Utilization of Nasal Esketamine for Treatment-Resistant Depression
Aubree Bast, PharmD
PGY-1, VA Texas Valley Coastal Bend

Abbreviations

- ADR(s) – adverse reaction(s)
- AUD – alcohol use disorder
- BPRS – Brief Psychiatric Rating Scale
- CADSS – Clinician Administered Dissociative States Scale
- CNS – central nervous system
- CYP – cytochrome P450
- DBS – deep brain stimulation
- DSM – Diagnostic and Statistical Manual of Mental Disorders
- IGT – internet-gambling therapy
- HI – homicidal ideation
- LS – least squared
- MAOI – monoamine oxidase inhibitor
- MOAA/S – Modified Observer’s Assessment of Alertness/Sedation
- NMDA – N-methyl-D-aspartate
- NNT – number needed to treat
- N/V – nausea/vomiting
- PCP – phencyclidine
- PK/PD – pharmacokinetics/pharmacodynamics
- SD – standard deviation
- SI – suicidal ideation
- SNRI – serotonin/norepinephrine reuptake inhibitor
- SSRI – selective serotonin reuptake inhibitor
- SUD – substance use disorder
- TCA – tricyclic antidepressant
- TMS – transcranial magnetic stimulation

Learning Objectives

- Define the mechanism of action (MOA) of esketamine
- Evaluate the literature regarding the safety and efficacy of esketamine for treatment of depression
- Summarize the short and long term benefits of esketamine in depression management
- Outline the place in therapy of esketamine in major depressive disorder

Major Depressive Disorder (MDD)

- 17 million people in US
- Leading cause of disability worldwide
- 10 year reduction in life expectancy
- Lifetime prevalence: 16.2%
- Risk factors: female sex, age 18-25, genetics

Diagnosis – DSM 5

- ≥ 5 symptoms present nearly every day over a 2 week period
- At least one symptom is either (1) or (2)
  1) Depressed mood most of the day
  2) Decreased interest/pleasure in almost all activities
  3) Significant change in weight or appetite
  4) Insomnia or hypersomnia
  5) Psychomotor agitation or retardation
  6) Fatigue or loss of energy
  7) Feelings of worthlessness or inappropriate guilt
  8) Impaired concentration or uncertainty
  9) Thoughts of death, SI ± intent, or a suicide attempt

Pathophysiology

- Monoamine hypothesis
  - Deficiency of serotonin, norepinephrine, and/or dopamine
- Neurotrophic hypothesis
  - Loss of volume in key brain structures involved in mood regulation
  - Decreased neurotrophic factors, decreased neurogenesis
- Altered glutamatergic and GABAergic neurotransmission
- Genetics, environmental factors, chronic stress also contribute
Assessment Tools

Montgomery-Asberg Depression Rating Scale (MADRS)
- Clinician administered
- 10 items to assess symptom severity during past week
  - Mild: 9-17
  - Moderate: 18-34
  - Severe: 35-60

Patient Health Questionnaire (PHQ-9)
- Patient administered
- 9 items to assess symptom severity during past 2 weeks
  - Mild: 5-9
  - Moderate: 10-14
  - Moderately-severe: 15-19
  - Severe: 20-27


Inventory of Depressive Symptomatology (IDS) and Quick Inventory of Depressive Symptomatology. http://www.ids-qids.org/about.html.

Definitions

- Response: reduction ≥ 50%
- Remission: absence of symptoms
  - MADRS ≤ 12
- Relapse: re-emergence of symptoms
  - MADRS > 22 on two occasions
  - Hospitalization for depression or suicide-related activities

MDD Treatment

- Patient-specific
- Goal: full recovery
- Long time to effect

First Line: SSRI, SNRI, mirtazapine, bupropion, vilazodone, vortioxetine

Partial response

Titrate up

Augment

Change to non-MAOI

No response

MAOI

LAST LINE

Treatment-Resistant Depression (TRD)

- Failure to remit after adequate trials of >2 antidepressants from different classes
  - SSRI, SNRI, TCA, MAOI, misc. agents
- Affects ~1/3 of patients with MDD
- High rate of relapse
- Increased morbidity, mortality, and healthcare costs
- 7-fold increase in suicide attempts
- Approximately $83 billion annually, including indirect costs

TRD Treatment

- Augmentation agents:
  - Atypical antipsychotic, lithium, bupropion, thyroid hormone, psychostimulant
- Non-pharmacologic:
  - Psychotherapy, behavioral modifications, ECT, DBS, TMS
- Ongoing research:
  - NMDA antagonists, anti-inflammatory agents

