Treatment-Resistant Depression: How to Diagnosis it and What to Do About it

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James J. Peters VA Medical Center

VISN 20 MIRECC Webinar Series
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Disclosures (Past 12 Months)

- **Consulting**
  - Clexio Biosciences, Boehringer Ingelheim

- **Patents (Murrough)**
  - Neuropeptide Y for the treatment of mood and anxiety disorders
    - Not awarded, no royalties
  - KCNQ channel modulators for the treatment of depression
    - Not awarded, no royalties

- **Patents (Mount Sinai)**
  - The Icahn School of Medicine (employer of Dr. Murrough) is named on a patent and has entered into a licensing agreement and will receive payments related to the use of ketamine or esketamine for the treatment of depression. The Icahn School of Medicine is also named on a patent related to the use of ketamine for the treatment of PTSD. Dr. Murrough is not named on these patents and will not receive any payments.
Disclosures: Institutional Ketamine Conflict

Dr. Charney (Dean of Mount Sinai) is a named co-inventor on several issued U.S. patents, and several pending U.S. patent applications filed by the Icahn School of Medicine at Mount Sinai (ISMMS) related to pharmacologic therapy for treatment-resistant depression, suicidal ideation and other disorders. ISMMS has entered into a licensing agreement with Janssen Pharmaceuticals, Inc. and it has and will receive payments from Janssen under the license agreement related to these patents. As a co-inventor, Dr. Charney is entitled to a portion of the payments received by the ISMMS. Since SPRAVATO (esketamine) has received regulatory approval for treatment-resistant depression, ISMMS and Dr. Charney as its employee and a co-inventor, will be entitled to additional payments, under the license agreement.
Learning Objectives

1. Understand how to recognize and diagnose Major Depressive Disorder (MDD)

2. Learn how to define Treatment-Resistant Depression (TRD) and appreciate the risk factors for treatment-resistance among individuals with depression

3. Describe what the evidence-based treatment options are for TRD.
Depression: The World’s Largest Health Problem

- Affects 350 million people worldwide \(^1\)
- More disability than any other disease \(^1\)
- Costs > $100 billion in U.S. annually \(^2\)
- 1 million suicides annually worldwide
- Leading cause of suicide in the U.S. \(^3\)
- 1/3rd do not respond to treatment

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Burden of Depression Among U.S. Military and Veterans

- Major depressive disorder (MDD) is a leading cause of disease burden in the United States (U.S.)
  - High prevalence
  - Large adverse effect on role functioning
- Exposure to stress is a powerful risk factor for MDD
  - Early life adversity / childhood trauma
  - Socio-economic life stress
  - Combat exposure
- 12% of deployed U.S. military personnel estimated to have MDD
- ~20% of Veterans in VHA care may suffer from MDD

Effects of Stress on Mental Health

- Stress may cause frustration, anxiety, or depression because they push us beyond our ability to successfully cope...
- Examples include:
  - **Chronic, Low Grade:** Daily hassles, time pressures, economic insecurity, poor health, interpersonal conflict
  - **Acute, Severe or Life-Threatening:** accidents, natural disasters, violence, others

Adapted from McEwen. Dialogues in Clinical Neurosci, 2006

Isolation and fear of infection are factors contributing to a rise in anxiety and depression.

**COVID’S MENTAL-HEALTH TOLL: SCIENTISTS TRACK SURGE IN DEPRESSION**

**COVID’S MENTAL STRESS**
The percentage of people experiencing symptoms of depression and anxiety has surged amid the COVID-19 pandemic, data from nationally representative surveys show.

- **UK adults reporting symptoms of depression**
  - July 2019–March 2020: 10%
  - June 2020: 19%

- **US adults reporting symptoms of anxiety or depression**
  - January–June 2019: 11%
  - December 2020: 42%

Major Depressive Disorder: Diagnostic Criteria

Major Depressive Disorder (MDD) is diagnosed when one or more Major Depressive Episodes (MDEs) occur.

