8th Annual Adult **Mental** Health Update
Portland, OR

Treatment Resistant Depression:
Theory & Practice

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Outline

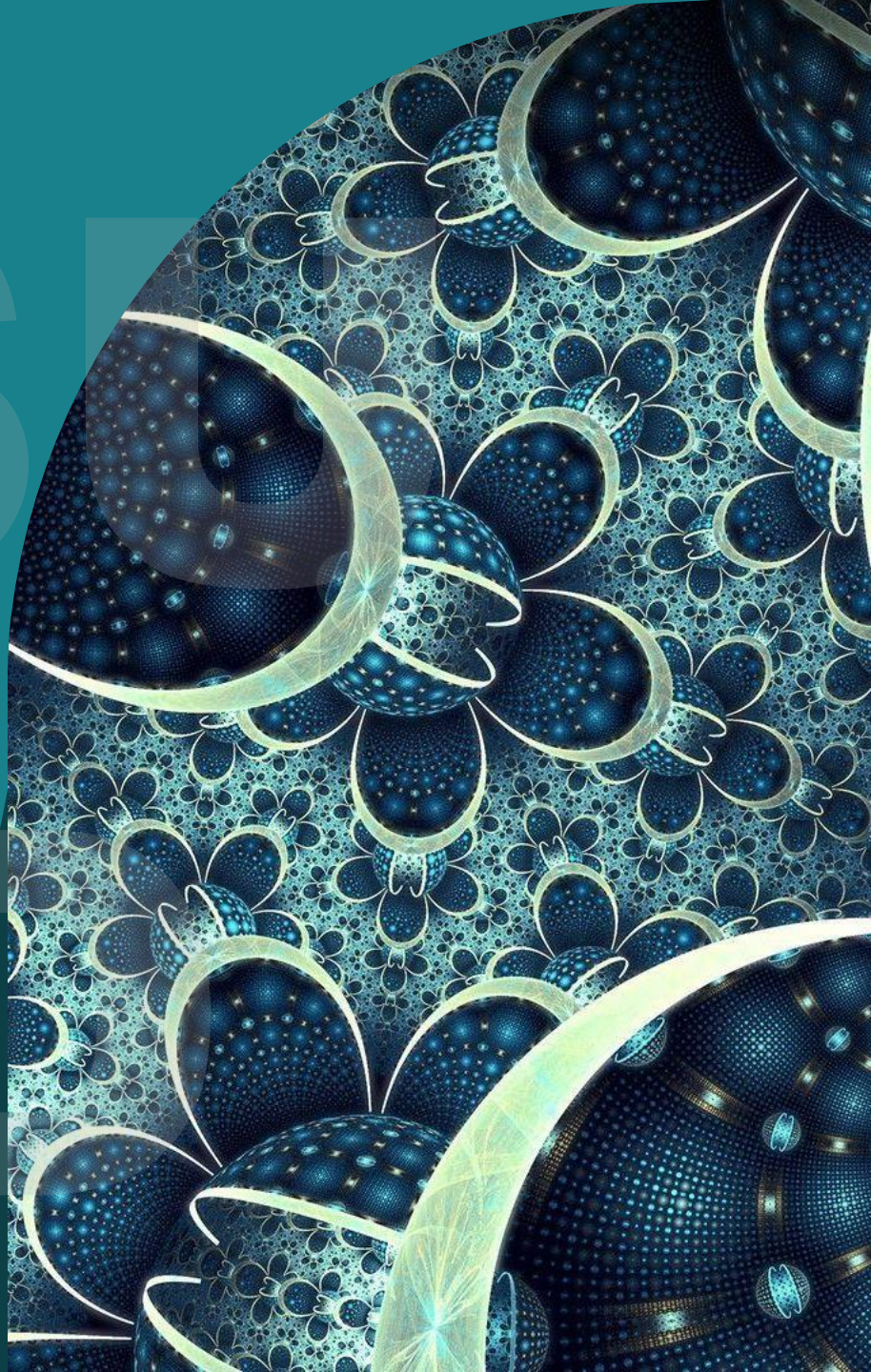
Treatment-Resistant Depression
April 19, 2024 // 1:05-2:05