Ketamine

- Background
  - Derivative of PCP, termed a “dissociative anesthetic”
  - Developed 1962, approved human use 1970
  - Abused as a club drug starting late 1970s
- Physical effects
  - Low doses: dissociative symptoms, feeling of floating, hallucinations
  - High doses: “K-hole” that produces an “out of body” or near death experience
  - esketamine = 5 enantiomer


Image: https://www.pharmacistanswers.com/storage/uploads/articles/width_750/xI8D7bgzPeWh3ulLuJyTF8JJ4v7AJb6XRXU1ZHnR.jpeg
Esketamine Pharmacology

- **MOA**: NMDA receptor antagonist
  - Higher affinity
- **PK/PD**
  - Metabolism: CYP2B6/3A4 to noresketamine (active)
  - Half-life: esketamine 7-12hrs, noresketamine 8hrs

**Adverse effects**
- Sedation, depersonalization, dissociation, dizziness, HA, anxiety
- Hypertension, N/V, nasal irritation

Administration Logistics

- REMS program, C-III
  - Sedation, dissociation, misuse, abuse
- FDA-approved dosing
  - Induction: 56mg (up to 84mg) twice weekly x4 weeks
  - Maintenance: decrease to weekly x4 weeks then every other week
- Each device contains 2 sprays (total 28mg)
  - 1 spray each nostril
  - 56 mg = 2 devices, separated by 5 minutes
- Monitored for 2 hours after administration

Historical: IV Ketamine

- A double-blind, randomized, placebo-controlled dose-frequency study in patients with treatment-resistant depression
  - IV ketamine 0.5mg/kg twice weekly vs. thrice weekly vs. placebo x2 weeks
  - MADRS decreased significantly both ketamine groups
  - Response or remission sustained through 4 weeks
  - ADRs > 20%: HA, anxiety, dissociation, nausea, dizziness

**Ketamine 2x** (n=18)
- Placebo 2x (n=16)
- Ketamine 3x (n=17)
- Placebo 3x (n=16)

<table>
<thead>
<tr>
<th></th>
<th>Ketamine 2x</th>
<th>Placebo 2x</th>
<th>Ketamine 3x</th>
<th>Placebo 3x</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change MADRS</td>
<td>-18.4</td>
<td>-5.7</td>
<td>-17.7</td>
<td>-9.1</td>
</tr>
<tr>
<td>Responders at day 15</td>
<td>69%</td>
<td>15%</td>
<td>54%</td>
<td>6%</td>
</tr>
<tr>
<td>Remitters at day 15</td>
<td>38%</td>
<td>8%</td>
<td>23%</td>
<td>0%</td>
</tr>
</tbody>
</table>

TRANSFORM-1

Fedgchin M, Trivedi M, Daly EJ, et al.
Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1).

Overview

- **Objective**
  - Assess safety and efficacy of fixed dose nasal esketamine
- **Design**
  - Randomised, double-blind, active-controlled, multicenter phase 3 trial
  - 1:1:1 to esketamine 56mg, 84mg, or placebo nasal spray twice weekly
  - Oral antidepressants: escitalopram, sertraline, duloxetine, venlafaxine ER

Patient Population

**Inclusion Criteria**
- 18-64 years old
- Recurrent MDD or single-episode > 2 years duration
- IDS-C ≥ 34 and MADRS ≥ 28
- Nonresponse to ≥2 antidepressants in current episode

**Exclusion Criteria**
- SI with intent in past 6 months or suicidal behavior in past year
- Any psychotic or bipolar disorder
- Moderate - severe SUD in past 6 months
- Positive urine drug screen
Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Esketamine 84mg</th>
<th>Esketamine 56mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>N = 116</td>
<td>N = 117</td>
<td>N = 113</td>
</tr>
<tr>
<td>Mean age</td>
<td>45.7</td>
<td>46.4</td>
<td>46.8</td>
</tr>
<tr>
<td>Female sex</td>
<td>69.3%</td>
<td>70.4%</td>
<td>71.1%</td>
</tr>
<tr>
<td>White race</td>
<td>74.6%</td>
<td>79.1%</td>
<td>76.1%</td>
</tr>
<tr>
<td>Mean age of diagnosis</td>
<td>32.1</td>
<td>30.3</td>
<td>31.8</td>
</tr>
<tr>
<td>Mean duration current episode (weeks)</td>
<td>212.7</td>
<td>202.8</td>
<td>193.1</td>
</tr>
<tr>
<td>≤ 3 Previous trials</td>
<td>48.2%</td>
<td>30.1%</td>
<td>40.7%</td>
</tr>
<tr>
<td>Mean PHQ-9</td>
<td>20.7</td>
<td>20.3</td>
<td>20.8</td>
</tr>
</tbody>
</table>

