Unmet Needs in the Pharmacotherapy of Depression: Is Help Really on the Way?

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## Faculty Disclosure: Past Three Years

### Consultant


### Grant/Research


### Advisory Board

Janssen and Lundbeck, A/S.
Objectives of Today’s Presentation

By attending this lecture, the participant will be able to:

● Describe the unmet needs that are not well addressed by the current state of the art for antidepressant pharmacotherapy
● State the recent developments that have led to new medications that address these problems
● Identify treatments that target glutamatergic mechanisms, such as ketamine/esketamine and neurosteroids that indirectly modulate glutamatergic neurotransmission
● Describe how, after 60+ years of exile, there is renewed interest in drugs once classified as psychedelics
Pretest Survey
Patient Perspective
Outpatient Treatment of Major Depressive Disorder:  
*Overview Circa 2023*

- Outpatients’ depressive episodes appear to be comparably responsive to antidepressant medications or focused, time-limited psychotherapies
- Differential outcomes may be influenced by preference, motivation and adherence
- When effective, time-to-benefit is shorter/faster for antidepressants
- Drugs often preferred when severity is high or there is urgency for improvement
- Combined pharmacotherapy + psychotherapy has additive benefits for patients with more chronic, severe or complicated illnesses
- Access to care is important and psychotherapy is not always readily or available
- A large body of research suggests that the nonspecific elements account for much of benefit done by 1st and 2nd line therapies
Antidepressant Therapy: Unmet Needs 2023

- Limited specific efficacy (~10% to 20% advantage vs placebo in RCTs of first- and second-line antidepressants)
- Intolerable side effects for up to 10%
- Inconsistent effects on key symptoms (insomnia, anxiety, cognition) and quality of life measures
- Relatively slow onset of action
- Approximately 20-30% do not respond to multiple medications

RCT = randomized controlled trial; TRD = treatment-resistant depression; MoAs = mechanisms of action

Across Three Generations, Antidepressant Efficacy in RCTs did not Improve Over 40 Years

**Antidepressant response rates over time**

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>Antidepressant</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980–1989</td>
<td>54.5</td>
<td>32.6</td>
</tr>
<tr>
<td>1990–1999</td>
<td>54.2</td>
<td>36.6</td>
</tr>
<tr>
<td>2000 to 5/1/2007</td>
<td>52.9</td>
<td>40.6</td>
</tr>
<tr>
<td>Pooled</td>
<td>53.8</td>
<td>37.3</td>
</tr>
</tbody>
</table>

***p<0.0001 versus placebo

The effect size (standardized drug vs placebo difference) for antidepressants in randomized clinical trials (RCTs) is only $0.3^3$

Antidepressant Therapy: Unmet Needs 2023

- Limited specific efficacy (~10% to 20% advantage vs placebo in RCTs of first- and second-line antidepressants)
- Intolerable side effects for 10%
- Inconsistent effects on key symptoms (insomnia, anxiety)
- Relatively slow onset of action
- Approximately 20-30% do not respond to multiple antidepressants

- As all 1st and 2nd line pharmacotherapies target monoamine neurotransmission, some patients may require treatments that target other MoAs

RCT = randomized controlled trial; TRD = treatment-resistant depression; MoAs = mechanisms of action

Shipwrecks Along the Way: Targeted MoAs That Didn’t Lead to New Antidepressants in the late 1990s & early 2000s

- Corticotrophin Releasing Factor (CRF) antagonists
- Selective norepinephrine reuptake inhibitors (NARIs)
- Melatonin receptor agonists
- Substance P (Neurokinin) antagonists
- Triple reuptake inhibitors
- Selective 5-HT receptor modulators
- Nicotinic partial agonists
By the Early 2000s, Impaired Glutamate Signaling Implicated in Pathophysiology of MDD

Model of glutamate function


Intravenous Ketamine: A Dissociative Anesthetic Turned Paradigm-Changing Antidepressant

The story of ketamine begins with two Parke Davis (Detroit, Michigan) scientists...