Criteria for MDE (Symptoms must occur most of the day, nearly every day; Symptoms cause functional impairment):

• Depressed mood
• Loss of interest or pleasure
• Significant weight loss or gain
• Insomnia or hypersomnia
• Psychomotor agitation or retardation
• Fatigue or loss of energy
• Feelings of worthlessness
• Diminished ability to concentrate
• Recurrent thoughts of death or suicide

Must have:
Depressed mood or loss of pleasure; 5 out of 9 symptoms

American Psychiatric Association, 2013
Major Depressive Disorder: Risk Factors and Screening

- **Depression Risk Factors**
  - Prior episodes of depression
  - Family history of depression
  - Life stress
  - Lack of social support
  - Female gender
  - Medical comorbidity

- **Depression Screening**
  - Patient Health Questionnaire 2 (PHQ-2) annually in primary care
    - “Over the past two weeks, how often have you been bothered by either of the following: A) Little interest in things; B) Feeling down
    - Response options: 0 (Not at all) to 3 (Nearly every day)
    - Score >2 should be followed up by PHQ-9
### Assessment Using the Patient Health Questionnaire 9 (PHQ-9)

(see 2009 MDD CPG Appendix B pp. 149-153)

**Purpose:** The Patient Health Questionnaire (PHQ) is designed to facilitate the recognition and diagnosis of depressive disorders in primary care patients. For patients with a depressive disorder, a PHQ Depression Severity Index score can be calculated and repeated over time to monitor change.

**Making a Diagnosis:** Since the questionnaire relies on patient self-report, definitive diagnoses must be followed up on and verified by the clinician, taking into account any presenting functional impairments and/or the patient’s understanding of the questions. The clinician should also consider relevant information obtained from the patient, their family, and other sources.

Over the last two weeks, how often have you been bothered by any of the following problems?

<table>
<thead>
<tr>
<th></th>
<th>Not at All</th>
<th>Several Days</th>
<th>More Than Half the Days</th>
<th>Nearly Every Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed, or the opposite—being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead, or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Score Severity**
- 1-4 None
- 5-9 Sub-threshold
- 10-14 Mild MDD
- 15-19 Moderate MDD
- 20-27 Severe MDD
Suicide: Risk Factors and Screening

• Risk Factors for Suicide
  • History of suicide attempts
  • Family history of suicide
  • Presence of any psychiatric illness
  • Psychosocial disruption
  • Access to method (i.e., firearms)
  • Active substance use disorder

• Screening for Suicide
  • Requires “free and honest exchange of information between patient and clinician”
  • Direct and empathic questioning regarding suicidal thinking and intent is required:
    • “Have you ever felt that life is not worth living?”
    • “Have you wished to be dead?”
    • “Have you made a plan to end your life?”
Major Depressive Disorder: Illness Course

Major Depressive Disorder: Many Treatment Options

- Evidence-Based Treatments for MDD are highly effective for many patients
  - Psychotherapy
    - Supportive therapy
    - Cognitive Behavioral Therapy (CBT)
    - Interpersonal Psychotherapy (IPT)
  - Pharmacotherapy
    - Selective Serotonin Reuptake Inhibitors (SSRIs)
    - Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
    - Others (‘atypical’ antidepressants; ‘SSRI+’)
  - Neurostimulation
    - Electroconvulsive Therapy (ECT)
    - Repetitive Transcranial Magnetic Stimulation (rTMS)
    - Vagal Nerve Stimulation (VNS)

Santarsieri et al, 2015; CANMAT Guidelines, 2016
Overview of Pharmacotherapy for MDD

- **Selective Serotonin Reuptake Inhibitors (SSRIs)**
  - Escitalopram
  - Sertraline
  - Fluoxetine

- **Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)**
  - Venlafaxine
  - Desvenlafaxine
  - Duloxetine

- **‘Atypical’ Antidepressants**
  - Bupropion
  - Mirtazapine
  - Trazodone

- **Tricyclic Antidepressants (TCAs)**
  - Imipramine
  - Amitriptyline
  - Nortriptyline

- **Monoamine Oxidase Inhibitors (MAOIs)**
  - Isocarboxazid
  - Phenelzine
  - Tranlycypromine
  - Selegiline

- **Glutamate Modulators**
  - Esketamine

Santarsieri et al, 2015; CANMAT Guidelines, 2016
Meta-Analysis of Antidepressant Efficacy in MDD

