WHICH OF MY PATIENTS WITH DEPRESSION ARE SUITABLE FOR ECT, IV KETAMINE OR rTMS?

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• No conflicts of interest to declare

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Learning Objectives

• To be aware of the evidence base for rTMS, ECT and intravenous ketamine in the treatment of major depressive disorder

• To be able to identify patients who are suitable candidates for rTMS, ECT or intravenous ketamine for depression.
American College of Physicians Guideline on MDD:

• “Select between either CBT or second-generation antidepressants to treat patients with major depressive disorder after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient”

• Grade: strong recommendation, moderate-quality evidence

• BUT THEN WHAT?

ECT – “do you still do that?”

- For specific selected patients, YES
- Important innovations:
  - Brief and ultra-brief pulse stimulus
  - EEG markers of ECT treatment adequacy (Early onset, high amplitude, symmetrical “polyspike and wave” and post-ictal electrical suppression)
  - Alternative electrode placements
  - Impact of stimulus intensity on efficacy and cognitive side effects
Brief & ultra-brief pulse stimuli for ECT

- Brief Pulsewidth (0.5-1.5 ms)
- Ultrabrief Pulsewidth (≤ 0.3 ms)
- Frequency = number of cycles/second
- 1 cycle
- Amplitude
- Stimulus Duration
Phases of ECT seizure activity

EEG Seizure Phase 1
Buildup (Recruitment)

EEG Seizure Phase 2
Hypersynchronous Polyspikes (Tonus)

EEG Seizure Phase 3
Polyspike-and-Slow Wave (Clonus)

EEG Seizure Phase 4
Suppression (Electrical Silence)

Abrams, 2002
Bilateral, Unilateral and Bifrontal ECT

Electrode placement

BT
RUL
d’Elia
BF
Letemendia
Electroconvulsive Therapy - Indications

• Diagnostic Indications:
  – Major depressive disorder
  – Bipolar disorder depressed/manic/mixed
  – Catatonia
  – Refractory schizophrenia
    (used along with antipsychotic medication)
Electroconvulsive Therapy – additional considerations

• Very severe episodes of illness
  – Psychotic symptoms
  – Melancholic symptoms
  – Pressing suicide concerns
  – Typically requiring hospital care

• Treatment refractoriness
  – In practice this is the most common indication
  – The typical ECT patient has received multiple therapies which were ineffective or not tolerated

Enns et al, Canadian Journal of Psychiatry, 2010
ECT availability in Winnipeg:

- Health Sciences Centre
- Victoria Hospital
- St. Boniface Hospital
- (Also, Brandon CAP, Selkirk SMHC, Eden MHC)
Ketamine and Esketamine
The mechanism(s) of action of ketamine and esketamine in depression is not known

- Clearly different mechanism and faster onset vs standard monoaminergic antidepressants
- NMDA receptor antagonism may be central
- Multiple other effects
  - Delta and mu-opioid receptor agonism
  - Glutamatergic facilitation
  - Monoaminergic and muscarinic receptor interactions
- Increases neuroplasticity
A few highlights of the evolving Ketamine story...

- Positive meta-analytic data for depression and SI (Wilkinson et al, 2018a; Witt et al, 2020)
- Positive clinical trials in depression vs midazolam (Grunebaum et al, 2018)
- Emerging clinical trial data in PTSD as well (Li & Loshak, 2019)
- Emerging longer-term efficacy and safety data (E.g. Wilkinson et al, 2018b)
- American Psychiatric Association weighed in with a consensus statement on the use of ketamine (Sanacora et al, JAMA Psych 2017)
A few highlights of the evolving esketamine story...

- Intranasal esketamine = Spravato® from Janssen
- FDA approved for use in conjunction with a conventional AD for treatment resistant depression – March 2019
- FDA granted “breakthrough therapy” designation for esketamine
- Positive RCT data for suicidality and treatment resistant depression (in combination with ADM)
  - Popova et al, AJP, 2019 (TRD);
  - Daly et al, JAMA Psychiatry, 2019 (Relapse prevention)
  - Canuso et al, AJP 2018 (Suicidality)
- Currently under review by Health Canada
“BOXED WARNING” for esketamine

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration. (5.1, 5.2)
- Potential for abuse and misuse. Consider the risks and benefits of prescribing SPRAVATO prior to using in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse. (5.3)
- SPRAVATO is only available through a restricted program called the SPRAVATO REMS. (5.4)
- Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients. (5.5)

https://www.spravatorems.com/
Risk Evaluation and Mitigation Strategy (REMS)