- Derivative of phencyclidine (PCP)
- N-methyl-D-aspartate (NMDA) receptor antagonist
- FDA approved anesthetic (Schedule III in US)
- Substance of abuse (e.g., “Special K”)
- Made the WHO’s List of Essential Medicines
- Studied as a model of psychosis – antidepressant effects completely unanticipated & observed serendipitously

Domino EF. Taming the ketamine tiger. 1965. Anesthesiology. 2010;113(3):678-684. doi:10.1097/ALN.0b013e3181ed09a2
Serendipity Yet Again: Ketamine Exerts a Rapid Antidepressant Effect in First Study of Depression

- After several depressed “controls” reported unexpected symptom relief, a small crossover study was performed
- MDD (n=7) or Bipolar Depression (n=1)
- Received single IV infusion of racemic ketamine 0.5 mg/kg or saline
- Double blind, cross over design
- Ketamine group separated from placebo at +240 min
- Effect sustained for >3 days

See source for original image:
https://www.biologicalpsychiatryjournal.com/article/S0006-3223(99)00230-9/fulltext

IV Ketamine: Replicated Efficacy in TRD

A

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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<tbody>
<tr>
<td>Diazgranados et al. (85)</td>
<td>26.053</td>
<td>1.359</td>
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<td>Lapidus et al. (84)</td>
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<td>Zarate et al. (88)</td>
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<td></td>
<td>9.865</td>
<td>4.366</td>
<td>22.293</td>
<td>5.503</td>
<td>0.000</td>
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</table>

B

At 1 week

<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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</thead>
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<td>Diazgranados et al. (85)</td>
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<td>Lapidus et al. (84)</td>
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<td>0.431</td>
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<tr>
<td>Murrough et al. (87)</td>
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<td>Sos et al. (91)</td>
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<td>23.302</td>
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<td>Zarate et al. (88)</td>
<td>19.783</td>
<td>1.060</td>
<td>369.109</td>
<td>1.999</td>
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<td>Zarate et al. (86)</td>
<td>3.222</td>
<td>0.176</td>
<td>58.849</td>
<td>0.789</td>
<td>0.430</td>
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<td></td>
<td>4.610</td>
<td>2.076</td>
<td>10.236</td>
<td>3.754</td>
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Intranasal Esketamine: First Descendant of Ketamine to Obtain Regulatory Approval for Treatment of Depressive Disorders

- S-ketamine (aka esketamine): more potent stereoisomer of ketamine
- Developed for intranasal (IN) delivery for patient/physician convenience
- 84 mg IN approximates 0.5 mg/kg IV racemic ketamine
- Program for TRD yielded multiple positive studies; US FDA approved on 3/19 for **adjunctive therapy** of TRD (level III)
- Two positive Phase 3 studies as an adjunctive therapy for Major Depression with Suicidal Ideation (MDSI): Approved by US FDA in 8/20

Summary of Findings of Phase III Studies of Adjunctive Esketamine for TRD: Intent to Treat Results at 4 Weeks

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Secondary Endpoints</th>
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<tbody>
<tr>
<td></td>
<td>MADRS</td>
</tr>
<tr>
<td><strong>TRANSFORM-1 (3001)</strong></td>
<td></td>
</tr>
<tr>
<td>Esketamine 56 mg + Oral AD</td>
<td></td>
</tr>
<tr>
<td>Esketamine 84 mg + Oral AD</td>
<td></td>
</tr>
<tr>
<td><strong>TRANSFORM-2 (3002)</strong></td>
<td></td>
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<tr>
<td>Flex Esketamine + Oral AD</td>
<td></td>
</tr>
<tr>
<td><strong>TRANSFORM-3 (3005)</strong></td>
<td></td>
</tr>
<tr>
<td>Flex Esketamine + Oral AD</td>
<td></td>
</tr>
</tbody>
</table>

Left and right of 0: better than AD + placebo, worse than AD + placebo, respectively
*As 84 mg was not significant at the 2-sided 0.05 level, 56 mg could not be formally evaluated, and the 2-sided p-value for this dose is considered to be nominal.