- Systematic analysis
- Adult MDD
- 522 RCTs
- N=116,477 participants
- All antidepressants more effective than placebo
- ORs between 1.37–2.13

Cipriani et al. Lancet 2018
# Stepped Approach to Treatment of MDD

**Treatment Response and Follow-up** (see 2009 MDD CPG p. 80)

<table>
<thead>
<tr>
<th>STEP</th>
<th>PATIENT CONDITION</th>
<th>OPTIONS</th>
<th>REASSESS AT:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initial Treatment</td>
<td>• Initiate low dose antidepressant</td>
<td>2 Weeks*</td>
</tr>
<tr>
<td>2</td>
<td>No response to initial low dose antidepressant</td>
<td>• Increase dose&lt;br&gt;• Consider longer duration&lt;br&gt;• Switch&lt;br&gt;• Consider referral to specialty care</td>
<td>4 to 6 Weeks</td>
</tr>
<tr>
<td>3</td>
<td>Failed 2\textsuperscript{nd} trial of antidepressant</td>
<td>• Switch&lt;br&gt;• Augment or combine&lt;br&gt;• Consider referral to specialty care</td>
<td>8 to 12 Weeks</td>
</tr>
<tr>
<td>4</td>
<td>Failed 3\textsuperscript{rd} trial, including augmentation</td>
<td>• Reevaluate diagnosis and treatment&lt;br&gt;• Consider referral to specialty care</td>
<td>12 to 18 Weeks</td>
</tr>
</tbody>
</table>

*If treatment is not tolerable, switch to another antidepressant.
Principles of MDD Treatment

• Patient preference is important
• Initial frequent contact (follow up within two weeks)
• Monitor response with PHQ-9 or similar
• Educate, support, reassure
• Adherence, adherence adherence!
• “If they don’t take it, it won’t work”
• Titrate to effective / highest tolerated dose
• Work with patients to manage side effects (enhance compliance)
• Re-assess diagnosis if non-response
• Consider role of environmental factors
What is Treatment-Resistant Depression?

• Only ~33% of outpatient adults treated with an SSRI achieved remission following an optimized 12-week treatment course

• Likelihood of treatment response decreases with each sequential treatment tried

• Up to 67% of treated adults will eventually achieve remission follow four or more sequential treatment steps

• That leaves about one-third of individuals with MDD who will suffer a recurrent or chronic course despite treatment


Remission Rates By Treatment Step in STAR*D

A Working Definition of 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 (is it really MDD?):**
  • Diagnostic reassessment (unipolar vs. bipolar)
  • Psychiatric and medical comorbidities
  • Previous trials adequate in dose and duration?
FDA-Approved Medications for TRD

• **Aripiprazole**
  • Approved in 2007 as adjunctive treatment for MDD
  • 5–15 mg/day
  • Monitor for weight gain, metabolic symptom, extrapyramidal symptom

• **Quetiapine XR**
  • Approved in 2009 as adjunctive treatment for MDD
  • 50–300 mg/day
  • Monitor for weight gain, metabolic symptom, extrapyramidal symptom

• **Olanzapine (in combination with fluoxetine; ‘OFC’)**
  • OFC approved in 2009 as first stand alone treatment for TRD
  • Olanzapine 5–20 mg/day / Fluoxetine 25–75 mg/day
  • Monitor for weight gain, metabolic symptom, extrapyramidal symptom

• **Brexpiprazole**
  • Approved in 2015 as adjunctive treatment for MDD
  • 1–3 mg/day
  • Monitor for weight gain, metabolic symptom, extrapyramidal symptom

• **Esketamine**
  • Approved in 2019 for TRD in combination with an oral antidepressant

Non-FDA Approved Medications for TRD

**Good Evidence**
- Lithium
  - Approved for Bipolar but good quality for efficacy as augmentation in unipolar
- Thyroid hormone
  - T3 25 – 75 mcg/day
- Other SGAs
- Ketamine
  - Typically intravenous (IV) dose of 0.5 mg/kg
  - Several small RCTs support efficacy

**Weak Evidence**
- Stimulants
  - Methylphenidate
  - Lisdexamfetamine
- Anticonvulsants
  - Valproic acid
  - Lamotrigine
- Buspirone
- Modafinil
- Pramipexole

