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Psychiatry and Addictions Case Conference

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ECT And Ketamine for Treatment-Resistant Depression

Anna Borisovskaya MD

SEATTLENTC

ANNA.BORISOVSKAYA@SEATTLENTC.COM

UW Medicine
UW SCHOOL OF MEDICINE

Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

SPEAKER DISCLOSURES

✓ Any conflicts of interest? NO

Planner disclosures

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

Mark Duncan MD
Rick Ries MD
Kari Stephens PhD
Barb McCann PhD
Anna Ratzliff MD PhD
Betsy Payn MA PMP
Esther Solano
Cara Towle MSN RN

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OBJECTIVES

1. Define treatment-resistant depression (TRD)
2. Compare ECT and ketamine for TRD
3. Discuss other options for treatment of TRD

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ECT: THE BASICS

- Still the gold standard for treatment-resistant depression (MDD is best studied); ECT with pharmacotherapy is superior to pharmacotherapy alone
- Also useful for catatonia, schizophrenia, schizoaffective disorder, bipolar depression, NMS, depression comorbid with Parkinson's disease, and less typical presentations on a case-by-case basis
- Efficacy is 70-80%, perhaps higher in well chosen populations/diseases (psychosis and increased age are positive predictive factors) (Hermida)
- Robust antisuicidal effect, replicated by several studies (Fink)
- Associated with reduced psychiatric readmissions in US (Slade)
- No medical contraindications, but stabilization of comorbidities is strongly encouraged
- Cognitive side effects are temporary and tolerable in majority of patients

WHOM TO REFER

- Ideal treatment candidate: severe major depressive disorder with psychotic features and suicidal ideation
- Slightly less ideal than that but absolutely indicated: treatment-resistant major depressive disorder (tried at least 2 antidepressants from different classes for sufficient period of time with no or minimal response)
- Ideal treatment candidate: catatonia related to any underlying psychiatric or medical disorder

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WHOM TO REFER CONTINUED

- Ideal treatment candidate: schizophrenia, poorly responsive to medications, symptomatic even with clozapine, has enough insight to understand the particulars of ECT
- Ideal treatment candidate: bipolar depression, poorly responsive to medications, tried a variety of mood stabilizers with minimal benefit
- While there are no absolute medical contraindications for ECT, medical conditions should be stabilized (concerns include space-occupying brain lesions, aneurysms, heart or lung disease, recent brain hemorrhage or stroke, ASA Class 4-5).

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WHEN TO REFER

- Earlier is better: prognosis of ECT is better with fewer medication failures and shorter length of depressive episode (Haq)
- Symptoms are severely debilitating
- Acute suicidality, psychosis, catatonia
- NMS: right away, as we still need a court order to proceed (presuming the patient is delirious and unable to consent)
- If the patient wants it sooner rather than later

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COMMON PATIENT CONCERNS (AND HOW TO ADDRESS THEM)

❖ What if I die?

Unlikely. The rate of death is 2.1/100,000 treatments (Torring)

❖ What if I forget who I am?

Unlikely. Short term memory loss is the likeliest cognitive problem due to ECT, and it is transient, resolving gradually over weeks to 6 months post ECT completion.

❖ I don't want to be a different person after ECT.

You won't be. Even if we tried, ECT cannot change your personality.

❖ But I watched "One Flew Over the Cuckoo's Nest" and I don't want a lobotomy!

Even in that movie, ECT was not portrayed in the same breath as a lobotomy. Watch "Dartmouth ECT" on YouTube instead, please.

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SIDE EFFECT PROFILE OF ECT

- Overall, safe and benign
- Most common: transient short term memory loss (see below)
- Benign side effects: muscle aches, headaches, nausea
- More serious adverse consequences: cardiovascular problems, stroke
- Very rare nowadays: broken teeth, bones, other musculoskeletal injuries

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COGNITION AND ECT

1. Meta analysis and systematic review of 84 studies, 2981 patients (Semkovska):

- Cognitive performance significantly decreased 0-3 days after ECT
- *No negative effect sizes were observed after 15 days, 57% of variables showed positive effect sizes*
- ECT had no demonstrable effect upon intellectual ability

2. Review of 9 studies of ECT v cognition in the elderly patients found that global cognitive functioning in patients with cognitive impairment improved, and global cognition remained stable after maintenance ECT for over a year (Tielkes).