Methods

- Primary outcome: change in MADRS from baseline to day 28
  - Response = ≥ 50% improvement
  - Remission = MADRS score ≤ 12
- Key secondary outcomes
  - Response by day 2 sustained through day 28
  - Change in total Sheehan Disability Scale (SDS) score
  - Change in Patient Health Questionnaire-9 (PHQ-9)
- Safety – vital signs, CADSS, BPRS, MOAA/S

Statistical Analysis

- Enrollment of 234 patients provides 90% power
  - Treatment difference of 6.5 points
- Analyses based on patients receiving ≥ 1 dose
- Fixed sequence procedure
  - 84mg dose: 2-sided alpha 0.05
  - 56mg dose: 2-sided alpha 0.045
- Outcomes
  - Mixed-effects/repeated measures model
  - Weighted combination test for between-group comparisons

Results

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Esketamine 84mg</th>
<th>Esketamine 56mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline MADRS (SD)</td>
<td>37.8 (5.58)</td>
<td>37.4 (4.76)</td>
<td>37.5 (6.16)</td>
</tr>
<tr>
<td>Mean change at day 28</td>
<td>-18.8 (14.12)</td>
<td>-19 (13.86)</td>
<td>-14.8 (15.07)</td>
</tr>
<tr>
<td>Difference of LS means (95% CI)</td>
<td>-3.2</td>
<td>-4.1</td>
<td>n/a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Esketamine 84mg</th>
<th>Esketamine 56mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response at day 2 sustained to day 28</td>
<td>8.8%</td>
<td>10.4%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Mean change in SDS score</td>
<td>-11.1</td>
<td>-11</td>
<td>-4.4</td>
</tr>
<tr>
<td>Mean change in PHQ-9</td>
<td>-11.7</td>
<td>-11</td>
<td>-9.1</td>
</tr>
</tbody>
</table>

Results cont’d

<table>
<thead>
<tr>
<th></th>
<th>Esketamine 84mg</th>
<th>Esketamine 56mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders at day 28</td>
<td>53.1%</td>
<td>54.1%</td>
<td>38.9%</td>
</tr>
<tr>
<td>Remitters at day 28</td>
<td>38.8%</td>
<td>36%</td>
<td>30.6%</td>
</tr>
</tbody>
</table>

- Safety
  - Transient, mild to moderate
  - ADRs > 15%: nausea, dissociation, dizziness, vertigo, headache, somnolence
  - Blood pressure increase approximately 15/9mmHg
  - ADRs peak within 40 minutes, resolve within 90 minutes
Study Evaluation

Strengths
- Validated assessment tools
- Active comparator
- Verification of treatment failure

Limitations
- Authors are employees of sponsor
- Exclusion of patients with recent suicidality, comorbidities
- Difficult to blind patients
- Short duration active comparator

Conclusion

- Authors’
  - Rapid antidepressant effect increases with repeated dosing
  - Clinically significant response
  - Safe and effective in combination with newly initiated antidepressant
- Personal
  - Efficacy questionable, but 50% response is potentially clinically significant
  - Optimal dosing and duration of therapy unknown

Overview

- Objective
  - Assess safety and efficacy of flexibly dosed nasal esketamine
- Design
  - Randomized, double-blind, active-controlled, multicenter phase 3 trial
  - 1:1 to esketamine (56mg or 84mg) or placebo nasal spray twice weekly
  - Oral antidepressants: escitalopram, sertraline, duloxetine, venlafaxine ER

Patient Population

Inclusion Criteria
- 18-64 years old, medically stable
- Recurrent MDD or single-episode ≥ 2 years duration
- ISD-C ≥ 34
- Nonresponse to ≥2 antidepressants in current episode

Exclusion Criteria
- SU/M with intent in past 6 months, suicidal behavior in past year
- Any psychotic, bipolar, personality, obsessive-compulsive, autistic spectrum disorder or intellectual disability
- Moderate-severe SUD (past 6 months) or lifetime ketamine use disorder
- Positive urine drug screen
- Non-response to ketamine, esketamine, study antidepressants, or ECT