Santarsieri et al, 2015; CANMAT Guidelines, 2016; Kutzer et al, 2020; Ruberto, Jha, Murrough. Pharmaceuticals, 2020
# Neurostimulation Approaches for TRD

## Good Evidence
- Electroconvulsive therapy (ECT)
  - Considered “gold standard” for TRD
- Repetitive transcranial magnetic stimulation (rTMS)
  - FDA cleared for the treatment of MDD
  - Moderate effect sizes

## Uncertain / Experimental
- Vagal nerve stimulation (VNS)
  - FDA cleared for TRD in 2007 but seldom used
  - CMS-Industry RCT underway to test efficacy
- Deep Brain Stimulation (DBS)
  - Experimental for TRD
  - Largest RCT negative
  - Further work underway

Antidepressant Efficacy in Veterans with TRD: The VAST-D Study

• N=1522 adults with MDD at 35 U.S. VHA medical centers, unresponsive to at least 1 antidepressant medication;
• Randomly assigned (1:1:1) to 1 of 3 treatments and evaluated for up to 36 weeks;
  • Switch to bupropion (N=511);
  • Augment current treatment with bupropion (N=506);
  • Augment with aripiprazole (N=505);
• Primary outcome was remission defined as QIDS-C16 score <5
Remission rates at 12 weeks: 22.3% for the switch group, 26.9% for the augment-bupropion group, and 28.9% for the augment-aripiprazole group.

Response was greater for the augment-aripiprazole group (74.3%) than for either the switch group (62.4%; RR, 1.19 [95% CI, 1.09-1.29]) or the augment-bupropion group (65.6%; RR, 1.13 [95% CI, 1.04-1.23]).

Adverse effects more frequent in the augment-aripiprazole group included somnolence, akathisia, and weight gain.
Glutamate Modulators for TRD: Discovery of Ketamine

- Ketamine is first drug to show rapid antidepressant effects (within hours)
- First to show rapid therapeutics effects in patients with treatment resistance
- First to show rapid anti-suicidal effects
- Re-directs drug discovery efforts to focus on the glutamate system
Off Label Use of IV Ketamine: Screening and Administration

- Typically dosed at 0.5 mg/kg over 4 min
- Induction phase of 2-3 treatments/week over 2-3 weeks
- Variable maintenance phase
- No published guidelines outlining specific training requirements that clinicians should complete before administering doses of ketamine that are lower than those used in anesthesia

Recommend:
- Comprehensive diagnostic assessment
- Thorough review of systems and risk factors for adverse reactions to anesthesia
- Physical exam; laboratory screening; utox
- Informed consent
- Measurement based care

Sanacora et al. JAMA Psych, 2017
Comparative Effectiveness of ECT vs. Ketamine in Patients with Treatment Resistant Depression

**ELectroconvulsive therapy (ECT) vs. Ketamine in patients with Treatment-resistant Depression: The ELEKT-D study protocol**

Sanjay J. Mathew\textsuperscript{a,b,1}, Samuel T. Wilkinson\textsuperscript{c,1}, Murat Altinay\textsuperscript{d,e,f}, Ali Asghar-Ali\textsuperscript{a,b}, Lee C. Chang\textsuperscript{g}, Katherine A. Collins\textsuperscript{h}, Roman M. Dale\textsuperscript{d,e,f}, Bo Hu\textsuperscript{i}, Kamini Krishnan\textsuperscript{i}, Charles H. Kellner\textsuperscript{k}, Donald A. Malone\textsuperscript{e,d,1}, James W. Murrough\textsuperscript{h,l}, Robert B. Ostroff\textsuperscript{h}, Gerard Sanacora\textsuperscript{a}, Mingyuan Shao\textsuperscript{j}, Amit Anand\textsuperscript{d,e,f,s}