- Healthcare Settings must be certified in the Spravato REMS in order to treat patients
- Pharmacies must be certified in the Spravato REMS in order to dispense it
- Patients must be enrolled in the Spravato REMS in order to receive the drug
Ketamine for TRD – Shared Health Guideline

• Modified version of Covenant Health (Edmonton) protocol per Dr. M. Demas

• Implemented at:
  – Inpatient MH Unit at Vic;
  – Inpatient MH Units and outpatient at HSC

• No new resources allocated to the service
Shared Health Ketamine Guideline - Inclusion

• Major depressive episode, with emphasis on acute or potential suicidality
• Refractory to at least 5 psychotropic medications.
• Refractory to, *unsuitable for*, or unwilling to receive Electroconvulsive Therapy.
Ketamine Guideline - Exclusion

- **Exclusion Criteria:**
  - Psychotic disorder or pervasive developmental disorder
  - Dementia/delirium
  - Uncontrolled severe hypertension
  - Pregnancy
  - Allergic to Ketamine

- **Relative contraindication:**
  - Past or current drug or alcohol dependency
Baseline Assessment (prior to the initiation of IV ketamine):

- Physical examination and EKG
- Medical, anesthesia or pharmacy consultation when necessary
- Hold benzodiazepines and antipsychotics for five hours prior to infusion
- Assessments for IV ketamine are being conducted by the Mood Disorders Program at HSC
Why not just wait for nasal esketamine?

- FDA has moved ahead; we don’t know the Health Canada OR MB Formulary timeline.
- Esketamine is going to be very expensive (1 – 3 spray units per treatment X $US325 per unit).
- It will also need to be tightly regulated in Canada (risk evaluation and mitigation strategy).
- Additional active controlled studies needed.
- Maintenance therapy data is critically needed (Papakostas, 2020).
rTMS
(Repetitive Transcranial Magnetic Stimulation)
Basic Principles of rTMS

- Repeated pulses of electric current into a coil, commonly a figure-8 shaped coil, generates a fluctuating magnetic field.
- The fluctuating magnetic field induces neural cell membrane potentials under the coil (modest depth of penetration).
- High frequency stimulation (>5 Hz) yields excitatory effects in the brain.
- Low frequency stimulation (<1 Hz) yields inhibitory effects in the brain.
- Repeated application of rTMS alters synaptic plasticity.
rTMS is Not a Unitary Treatment

- Can vary the site of stimulation
- Alternative coils can change the depth of penetration of the magnetic field
- High or low frequency stimulation can be used
- The number of pulses applied can vary and the treatment can be given one or more times per day (e.g. ½ hour am and ½ hour pm)
- The intensity of the treatment can be varied
- (The intensity of the applied field is individualized based on measurement of the motor threshold for the first dorsal interosseous muscle)
The rTMS Clinic at St. Boniface Hospital
rTMS for Major Depression: Target Brain Region
Depression Treatment Protocol for rTMS

- High frequency rTMS of left DLPFC (strong evidence of efficacy)
- Low frequency rTMS of right DLPFC (lower level evidence of efficacy)
- Combination of the above
- Coil placement can be determined with surface anatomy OR neuronavigation (computer assisted based on MR imaging)
- U.S. FDA approved rTMS in 2008 as a treatment for depression after one Rx failure
Access to rTMS in Winnipeg

• Not an independently funded program
• Two Magstim rTMS machines purchased through fundraising by St. Boniface Hospital Research Foundation
• Staffed with part time allocation of existing staff
• Consult Dr. Modirrousta at SBGH
Practical Summary: Options for refractory depression

- **rTMS** – moderate depression in patients who don’t respond to or tolerate Rx – consult Dr. Modirrousta at SBGH
- **ECT** – severe acute depression and high risk, usually requiring hospital care – send patients to CRC or ED
- **IV Ketamine** – multiple treatment resistant depression, moderate to severe symptoms – consult psychiatry through Central Intake
Additional “Emerging Options” for TRD

- Magnetic seizure therapy (investigational alternative to ECT)
- Vagus Nerve Stimulation (for chronic refractory depression)
- Deep Brain Stimulation (investigational)
• QUESTIONS?
Further reading on these topics:

- Somani A & Kar SK. Efficacy of rTMS in treatment-resistant depression: the evidence so far. General Psychiatry 2019, 32: e100074