COMMON REFERRAL PROBLEMS

- Comorbid untreated personality disorders – borderline personality disorder being the greatest concern due to the lesser efficacy of ECT
- Untreated medical conditions that impact safety of ECT and/or general anesthesia
- Patients believing ECT will be the fix to all their problems (including conditions not usually responsive to ECT such as dysthymia or BPD)
- Patients wanting ECT because it will erase their memories of past trauma
- Patients being told they must be hospitalized for ECT – our service is predominantly outpatient
- Homeless patients being referred to ECT before stabilizing their housing

MEDICATIONS AND ECT

- No clear evidence that benzodiazepines impact response to ECT (Tang) and they can be reversed with flumazenil
- Lithium has an interaction with ECT – can cause more postictal confusion, needs to be held for 24 hours
- Anticonvulsants/mood stabilizers should be held for 24 hours UNLESS necessary for treatment of other conditions
- In case of epilepsy, discuss with Neurology re: ideal dosing of anticonvulsants during ECT

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MEDICATIONS AND ECT CONTINUED

- During an intensive course for mania, lithium or mood-stabilizing antipsychotic must be on board for the entire course
- After ECT, nortriptyline with Li or even just Li alone can improve durability of mood response
- Nortriptyline or venlafaxine can enhance ECT efficacy
- Clozapine with ECT is a great combo for schizophrenia/schizoaffective disorder
- Consider MAOIs – if someone is sick enough for ECT they're probably sick enough for MAOIs

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KETAMINE IN PSYCHIATRY: THE BASICS

- Substantial effect on depression and suicidal ideation
- Comes in many forms only one of which is strictly regulated (Spravato – esketamine)
- Early RCTs demonstrated benefit from just one IVK infusion, the effect was temporary but extended if infusions were repeated
- Now, intramuscular, oral, subcutaneous, intranasal, and intravenous forms of ketamine are widely prescribed
- Best evidence exists for IVK (racemic ketamine) and esketamine (intranasal, Spravato)
- Oral treatment is widely available but bioavailability is poor and dosing needed to achieve therapeutic benefit is unpredictable.

IV KETAMINE FOR DEPRESSION: EVIDENCE BASE

- Review of 7 double blind placebo-controlled RCTs of ketamine usage in depression demonstrates a statistically significant improvement over placebo or midazolam in MDD and significant improvement over placebo in bipolar depression (Grady).
- *A single dose of ketamine, 0.5 mg/kg infused over 40 minutes produces a quick antidepressant response within 2-4 hours of administration and may reach the highest impact 24 hrs after infusion and last up to 7 days*. Ketamine's efficacy was not affected from day 1 through day 7, but bipolar patients only saw efficacy through day 4 (Romeo, Grady).
- In a midazolam-controlled RCT of IV ketamine for suicidal ideation in MDD in 80 patients, the Scale for Suicidal Ideation (SSI) at day 1 was reduced by 4.96 points (p=0.0003). Benefit was sustained for up to 6 weeks with pharmacotherapy.
- A meta-analysis of 36 studies with 2903 participants found that ketamine (racemic and esketamine) is associated with improved response (65%), remission (39%) and depression severity (78%) against placebo (Bahji)

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HOW ABOUT LONG-TERM?

- A systematic review of 2665 patients suggest substantial antidepressant effect though more treatment-resistant cases remit less often. Therapeutic effect doesn't decline with repeated treatments (Alnefeesi)
- A systematic review of 7 RCTs of esketamine v placebo was safe and more effective at decreasing depressive symptoms. Esketamine with antidepressant decreased the risk of relapse by 51% among stable remitters and 70% among stable responders, in long-term studies. (Jawad)

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KETAMINE MECHANISM OF ACTION

- Phencyclidine derivative
- Opioid receptor agonist
- Non-competitive NMDA receptor antagonist
- AMPA receptor agonist
- Dissociative anesthetic
- Sedative, hallucinogenic, antidepressant, drug of abuse
- Exerts antidepressant effect via neurotransmitter changes and intracellular signaling/neurotrophic factor modulation
- Increases levels of BDNF through modulation of eEF2 kinase