LS, least squares; MADRS, Montgomery–Åsberg Depression Rating Scale; PHQ-9, Patient Health Questionnaire; SDS, Sheehan Disability Scale.


Adjunctive Intranasal Esketamine: Outcomes in Two Inpatient Studies of Treatment of MDSI


Relapse Prevention Following Remission or Response to Adjunctive Esketamine: 28+ Week Placebo Controlled Trial of TRD

Patients With Stable Remission

Patients With Stable Response

Risk reduction: 51%

Risk reduction: 70%

Appraising Adjunctive Intranasal Esketamine (ESK) for TRD

Pooling the acute studies, ESK is 4.1 times more likely to result in a therapeutic response than stopping because of an adverse event

<table>
<thead>
<tr>
<th>Agent</th>
<th>Response (≥50% Decrease in Rating Scale) vs Placebo</th>
<th>Discontinuation Because of an AE</th>
<th>LHH for Response vs Discontinuation Because of an AE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rates NNT</td>
<td>Rates NNT</td>
<td></td>
</tr>
<tr>
<td>Esketamine (pivotal study)</td>
<td>63.4% vs 49.5% 8</td>
<td>7.0% vs 0.9*% 17</td>
<td>2.1</td>
</tr>
<tr>
<td>Esketamine (all studies)</td>
<td>49.3% vs 36.4% 8</td>
<td>4.8% vs 1.7% 33</td>
<td>4.1</td>
</tr>
<tr>
<td>Olanzapine-fluoxetine</td>
<td>40.3% vs 27.8% 8</td>
<td>11.6% vs 2.6% 12</td>
<td>1.5</td>
</tr>
<tr>
<td>Adjunctive aripiprazole</td>
<td>37.4% vs 22.5% 7</td>
<td>3.8% vs 1.5% 43</td>
<td>6.1</td>
</tr>
<tr>
<td>Adjunctive quetiapine XR</td>
<td>56.0% vs 46.3% 11</td>
<td>12.1% vs 2.3% 11</td>
<td>1.0</td>
</tr>
<tr>
<td>Adjunctive brexpiprazole</td>
<td>25.2% vs 15.6% 11</td>
<td>2.6% vs 0.7% 53</td>
<td>4.8</td>
</tr>
</tbody>
</table>

- 4 weeks of ESK evidenced similar NNT compared to 6-8 weeks of SGA as adjunctive therapies for TRD
- Overall tolerability (measured by discontinuation because of an adverse event) was also generally similar, if not superior in this TRD population

Citrone L, DiBernardo A, Singh J. Appraising esketamine nasal spray for the management of treatment-resistant depression in adults: Number needed to treat, number needed to harm, and likelihood to be helped or harmed. J Affect Disord. 2020;271:228-238. doi:10.1016/j.jad.2020.03.106
Clinical Experience with Intranasal Esketamine

- Access is still problematic
- Can be used relatively early in treatment hierarchies – Level II - when justified by clinical urgency
- Benefit often begins within 24 hours of first treatment
- Most people can tolerate the higher (84 mg intranasal) dose
- Side effects almost always dissipate within 90 minutes
- Few people (<10%) drop out b/c side effects
- No surprises YET during longer courses of therapy (up to three years)

Safety and Clinical Considerations with Esketamine

- Transient elevation of blood pressure and occasional cases of over-sedation
- Abuse liability (schedule III: same as ketamine)
- In US the Risk Evaluation and Mitigation Strategy (REMS) includes a registry, safety protocol with 2 hour observation; patients cannot drive the same day
- Patients do not possess the drug, which is not sold at retail pharmacies: access tied to systems/prescribers
- Concerns about relationships to opioids and other drugs
More help on the way: Oral NMDA antagonists not directly related to ketamine

- AXS-305 (Auvelity): FDA approved 08/19/22
  - Extended release combination of:
    * bupropion (105 mg) and dextromethorphan (45 mg)
    * BID dosing (total: 210 mg BUP + 90 mg DEX)
- REL-1017 (Esmethadone): In Phase III (25-50 mg/day)
  - S-enantiomer of methadone with *minimal* opioid activity
  - Preferential NR1-2D antagonist
Dextromethorphan Receptor Profile Comparable to Ketamine