**Inclusion and exclusion criteria.**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Patients with treatment resistant depression (TRD) who have been referred for ECT and are eligible for ECT are candidates for the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject eligibility</td>
<td></td>
</tr>
<tr>
<td>1. Written informed consent before any study related procedures are performed</td>
<td></td>
</tr>
<tr>
<td>2. Inpatients or outpatients referred by their providers for ECT treatment and eligible for ECT treatment</td>
<td></td>
</tr>
<tr>
<td>3. Males/females at least 21 years of age, but no older than 75 years of age</td>
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</tr>
<tr>
<td>4. Meet DSM-5 criteria for Major Depressive Episode as determined by both:</td>
<td></td>
</tr>
<tr>
<td>A. Clinician's diagnostic evaluation and</td>
<td></td>
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<tr>
<td>B. Confirmed with the MINI International Neuropsychiatric Interview (MINI)</td>
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<tr>
<td>5. A current depressive episode that has lasted a minimum of 4 weeks</td>
<td></td>
</tr>
<tr>
<td>6. Meet all of the following criteria on symptom rating scales at screening:</td>
<td></td>
</tr>
<tr>
<td>C. Montgomery-Asberg Depression Rating Scale (MADRS) score ( \geq ) 20</td>
<td></td>
</tr>
<tr>
<td>D. Young Mania Rating Scale (YMRS) ( \leq ) 5</td>
<td></td>
</tr>
<tr>
<td>E. Montreal Cognitive Assessment (MoCA) ( \geq ) 18</td>
<td></td>
</tr>
<tr>
<td>7. Have had ( \geq ) 2 adequate trials of antidepressants or augmentation strategies during their lifetime (An adequate trial is defined as 4 weeks of a medication at a minimum FDA approved dose, with a trial rating of 3 or greater)</td>
<td></td>
</tr>
<tr>
<td>8. In the opinion of the investigator, the patient is willing and able to comply with scheduled visits, treatment plan, and other trial procedures for the duration of the study.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Meet DSM-5 criteria for bipolar disorder, schizophrenia, schizoaffective disorder, or pervasive developmental disorder</td>
<td></td>
</tr>
<tr>
<td>2. Meets any exclusion criteria for ECT or ketamine treatment as described in the clinical guidelines or according to investigator judgment</td>
<td></td>
</tr>
<tr>
<td>3. The patient is pregnant or breast feeding</td>
<td></td>
</tr>
<tr>
<td>4. The patient has a severe medical illness or severe neurological disorder</td>
<td></td>
</tr>
<tr>
<td>5. The patient has a known ketamine allergy or is taking medication that may interact with ketamine</td>
<td></td>
</tr>
<tr>
<td>6. Diagnosis of major depressive disorder with psychotic features during the current depressive episode</td>
<td></td>
</tr>
<tr>
<td>7. Unable to give informed consent</td>
<td></td>
</tr>
<tr>
<td>8. Was previously enrolled/randomized into the trial</td>
<td></td>
</tr>
</tbody>
</table>

Mathew et al. Contemp Clin Clin Trial 2019
**Meta-Analysis of Efficacy of Esketamine for TRD**

Five RCTs with N=774 patient identified for meta-analysis

- Adjunctive esketamine was significantly more effective than placebo:
  - MADRS score change (SMD = 0.36, 95% CI = 0.24–0.49, P < .0001)
  - Response (risk ratio [RR] = 1.40, 95% CI = 1.22–1.61, P < .0001)
  - Remission (RR = 1.45, 95% CI = 1.20–1.75, P < .0001)