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KETAMINE MECHANISM OF ACTION

- Ketamine reduces self-monitoring, increases emotional blunting (which reduces limbic responses to emotional stimuli)
- Most effects in subgenual ACC, PCC, PFC, and hippocampus
- Dissociation caused by reducing subgenual ACC blood flow disconnects “excessive effects of an aversive visceromotor state on cognition and the self”
- Ketamine shifts focus away from internal states of anxiety, depression, somatization, and more toward the perceptual changes induced by ketamine
- Ketamine increases neural activation in the bilateral cingulate cortices, insula, and right thalamus, activating reward processing areas

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IVK AND SPRAVATO COMPARISON:

A SYSTEMATIC REVIEW OF 24 TRIALS WITH 1877 PARTICIPANTS SHOWED THAT RACEMIC KETAMINE RELATIVE TO ESKETAMINE DEMONSTRATED GREATER OVERALL RESPONSE AND REMISSION RATES WITH LOWER DROPOUTS (BAHJI)

IV Ketamine infusions

- Not FDA-approved, usually cash payment
- Can be used for MDD, bipolar depression, PTSD, promising for substance abuse
- Initial course: 6 treatments, 2/week
- Usual improvement is after 1-3 treatments
- Dose can be increased from 0.5 to 1 mg/kg provided it's well-tolerated
- Infusion is 40 minutes
- Maintenance option exists

Spravato (intranasal esketamine)

- FDA-approved, usually insurance covered
- Only used for MDD
- Initial course: 8 treatments, 2/week
- Usual improvement is after 4 treatments
- Dose is increased from 56 mg for 2 treatments to 84 mg for subsequent treatments
- Patients observed for 2 hours after self-administration
- Maintenance option exists

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COMMON SIDE EFFECTS WITH KETAMINE

- Increases HR and BP – these changes are transient and not clinically significant, usually
- Dissociation, derealization, perceptual changes are common
- Usually, pleasant changes in mood
- Sleepiness/fatigue after the treatment
- Rarely patients may experience more anxiety, dysphoria, exacerbation of suicidal ideation
- Other concerns have not come to pass with treatment within guidelines (cystitis, liver injury, cognitive impairment, psychosis, abuse, addiction)
- Monitoring and support are essential to safe treatment no matter the formulation

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ORAL KETAMINE?

- Review of available evidence (4 RCTs, 1 case series, 6 case reports, 5 open-label trials, 6 retrospective chart reviews) found it to be a promising treatment. Most studies were low quality.
- 2336 patients with unipolar or bipolar depression included.
- Difficult to compare dosing regimens – most started with 0.5 mg/kg but titrated up as tolerated (range was 0.25 to 1.5 mg/kg).
- Variable treatment schedules, from 1/week to 1/every 2 days to 3/day.
- Most studies report benefit, treatment is well-tolerated (Meshkat)

ORAL KETAMINE: PROS AND CONS

Pros:

- Cheaper
- More convenient, more accessible
- Can be very effective
- Fewer adverse events than IVK

Cons

- Bioavailability is poor, 10-20%
- Potential for misuse and abuse
- Difficulty monitoring changes in HR/BP
- Managing side effects is a challenge over telehealth
- Insufficient data to determine the best regimen and dose
- Long term use in addicted people can lead to dementia, bladder disease, liver failure

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SO WHAT'S BETTER??

- A comparison study ELECT-D (open-label, randomized, noninferiority trial) of patients with TRD without psychosis assigned to either ECT (170 patients) or IVK (195 patients) found that ketamine was noninferior to ECT as therapy for treatment-resistant major depression without psychosis (Anand)
- Improvement in QOL was similar in two groups
- ECT was associated with musculoskeletal adverse effects and short-term memory loss after 3 weeks of treatment
- Ketamine was associated with dissociation

WHAT IF NEITHER ECT NOR KETAMINE DOES THE TRICK?

- Consider TMS
- Consider VNS
- Consider CBT, DBT
- There are always meds – most often people haven't tried some promising options like MAOIs, TCAs, Auvelity (bupropion/dextromethorphan)
- A recent review found that Li was better than esketamine with risk/benefit ratio 1.8 compared to esketamine 0.71 (Vazquez)

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