)
• EVT 101 (NR2B)
• CP-101,606
• Org 26576 (AMPA)
• Riluzole

Still Early in Development
• D-cycloserine
• Rapastinel (GLYX-13)
  – Glycine site

Is there another mechanism that explains the effects of ketamine?
RCT of the NMDA Receptor Partial Agonist D-Cycloserine (1g/d) Augmentation for TRD

Heresco-Levy et al. *Int J Neuropsychopharm.* 2013
GLYX 13 Has Ketamine-like Effects in Several Animal Models of Depression

GLYX 13 Phase 2A Single-Dose Study
U shaped dose response: max effect at 5 and 10 mg

**GLYX-13 at 5 and 10 mg/kg:**
- Drug Effect: p<0.05
- Time Effect: p<0.0001
- Drug x Time: p<0.0001

**Effect size of GLYX-13 after a single dose was roughly double that of SSRIs after weeks of repeated dosing**

| GLYX-13 (one 5 mg/kg dose) = 0.41-0.49 | Abilify (6 wks daily dosing) = 0.36 |
| GLYX-13 (one 10 mg/kg dose) = 0.43-0.58 | SSRIs (6-8 wks daily dosing) = 0.20-0.25 |

GLYX 13 Phase 2B Repeated-Dose Study
Weekly IV dosing (5 mg, 10 mg, or PBO)

HDRS-17 decreased after GLYX-13 and increased after PBO

Burch et al. Poster presented at ACNP, 2014
6 weeks post GLYX-13 withdrawal
HDRS-17 did not return to baseline

GLYX-13 10 mg/kg weekly
performed less well than
other dosing regimens

No psychotomimetic adverse events

Burch et al. *Poster presented at ACNP, 2014*
Endogenous Opioids and Their Receptors - Abnormal in MDD

Sadness and chronic stress lead to alterations in opioid receptors neurotransmission\(^1\)\(^-\)\(^4\)

The opioid system: mu-, delta-, and kappa receptors (G protein-coupled)

mu-receptors: analgesia, reward, and dependence\(^2\)

delta-receptors: anti-depressant and anti-anxiety-like behavior\(^3\)

kappa receptors: anti-reward, dysphoria, pro-depression\(^4\)

Reductions in mu-opioid receptor-mediated neurotransmission during a sustained sadness state\(^1\)

1) Zubieta et al, Arch Gen Psychiatry, 2003.
3) Filliol et al. Nat Genet 2000;
Opioid Receptors Regulate Monoaminergic Systems Relevant to Mood Control

Buprenorphine

- Partial mu opioid agonist
- Kappa antagonist
- Used in addiction treatment
- Open label, positive data in refractory depression
- RCT of Low Dose Buprenorphine for Suicidal Ideation
  - N=88 patients with clinically significant suicidal ideation
  - Buprenorphine 0.1-0.8 mg/day (mean 0.44 mg/day) or placebo for 4 weeks
  - Buprenorphine superior to PBO for reducing suicidal ideation at 2 and 4 weeks
  - No withdrawal symptoms after treatment discontinuation

RCT of ALKS 5461 (buprenorphine + mu antagonist ALKS 33) in SSRI non-responders

Figure 4: MADRS Change from Baseline at Week 4

ALKS-5461 As Adjunct in MDD

- FORWARD-3 and FORWARD-4
- 814 patients in DB, PBO controlled 11 week trials in antidepressant non-responders
- Doses of buprenorphine/samidorphan (0.5/0.5 mg and 2/2 mg)
- Both doses not superior to PBO
- FORWARD-5 (1/1 mg and 2/2 mg) continues
A Kappa Opioid Receptor Agonist Increases Anhedonia and Depression

Selective kappa agonist U-69593 produces anhedonia (increase in reward threshold on FST) and depression (FST)

Todtenkopf et al 2004; Mague et al 2003
Selective Kappa Antagonists Normalize Reward and Produce Antidepressant-Like Effects

Intracranial Self-Stimulation Thresholds

Kappa Opioid Antagonist ANTI – Forced Swim Test

CERC 501 – a novel kappa opioid receptor antagonist currently evaluated as treatment for depression and anhedonia

The Cholinergic System and Mood Disorders

- Elevated cholinergic function is implicated in the pathophysiology of mood disorders.¹
- Physostigmine (an anticholinesterase inhibitor) exacerbates depressive symptoms in MDD and BD patients¹
- Muscarinic receptor gene polymorphisms are associated with an elevated incidence of depression.²
- Scopolamine (an acetylcholine muscarinic receptor antagonist), produces rapid antidepressant effects in MDD patients³