I. Major Depressive Disorder – General Statistics
II. Introduction to Treatment Resistant Depression
III. Management of TRD – Treatments & Pitfalls
IV. Psychology of Depression
V. Resources in Oregon
VI. References

General Statistics –

Major Depressive Disorder in Ambulatory Settings

- Prevalence rates vary
  - Point prevalence 25% worldwide; similar in USA
  - 12-mo prevalence in US is 10%; lifetime prevalence is 27%
- Morbidity rates are striking
  - 11th greatest cause of morbidity world-wide
  - 2nd highest cause of morbidity in the United States
- Regarding Management:
  - 67% of patients with MDD begin treatment with PCP
  - 50% of depressed patients are missed in primary care settings
  - 80% lost to follow-up rate in primary care settings



Antidepressants – Response & Remission Rates

- STAR*D trial cited 67% cumulative remission rate

"Half of STAR*D's participants had significantly improved after using either the first or second medication, and nearly 70% of people had become symptom free by the fourth antidepressant."

– Dana G Smith PhD, Reporter for the NYT, 2022

- Update shows 35% cumulative remission rate – in line w/ practice?

Treatment Resistant Depression

No consensus definition; generally defined as:

Failure of TWO or more novel antidepressants at adequate dose and duration

Recurrance rate>40% after one major depressive episode; 75% recurrence rate after two major depressive episodes