DM: dextromethorphan

Dextromethorphan-Bupropion in MDD: Change from Baseline in MADRS Total Score

Early Clinical Experience with Auvelity

- Access can be problematic (i.e., Tier 3-4)
- When practicable, could be used earlier in treatment hierarchies – Level II or Level III (not indicated in TRD)
- Benefit often evident within 1-2 weeks of treatment
- Side effects are minimal
- No evidence of dissociative or psychotomimetic side effects
- The constituent drugs can be cobbled together, but the FDA approved drug cannot be exactly duplicated
REL-1017 Preferentially Blocks Hyperactive NR1-2D Subtypes, Decreasing Tonic Ca\(^{2+}\) Influx & Promoting BDNF synthesis

Once REL-1017 blocks the pore of NR1-2D channels, tonic Ca\(^{2+}\) influx into the postsynaptic cell is downregulated\(^ {1,2}\)

The block of NR1-2D channels by REL-1017 restores neural plasticity by promoting transcription and production of synaptic proteins, including BDNF\(^ {3}\)

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Adjunctive Esmethadone (REL-1017) in MDD Patients with Inadequate Response To Antidepressants: 7 Days of Treatment

Results for REL-1017 suggest a favorable safety and tolerability profile and rapid, robust, and sustained efficacy that will be assessed further in ongoing Phase III studies.

**Change from Baseline in MADRS Total Score***

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>LS Mean Difference vs Placebo</th>
<th>Effect Size</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REL-1017 25 mg</td>
<td>-8.7</td>
<td>0.8</td>
<td>0.0122</td>
</tr>
<tr>
<td>REL-1017 50 mg</td>
<td>-7.2</td>
<td>0.7</td>
<td>0.0308</td>
</tr>
<tr>
<td>Day 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REL-1017 25 mg</td>
<td>-9.4</td>
<td>0.9</td>
<td>0.0103</td>
</tr>
<tr>
<td>REL-1017 50 mg</td>
<td>-10.4</td>
<td>1.0</td>
<td>0.0039</td>
</tr>
</tbody>
</table>

*Trial not powered for efficacy detection; p-values and effect size calculations were performed for efficacy measures, with no adjustments for multiple comparisons. LS Mean, least-squares mean; MADRS, Montgomery-Åsberg Depression Rating Scale.

Now the bad news on Esmethadone

● The 1st Phase 3 study (Reliance III) failed to find a significant difference for Esmethadone over Placebo
  - drug vs pbo difference: 0.9 points
  - secondary analyses suggested too many sites had a high PBO response, possibly ruining signal detection
  - this problem may reflect impact of CoVID-19
● Two more Phase 3 studies are underway: let’s wait & see
Glutamate Synapse Offers Multiple Other Targets

See source for original image: https://www.nature.com/articles/nrd.2017.16
GABAergic Drugs Can Also Modulate Glutamate Synapses

● Antidepressant effects of BZs documented for more than 40 years; multiple positive RCTs for alprazolam and adinazolam
● Potential therapeutic benefits diminished by:
  ○ Risks of misuse, abuse and addiction/dependence
  ○ Concerns about tolerance to therapeutic effects
  ○ Pharmacoepidemiologic risks of chronicity, falls and dementia
● Allopregnanolone (3α,5α-tetrahydroprogesterone ([THP])) is:
  ○ An endogenous, inhibitory pregnane neurosteroid
  ○ Synthetic derivative of progesterone
  ○ Positive allosteric modulator of GABA_A receptors
A Neurosteroid Class of Antidepressants?