RCT of IV Scopolamine (4 μg/kg) in TRD (n=18)

• IV Scopolamine has rapid antidepressant effects¹

• Mechanism associated with increased mTOR and synaptogenesis² (like ketamine)

RCT of Oral Scopolamine (1 mg/d) Augmentation of Citalopram in MDD

Figure 2. Results of 2-Factor Repeated-Measures Analysis of Variance

*P < .05, **P < .01.  
High Prevalence of Inflammation in Depression

Meta-analysis of Cytokine Levels in MDD

- Cytokines = non-antibody proteins released by cells on contact with antigens
- Cytokines induce depressive symptoms and HPA axis activation
- Depressed patients have high levels of cytokines

2) Yirimya R et al, Ann NY Acad Sci, 2000;
RCT of Adjunctive Cyclooxygenase-2 inhibitor Celecoxib in MDD

Figure 1. Mean ± SD of the two protocols on the Hamilton Depression Rating Scale scores. ns, nonsignificant; ** ≤ 0.01 and *** ≤ 0.001.

Akhondzadeh et al. Depression and Anxiety. 2009, 26:607–611
Adding NSAIDs to SSRIs is Associated with Worsening of Antidepressant-Like Effects

Antidepressants \( \rightarrow \) Cytokines \( \rightarrow \) p11 \( \rightarrow \) behavioral response

NSAIDs

Tail Suspension Test

Forced Swim Test

Warner-Schmidt JL et al. PNAS. 2011.
TNF-α Antagonist Infliximab – Effective Only for TRD Subjects with Pre-Existing Inflammation (high CRP)

Somatic Treatments for TRD

- Repetitive Transcranial Magnetic Stimulation (rTMS)
- Deep Transcranial Magnetic Stimulation (DTMS)
- Synchronized Transcranial Magnetic Stimulation (sTMS)
- Low Field Magnetic Stimulation (LFMS)
Right Unilateral Ultrabrief ECT + Venlafaxine in Geriatric MDD


www.mghcme.org
Continuation ECT + Venlafaxine + Lithium for Maintenance of Treatment Response

ECT Superior to Pharmacotherapy in Treatment-Resistant Bipolar Depression

Response Rates
ECT 73.9%
Pharmacotherapy 35.0%

Meta-analysis of Repetitive TMS (rTMS) for MDD


*Add-on therapy.  
Abbreviation: rTMS = repetitive transcranial magnetic stimulation.
Deep TMS: Improved Remission Rates in TRD

Remission Rates Stratified by Treatment Resistance

Levkovitz et al. World Psych. 2015
## Comparison of FDA-approved device treatments

<table>
<thead>
<tr>
<th></th>
<th>ECT</th>
<th>rTMS</th>
<th>Deep TMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy in TRD</strong></td>
<td>++</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Most concerning AE</strong></td>
<td>Cogn. def. (som. chronic)</td>
<td>Seizures (rare)</td>
<td>Seizures (rare)</td>
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<tr>
<td><strong>Duration of acute treatment</strong></td>
<td>2-4 wks (3/week)</td>
<td>4-6 wks (5/week)</td>
<td>4-6 wks (5/week)</td>
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RCT of Synchronized TMS (sTMS) in MDD

- Frequency of stimulation = intrinsic alpha rhythm of the individual
- Low intensity of magnetic field
- Potential to become a take-home TMS device

Low Field Magnetic Stimulation

Change in Mood after LFMS

Change in VAS
- All subjects
- BPD
- MDD

Change in HDRS
- All subjects
- BPD
- MDD

Change in PANAS+
- All subjects
- BPD
- MDD

Change in PANAS-
- All subjects
- BPD
- MDD

Conclusions

- A variety of novel pharmacological and somatic treatments, **with new mechanisms of action**, currently undergoing validation for TRD.
  - Ketamine – replicated, rapid efficacy
    - GLYX 13 with promising data
    - Unclear why many other glutamategic strategies have failed
  - Early promising data for
    - Opioid agents: CERC 501, ALKS 5461
    - Scopolamine
  - Anti inflammatory agents: possibly helpful in subset with high inflammation
  - Somatic treatments:
    - ECT – gold standard; novel methods of delivery
    - rTMS - well tolerated, lower efficacy; DTMS – possibly improved efficacy for TRD
    - Many other under development: LFMS, sTMS, Onabotulinumtoxin A
- Vibrant area of research, other treatments under development
Thank you!