Selective Serotonin Reuptake Inhibitors

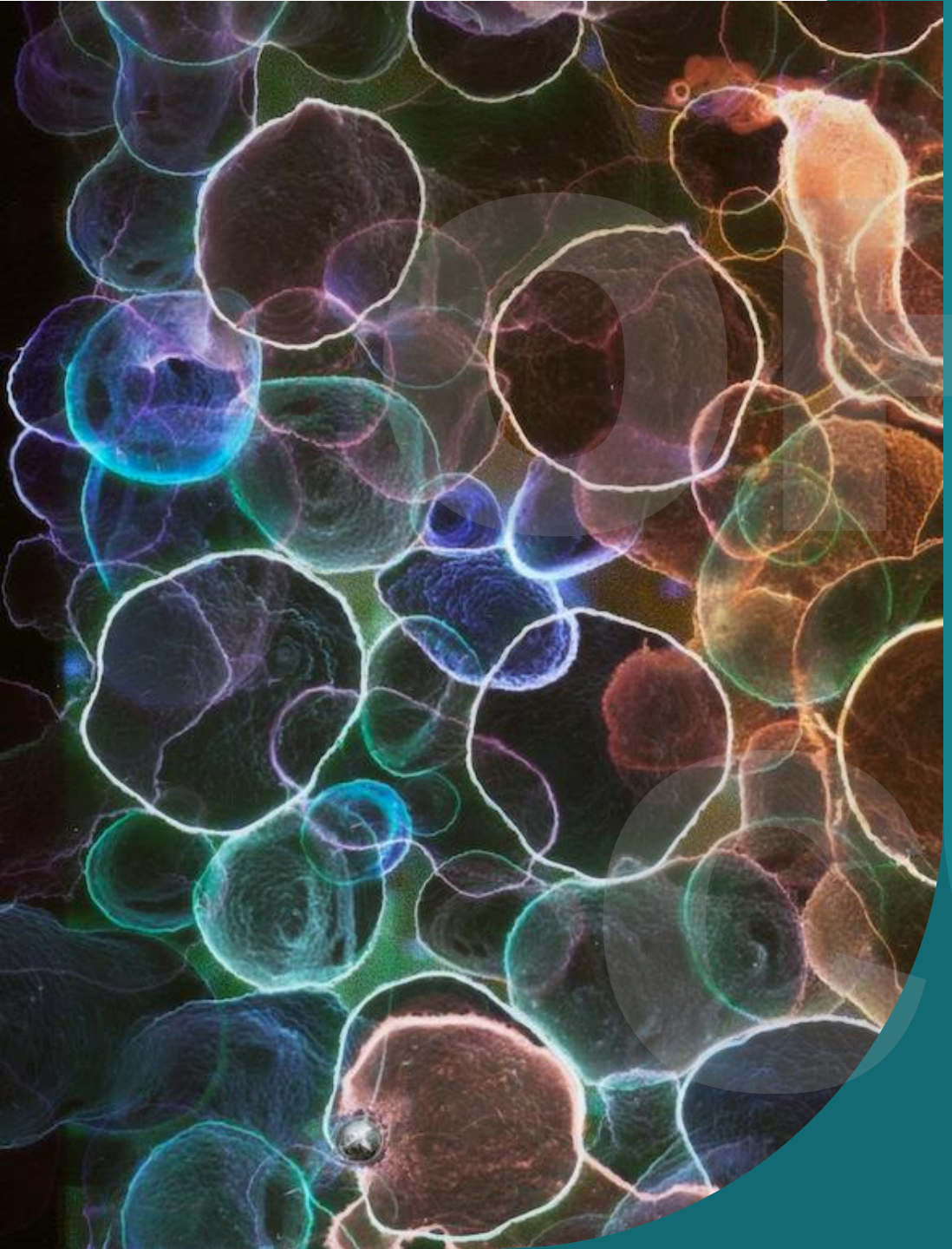
Drug	Elimination (hours)	Dose Range (mg/d)	Indications	Details
Citalopram (Celexa) Escitalopram (Lexapro)	36	20-40 10-30	MDD, GAD	Low GI side effects, watch for QTc prolongation (not in elderly)
Fluoxetine (Prozac)	88-384	20-80	MDD, OCD, panic d/o, Bulimia, PMDD	Activating, 2D6 inhibition, safe in pregnancy, old and effective, very long t1/2
Sertraline (Zoloft)	26-32	50-200	MDD, OCD, PTSD, & panic d/o	Variable side effects, GI distress, don't take w/ food, DA-I
Paroxetine (Paxil)	24	20-50	MDD, OCD, panic d/o, GAD, PTSD	Anticholinergic, NE-I, NO in pregnancy, very short t1/2
Fluvoxamine (Luvox)	15	50-300	OCD	BID dosing, monitor Clozapine & Coumadin, QTc prolongation

Serotonin & Norepinephrine Reuptake Inhibitors

Drug	Elimination (hours)	Dose Range (mg/d)	Indications	Details
Venlafaxine (Effexor)	5	37.5–225 mg/d	MDD, GAD, panic d/o, social anxiety d/o	Increased BP, so monitor in pt's w/ known HTN; use in pain
Desvenlafaxine (Pristiq)	Variable	50–100 mg/d	MDD	Metabolite (O-desmethylvenlafaxine) is the active compound, thus variable responses
Duloxetine (Cymbalta)	2–5 h	30–120 mg/d	Chronic pain, MDD, GAD, fibromyalgia, diabetic neuropathic pain	Increases hepatic transaminases
Milnacipran (Savella)	Variable	Day 1: 12.5 mg PO daily Day 2-3: 12.5 mg PO BID Days 4-7: 25 mg PO BID Day 7+: 50 mg PO BID	Chronic pain; Off-label for MDD	Preferentially blocks NE-reuptake over 5-HT-reuptake