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### Figure 1. Forest Plot of Standardized Mean Difference (SMD) in Change in Primary Outcome Scores Between Adjunctive Esketamine (EK) and Placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daly et al, 2018&lt;sup&gt;15&lt;/sup&gt; Stage I 28 mg EK (N=44)</td>
<td>−0.50 (−1.19 to 0.19)</td>
<td>3.4</td>
</tr>
<tr>
<td>Daly et al, 2018&lt;sup&gt;15&lt;/sup&gt; Stage I 56 mg EK (N=44)</td>
<td>−0.77 (−1.47 to −0.07)</td>
<td>3.3</td>
</tr>
<tr>
<td>Daly et al, 2018&lt;sup&gt;15&lt;/sup&gt; Stage I 84 mg EK (N=45)</td>
<td>−1.07 (−1.77 to −0.37)</td>
<td>3.4</td>
</tr>
<tr>
<td>Daly et al, 2018&lt;sup&gt;15&lt;/sup&gt; Stage II 28 mg EK (N=14)</td>
<td>−0.44 (−1.51 to 0.64)</td>
<td>1.4</td>
</tr>
<tr>
<td>Daly et al, 2018&lt;sup&gt;15&lt;/sup&gt; 56 mg EK (N=15)</td>
<td>−0.60 (−1.65 to 0.46)</td>
<td>1.5</td>
</tr>
<tr>
<td>Daly et al, 2018&lt;sup&gt;15&lt;/sup&gt; 84 mg EK (N=11)</td>
<td>−1.04 (−2.32 to 0.24)</td>
<td>1.0</td>
</tr>
<tr>
<td>Canuso et al, 2018&lt;sup&gt;25&lt;/sup&gt; 84 mg EK (N=66)</td>
<td>−0.26 (−0.75 to 0.22)</td>
<td>7.0</td>
</tr>
<tr>
<td>Fedgchin et al, 2019&lt;sup&gt;30&lt;/sup&gt; 56 mg EK (N=219)</td>
<td>−0.29 (−0.56 to −0.02)</td>
<td>23.1</td>
</tr>
<tr>
<td>Fedgchin et al, 2019&lt;sup&gt;30&lt;/sup&gt; 84 mg EK (N=206)</td>
<td>−0.27 (−0.55 to 0.00)</td>
<td>21.7</td>
</tr>
<tr>
<td>Popova et al, 2019&lt;sup&gt;27&lt;/sup&gt; 56–84 mg EK (N=201)</td>
<td>−0.34 (−0.61 to −0.06)</td>
<td>21.2</td>
</tr>
<tr>
<td>Ochs-Ross et al, 2019&lt;sup&gt;28&lt;/sup&gt; 28–84 mg EK (N=123)</td>
<td>−0.34 (−0.69 to 0.02)</td>
<td>12.9</td>
</tr>
</tbody>
</table>

Overall (95% CI)                     | −0.36 (−0.49 to −0.24) |
Esketamine: Indications, Contraindications, Warnings

- **Indication**
  - For the treatment of treatment-resistant depression (TRD) in adults, in conjunction with an oral antidepressant

- **Contraindications**
  - Aneurysmal disease
  - Arterio-venous malformation
  - Intra-cerebral hemorrhage
  - Hypersensitivity to esketamine or ketamine

- **Warnings**
  - Increases in blood pressure
  - Cognitive impairment
  - Impaired ability to drive
  - Embryo-fetal toxicity

- **Adverse Reactions:** dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting, feeling drunk
My Patient with MDD is Not Responding to Treatment, What do I Do!?

1. Reassess diagnosis
2. Rule out occult medical or substance use disorders
3. Reassess evidence-base for prescribed treatment
4. Ensure that treatment was given for adequate dose and duration
5. Assess for non-adherence to treatment (very common!)
6. Is the treatment poorly tolerability?
7. Consider the role of personality disorders; psychological factors
8. Consider the role of psychosocial stress
9. Initiate stepped treatment approach based on current guidelines
Treatment Guidelines for MDD/TRD

- VA / DoD Clinical Practice Guidelines
- American Psychiatric Association (APA; 2010)
- Canadian Network for Mood and Anxiety Treatments (CANMAT; 2009, 2016)
- National Institute for Health and Clinical Excellence (NICE; 2009)
- British Association for Psychopharmacology (BAP; 2008)
- Texas Medication Algorithm Project (TMAP; 2008)
- World Federation of Societies of Biological Psychiatry (WFSBP; 2007)

Where Can I Find More Information?
National Institute of Mental Health: https://www.nimh.nih.gov/health/topics/depression/index.shtml
American Psychological Association: http://www.apa.org/topics/depress/
Centers for Disease Control and Prevention: http://www.cdc.gov/mentalhealth/basics/mental-illness/depression.htm
Depression and Anxiety Center
for Discovery and Treatment

James Murrough
Matthew Klein
Adriana Feder
Dennis Charney
Laurel Morris
Yael Jacobs
Johnathan Depierro
Sarah Boukezzi
Chris Kelly
Sara Hameed
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