- Brexanolone (allopregnolone)
  - FDA approved 03/19 for PPD
  - Delivered via slow (60 hour) IV infusion
- Zuranolone (orally ingested analogue)
  - positive results in PPD
  - positive studies in MDD
  - now under “rolling review” by FDA
Brexanolone Injection in Post-partum Depression: Two Multicenter, Double-Bind, Randomized, Placebo-Controlled, Phase 3 Trials

- Brexanolone 60 hour IV infusion
- Results served as pivotal trial basis for FDA approval (03/19/19)

See source for original images: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31551-4/fulltext
Zuranolone: Summary of Acute Efficacy Data to Date

- 1 PPD and 3 MDD phase 2 or 3 studies with doses of 30 mg or 50 mg
- **End Point**: Change from Baseline in HAMD-17 Total Day 15

The clinical trials above differ in sample size, patient population, entry criteria, and study sites as well as other design elements. No direct comparison can be made across these clinical trials based on the graph above. ROBIN enrolled patients with PPD; MDD-201B, MOUNTAIN, and WATERFALL enrolled patients with MDD.

n = number of patients at that visit. *P<.05 vs placebo.

Clayton AH, et al. Poster presentation at American College of Neuropsychopharmacology Annual Meeting, December 5-8, 2021 (San Juan, PR)
Psychedelic Redux: Can a “guided trip” have sustained antidepressant effects for depressed patients?

- Potential therapeutic applications of psychedelics were briefly studied in the 1950s and early 1960s.
- After 50+ years of virtually complete legal injunctions against use, there has been renewed interest in the past decade.
- Among psychedelics, Psilocybin (derived from a number of mushroom plants) has a short duration of effect (2-6 hours) and a relatively benign tolerability profile.
- Small uncontrolled studies in depressed patients with TRD\(^1\) and terminal cancer\(^2\) suggested significant, sustained antidepressant effects.
  - Treatment protocol included 8 hours of guided therapeutic support.
  - Improvement linked to changes in emotional processing and brain circuitry.
- Small randomized study\(^3\) (n=27) using wait-list control also showed a large effect.

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Lysergic acid diethylamide (LSD) and dimethyltryptamine (DMT), increase extracellular glutamate levels in the prefrontal cortex through stimulation of postsynaptic serotonin (5-hydroxytryptamine) 2A (5-HT2A) receptors that are located on large glutamatergic pyramidal cells in deep cortical layers (v and vi) projecting to layer v pyramidal neurons.

Psilocybin in MDD: decreased amygdala activity predicts reduced depression

Quality pre- and post-treatment fMRI data were collected from 16 of 19 patients. Decreased depressive symptoms were observed in all 19 patients at 1-week post-treatment and 47% met criteria for response at 5 weeks.

Carhart-Harris RL, Roseman L, Bolstridge M, et al. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. Scientific Reports. 2017;7(1). doi:https://doi.org/10.1038/s41598-017-13282-7
Multiple studies report that characteristics of the acute psychedelic experience (e.g., mystical-type, emotional breakthrough) predict longer-term reductions in depression, anxiety and substance use. Long-term increases in connectedness to self, others and the wider world is associated with response to psilocybin but not the SSRI escitalopram.

Escitalopram-Controlled RCT of Psilocybin for Major Depressive Disorder: Primary Outcomes

Compare 8-point QIDS reduction in psilocybin group with 10.9-point reduction in Davis et al. study

WEMWBS = Warwick Edinburgh Mental Wellbeing Scale

Unpublished Results from Compass 2b Study of Psilocybin in Treatment Resistant Depression (TRD)

Primary endpoint - change from baseline in MADRS total score

Statistically significant primary endpoint (p<0.001) at week 3 (25mg vs 1mg). There was a rapid onset of action and durable effects with treatment differences between the 25mg vs 1mg group apparent from the day after COMP360 psilocybin administration.

Summary and Conclusions

- MDD is one of the world’s greatest public health problems, but many patients do not respond to standard therapies
- Serendipitous discovery of IV ketamine’s antidepressant effects led to a new generation of novel therapies
- Esketamine, Brexanolone and Auvelity are the 1st drugs of a 3rd generation of antidepressants to reach US market
- Whether (or not) zuranolone, esmethadone or psilocybin are next to reach market, optimism about novel therapies is higher than any time in decades
Questions?
Posttest Survey