Other Antidepressants

Drug	Elimination (hours)	Dose Range (mg/d)	Indications	Details
Bupropion (Wellbutrin) Wellbutrin IR Wellbutrin SR (12h release) Wellbutrin XL (24h release)	Variable 21-28h	Max 450 mg/d 75 mg & 100 mg 100 mg, 150 mg, & 200 mg 150 mg & 300 mg	MDD, SAD, and smoking cessation (SR form); Off-label use for 1. Sexual-dysfunction w/ SSRIs 2. ADHD	Structurally similar to amphetamine
Vilazadone (Viibryd)	24h	10-40 mg/d 10 mg/d x 7 d, then 20 mg/d x 7 d; then 40 mg/d	MDD	In addition to SSRI, 5-HT1A -R & 5-HT1A -R partial agonist
Vortioxetine(Trintellix)	66h	5-20 mg/d Increase dose in increments of 5-10 mg over 7d	MDD	Inhibits reuptake of serotonin (5-HT); also has agonist activity at the 5-HT1A receptor and antagonist activity at the 5-HT3 receptor.



Titration Schedule

- Discontinuing antidepressant medications:
  - If <3w treatment, significant adverse reactions, or not extreme doses: can cold turkey or titrate off in 5-7d by decreasing by 50%
  - If >3w treatment, high doses: titrate off over 2-4w; note: increase titration schedule q4w if using a drug with short t1/2 (eg, paroxetine, venlafaxine), prior history of antidepressant withdrawal symptoms, or high doses of antidepressants.
- Switching antidepressant medications:
  - Cross-titration is preferred: over course of 1-4 weeks, lower original medication at 50% increments while gradually increasing the newer medication per guidelines
- Direct switch is useful in three scenarios:
  - When switching to another agent in the same or similar class
  - When original antidepressant has been used for <1 week
  - When the discontinuation is due to adverse effects

Common Pitfalls

- Subtherapeutic dosing of medications
- Inadequate duration of medication trial
- Adding adjunctive strategies too early
- Understanding when to refer
- Obtaining collateral (if time and patient allows)
- Management of side effects
- Consideration of comorbidities

Reconsider Diagnosis

PTSD	• Still a role for medications • Specific therapies
Borderline personality disorder	• Specific therapies
Bipolar Disorder	• Explore mania or hypomanic episodes • Question risk of switching with SSRIs
Persistent depressive disorder	• Explore any presence of episodic depression
Chronic pain	• Still a role for medications-SNRIs • Multimodal approach
Complex grief and loss	• Actual loss of loved one • Loss of role or purpose in life

Specifiers of Depression

- **With anxious distress**
  - Identify obsessive sxs, trauma sxs
  - Start w/ SSRI
- **With mixed features**
  - Consider bipolarity
  - SSRIs with short half life, avoid duloxetine
  - Consider adjunctive strategies: antipsychotic, lithium, lamotrigine
- **With melancholic features**
  - Will see a listless, melancholic depression
  - Guilt & grief as predominant emotional condition
  - Often see poor concentration
  - Start w/ bupropion
- **With atypical features**
  - Hypersomnia, hyperphagia, rejection anxiety
  - Start w/ SSRI, consider SNRI
- **With psychosis**
  - Note psychosis can be subtle
  - Use adjunctive antipsychotic
- **With pain**
  - With regards to depression, no need to establish "real" or "imagined," often h/o bodily injuries/trauma
  - Begin with SNRI (duloxetine), can consider TCA (monitor for anticholinergic side effects)
- **With anorexia**
  - Ensure hemodynamically stable
  - Start with SSRI, but may consider addition of mirtazapine
  - Avoid bupropion, due to increased seizure risk (particularly in eating disorders)

Psychology of Depression

- General Characteristics:
  - Strong fixation on loss
  - Objects are narcissistically invested; i.e. sense of self is linked to the lost object
  - Intolerance of ambivalent feelings; leads to a kind of splitting as seen in Borderline Pathology
  - Internal attribution style – allows for the individual to gain control over a helpless situation
- Recommendation rates for psychotherapy as a recommendation have dropped since 2012
- Regarding therapeutic modality: note that there is no difference between different forms of therapy; biggest predictor for improvement is the patient-therapist relationship