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Esketamine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>N = 114</td>
<td>N &gt;109</td>
</tr>
<tr>
<td>Mean age</td>
<td>44.9 (12.6)</td>
<td>46.4 (11.1)</td>
</tr>
<tr>
<td>Female sex</td>
<td>65.8%</td>
<td>57.8%</td>
</tr>
<tr>
<td>White race</td>
<td>93%</td>
<td>93.6%</td>
</tr>
<tr>
<td>Mean age of diagnosis</td>
<td>32.1 (22.5)</td>
<td>35.3 (13.04)</td>
</tr>
<tr>
<td>Mean duration current episode (weeks)</td>
<td>114 (124.3)</td>
<td>118 (187.4)</td>
</tr>
<tr>
<td>≥ 3 Previous trials</td>
<td>31.6%</td>
<td>33.9%</td>
</tr>
<tr>
<td>Mean MADRS</td>
<td>37 (5.7)</td>
<td>37.3 (6.24)</td>
</tr>
</tbody>
</table>
Methods

• Primary outcome: change in MADRS from baseline to day 28
  • Response = ≥ 50% improvement
  • Remission = MADRS score < 12

• Key secondary outcomes
  • Response by day 2 sustained through day 28
  • Change in total SDQ score
  • Change in PHQ-9 score

• Safety – vital signs, CADSS, BPRS, MOAA/S

Statistical Analysis

• Enrollment of 98 patients in each arm provides 90% power

• Analyses based on patients receiving ≥ 1 dose

• Fixed sequence procedure
  • 2 sided alpha 0.05

• Outcomes
  • Mixed-effects repeated measures model
  • Secondary #1: chi square test

Results

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Esketamine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline MADRS (SD)</td>
<td>37 (5.7)</td>
<td>37.3 (6.24)</td>
</tr>
<tr>
<td>Mean change (SD)</td>
<td>-21.4 (12.32)</td>
<td>-17 (13.88)</td>
</tr>
<tr>
<td>Difference of LS means (p, 95% CI)</td>
<td>-4</td>
<td>n/a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Esketamine</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained response from day 2</td>
<td>7.9%</td>
<td>4.6%</td>
<td>0.321</td>
</tr>
<tr>
<td>Mean change in SDS score</td>
<td>-13.6</td>
<td>-9.4</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean change in pHQ-9</td>
<td>-13</td>
<td>-10.2</td>
<td>n/a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in MADRS Over Treatment Phase</th>
</tr>
</thead>
</table>

Results cont’d

<table>
<thead>
<tr>
<th></th>
<th>Esketamine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders at day 28</td>
<td>69.3%</td>
<td>52%</td>
</tr>
<tr>
<td>Remitters at day 28</td>
<td>52.5%</td>
<td>31%</td>
</tr>
</tbody>
</table>

• Safety
  • Transient, mild to moderate
  • ADRs > 15%: dissociation, nausea, vertigo, dysgeusia, dizziness, headache
  • Blood pressure increase approximately 11/8mmHg
  • ADRs peak within 40 minutes, resolve within 90 minutes

Study Evaluation

Strengths

• Validated assessment tools
• Active comparator
• Verification of treatment failure
• Flexible dosing based on response

Limitations

• Authors are employees of sponsor
• Exclusion of patients with recent suicidality, comorbidities
• Difficult to blind patients
• Short duration active comparator
Conclusion

• Authors’
  • Statistically and clinically significant improvements
• Personal
  • Similar but more robust results than in TRANSFORM-1
  • Flexible dosing strategy appears more effective than fixed dosing

SUSTAIN-1
Daly EJ, Trivedi MH, Janik A, et al.
Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial.

Overview

• Objective
  • Assess long-term safety and efficacy of nasal esketamine to prevent relapse
• Design
  • Randomized, double-blind, active-controlled, multicenter phase 3 study
• Screening & Observation (5-7 weeks)
• Open-Label Induction (4 weeks)
• Optimization (12 weeks)
• Maintenance (Variable)
• Follow-up (2 weeks)
  • Maintenance phase – 1:1 to continue esketamine or change to placebo nasal spray
  • Oral antidepressant dose unchanged after induction

Patient Population

Inclusion Criteria
• 18-64 years old
• Recurrent MDD or single-episode > 2 years duration
• ISD-C > 34 and MADRS > 28
• Nonresponse to ≥1 but <5 antidepressants in current episode
• Different ongoing trial > 2 weeks
• Responded upon completion of TRANSFORM-1 or 2