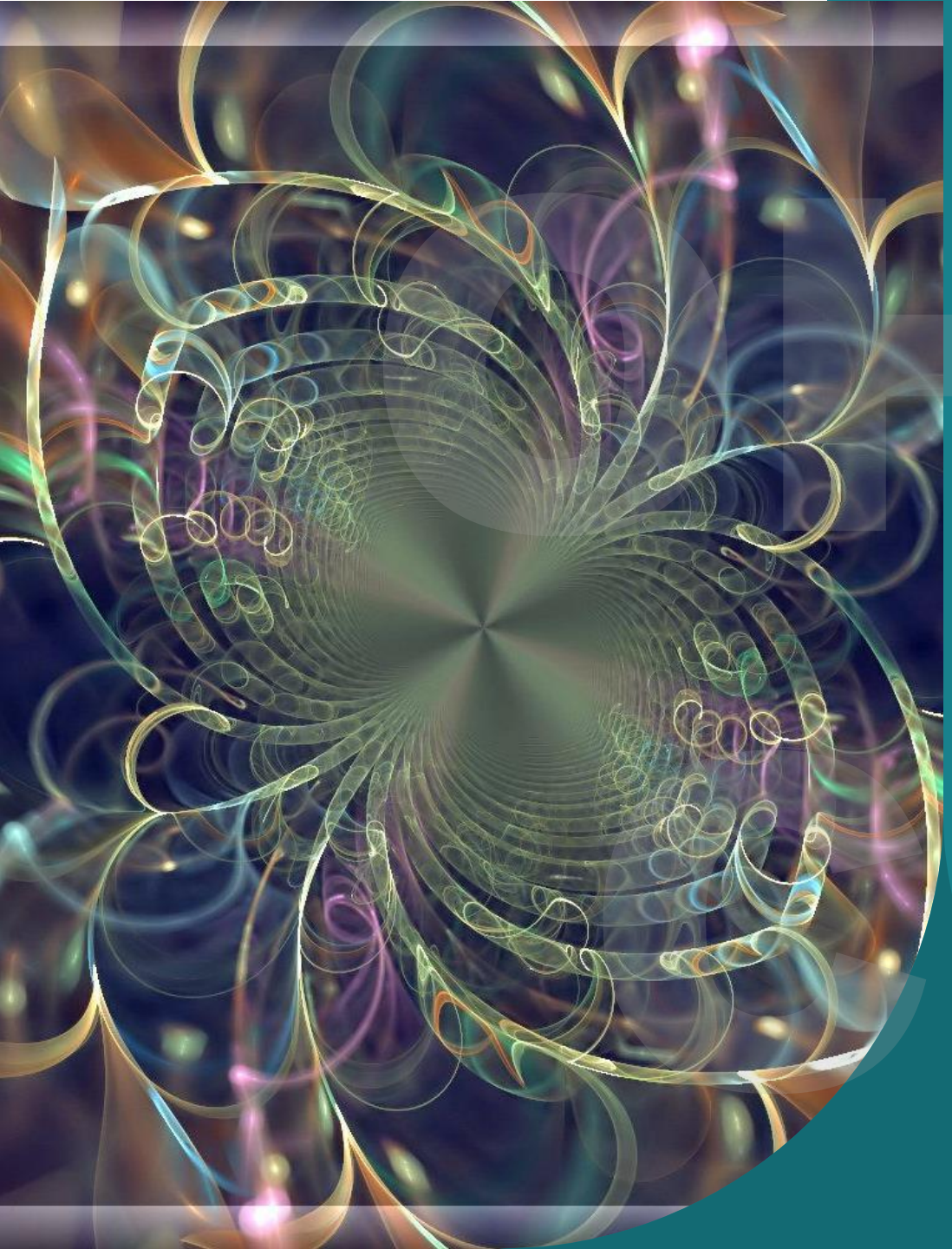
Electroconvulsive Therapy

Estimated remission rate of 70-90%

- Consider the following (although no established criteria):
  - Greater than 2-3 medication failure
  - Cannot tolerate medications: Elderly, Pregnancy
- Nature and severity of the depressive episode
  - Atypical (neurovegetative)
  - Bipolar depression
- Symptoms are urgent requiring rapid response
  - Catatonia
  - Psychosis
  - Suicidality
  - Poor ADLs, malnutrition
- Generally fastest response rate

Electroconvulsive Therapy

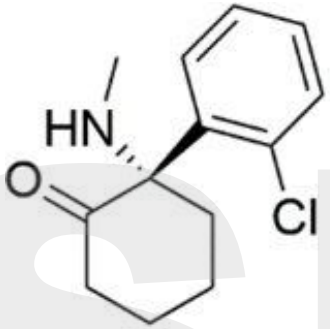
- Will require psychiatrist to monitor
- Referral to limited resource
  - Few institutions offer and of those there are limited spots
  - Requires pre-anesthesia clearance
- Consent
  - Must be able to fully consent or have a guardian with clause to consent specific to ECT
  - Next of kin CANNOT consent
- Time commitment
  - Index course: 1-2 sessions per week for 9-12 sessions
  - Maintenance: Dependent on patient and availability
- Education and Stigma
  - Electroconvulsive Therapy (ECT) | Department of Psychiatry | DHMC and Clinics (dartmouth-hitchcock.org)



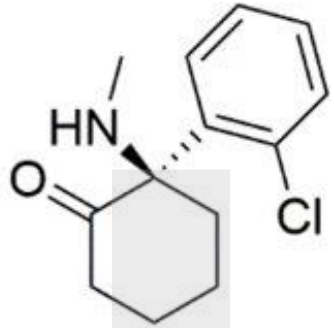
Repetitive Transcranial Magnetic Stimulation (rTMS)

- ECT consistently shown to be superior to rTMS
- Electrical current passed through coil, generating magnetic fields to depolarize neurons; 1.5-3 T
- Treatment session: 20-30 min, 4-5x/w x 6-7w
- Indications: MDD, OCD, bipolar depression, smoking cessation
- Side effects: headache, mania/hypomania, dizziness, seizure, increased auditory threshold
- Contraindications:
  - At risk for seizures
  - Implanted metallic hardware
  - Metal fragments (eg, bullets)
  - Cochlear implants
  - Implanted electrical
  - Unstable general medical disorders

Ketamine and Esketamine



(*S*)-Ketamine



(*R*)-Ketamine

Ketamine: non-FDA approved; often refers to the racemic mixture R-/S-ketamine which has IV, IM, PO, SL, and IN formulations; acts as a strong antagonist for NMDA-R

Esketamine: Spravato®, FDA-approved intranasal treatment, refers to S-ketamine enantiomer; 2x more potent than racemic ketamine and 3x more potent than R-ketamine

Mechanism of action: NMDA-R antagonism and GABA-inhibition leading to glutamate surge increasing BDNF and mTOR activity; neuroplasticity and neurogenesis

Ketamine and Esketamine

Evidence For Use

- Multiple trials unequivocally showing rapid and significant efficacy using both formulations
- One trial showing IV > Inhaled; no difference in subsequent meta-analytic reviews
- Esketamine:
  - Two FDA-approved indications: TRD & MDSI
  - Lasting benefit for TRD ~ 28d
  - Decreased risk of depression relapse by 51%
  - No decrease in suicidal thinking, but strong reduction in depressive symptoms in MDSI

Ketamine and Esketamine

- Common Side Effects: elevated BP, dissociation, brain fog, dizziness, N/V, sedation, vertigo, hypoesthesia, anxiety, lethargy
- Warnings & Precautions:
  - Sedation and dissociation: must monitor patients for at least two hours post administration;
  - Abuse and misuse of ketamine
  - Elevated BP;
  - Cognitive impairment/impaired ability to drive or operate machinery
  - Ulcerative or Interstitial cystitis assoc w/long-term use