Exclusion Criteria
• SI/HI with intent in past 6 months
• Any psychotic, bipolar, personality, obsessive-compulsive, autistic spectrum disorder or intellectual disability
• Moderate - severe SUD or AUD
• Non-response to ketamine, esketamine, all study antidepressants, or ECT
• Vagal nerve stimulation or DBS

Baseline Characteristics

<table>
<thead>
<tr>
<th>REMISSION</th>
<th>RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esketamine (n=90)</td>
<td>Placebo (n = 86)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>45.4 (12.12)</td>
</tr>
<tr>
<td>Female sex</td>
<td>64.4%</td>
</tr>
<tr>
<td>White race</td>
<td>88.9%</td>
</tr>
<tr>
<td>Mean age of diagnosis</td>
<td>32.5 (11.4)</td>
</tr>
<tr>
<td>Mean duration (wks)</td>
<td>112 (177)</td>
</tr>
<tr>
<td>&gt;2 previous trials</td>
<td>23.1%</td>
</tr>
<tr>
<td>Mean MADRS</td>
<td>37.4 (5.2)</td>
</tr>
<tr>
<td>Dosing pre-randomization</td>
<td>44%</td>
</tr>
<tr>
<td>Dosing pre-randomization</td>
<td>65%</td>
</tr>
<tr>
<td>Weekly dosing</td>
<td>41%</td>
</tr>
</tbody>
</table>
Methods

• Primary outcome: time to relapse in stable remitters
  • Stable remission: MADRS ≤ 12
  • Relapse: MADRS score > 22 for two consecutive assessments
  • Hospitalisation for worsening depression or suicide-related activities
• Key secondary outcome: time to relapse in stable responders
• Safety – vital signs, CADSS, BPRS, MOAA/S

Statistical Analysis

• Initially: 84 relapses provides 90% power; HR 0.49, alpha 0.05
  • Adjusted: 59 relapses provides 90% power; alpha 0.046
• All patients included in analyses
• Outcomes
  • Kaplan-Meier method
  • Between group differences: log-rank test
  • Hazard ratios: Cox proportional hazards regression model

Results: Patients Achieving Remission

<table>
<thead>
<tr>
<th></th>
<th>Esketamine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse during</td>
<td>2%</td>
<td>45%</td>
</tr>
<tr>
<td>maintenance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (p, 95% CI)</td>
<td>HR 0.49 (0.003, 0.29-0.84)</td>
<td>NNT = 6</td>
</tr>
</tbody>
</table>

• 19/39 patients who changed to placebo relapsed within 4 weeks

Results: Patients Achieving Response

<table>
<thead>
<tr>
<th></th>
<th>Esketamine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse during</td>
<td>25.8%</td>
<td>57.6%</td>
</tr>
<tr>
<td>maintenance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (p, 95% CI)</td>
<td>HR 0.3 (0.001, 0.16-0.55)</td>
<td>NNT = 4</td>
</tr>
</tbody>
</table>

Study Evaluation

Strengths
- Utilization of existing patients
- Stable oral antidepressant dose

Limitations
- Primary outcome reporting
- Complex study design
- Different trial design than TRANSFORM for new starts
- Changed power during study

Conclusion

• Authors’
  • Statistically and clinically significant delayed relapse
  • Esketamine appears safe for long-term use
• Personal
  • Applicability of study is limited
  • Optimal duration of therapy still undetermined
Other Pertinent Findings

- **TRANSFORM-3**: patients ≥ 65 years old
  - Not statistically significant: change in MADRS -10 vs. -6.3
- **SUSTAIN-2**: long-term open label safety trial
  - No new/serious ADRs
- **Ongoing studies**
  - TRD 3006 (short term), SUSTAIN-3 (continuation phase 3)
  - ASPIRE-1 and 2: MDD with active suicidal ideation
  - Results not yet published

Final Thoughts/Clinical Application

- Both 56mg and 84mg doses are somewhat effective
- Rapid antidepressant effect is sustained with repeat dosing
- Optimal dosing schedule still undetermined
- Last line option for patients with TRD
  - Time consuming, expensive, resource intensive
  - Role in suicidal patients?
    - ASPIRE-1 and 2

Self-Assessment Questions

- What is the MOA of esketamine?
  A. Serotonin reuptake inhibitor
  B. Norepinephrine reuptake inhibitor
  C. NMDA antagonist
  D. NMDA agonist
- What is the FDA-approved dosing for treatment resistant depression?

Acknowledgements

- Kendra Saxvik, PharmD, BCPP
- Gordon Ang, PharmD, BCPP

Questions?

Aubree.Bast1@va.gov

References

References cont’d