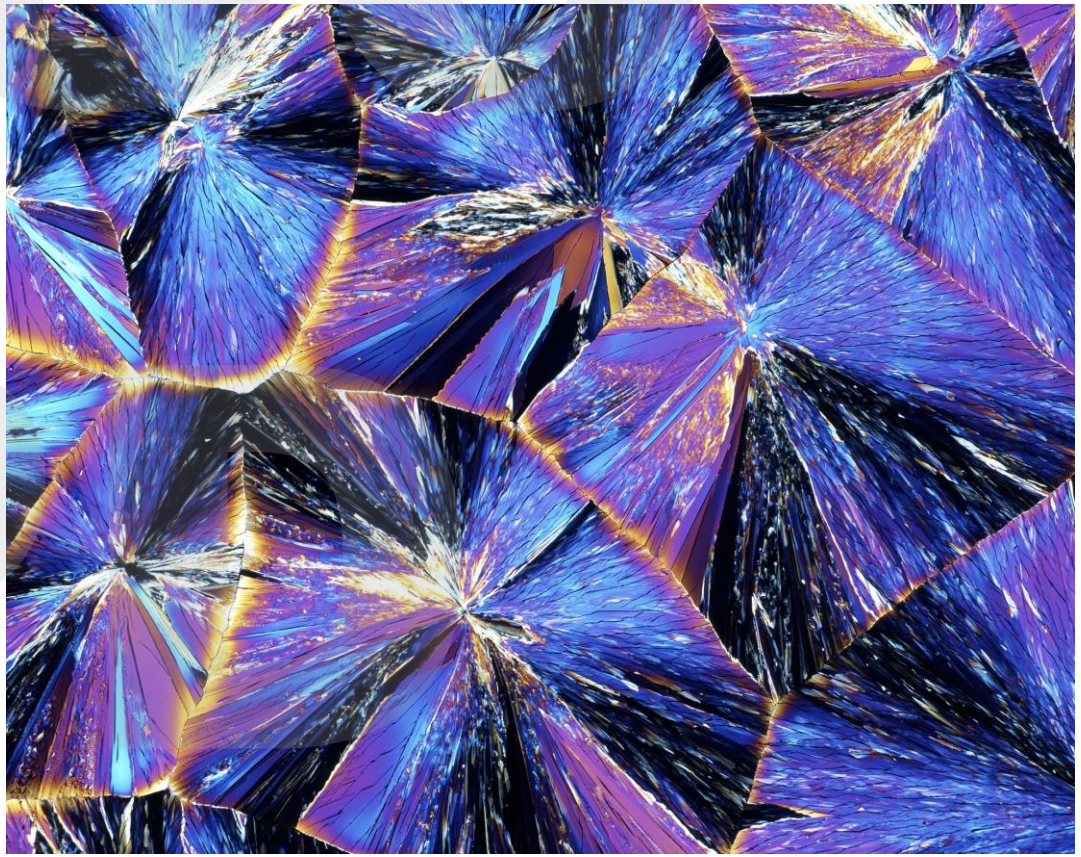
Esketamine (Spravato®)

- Treatment Resistant Depression (TRD): a diagnosis of **Major Depressive Disorder** with **failure of two or more antidepressants** of adequate dose and duration utilized in the current depressive episode.
- Protocol for TRD:
  - Induction Phase (weeks 1-4):
    - Day 1 (starting dose): 56 mg
    - Subsequent dosing: 56 mg or 84 mg twice weekly
  - Maintenance Phase:
    - Weeks 5–8: 56 mg or 84 mg weekly
    - Weeks 9+: 56 mg or 84 mg q2 weeks

Esketamine (Spravato®)

- MDD w/ Suicidal Thoughts or Actions (MDSI): depressive symptoms in adults with Major Depressive Disorder & acute suicidal ideation/behaviors
- Protocol for MDSI:
  - Weeks 1–4: 84 mg twice weekly x 4w
  - Weeks 5+: no established guidelines established, must systematically evaluate patient for continued treatment

— Note that in BOTH categories, the patient MUST be on a concomitant antidepressant —



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