Brigham and Women's Hospital
Founding Member, Mass General Brigham

Depression and Anxiety

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Current position:

- Medical Director for Behavioral Health, Included Health
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DISCLOSURES

Employment: Included Health

OBJECTIVES

1. Explain how antidepressant medication fits into a more comprehensive and holistic treatment plan for depression
2. Comfortably use the 4 classes of antidepressant medication identified as first-line
3. Appropriately identify patients with treatment-resistant depression and refer to advanced or off-label therapies

Case #1

SG is a 43F presenting with a major depressive episode. She has felt increasingly depressed and anxious over the past 9 months in the setting of recent stress. The startup that she works for has not been doing well, and she is worried about losing her job. Her father was diagnosed with Alzheimer disease, and she is the only one of her siblings who lives locally. She has a family history of MDD, and she has a childhood history of trauma. She reports low energy, poor concentration, excessive appetite with binge eating, and persistent back pain. She drinking 4 nights per week, which is more than she usually does.

Quiz: What is most likely going on in SG's brain?

A. There isn't enough serotonin
B. Progressive atrophy
C. Direct depressive effects from alcohol
D. Toxic memories from childhood trauma
E. Exhaustion from excessive stress

The “target” of antidepressant treatment probably is not a neurotransmitter or psychological experience but rather a lack of **plasticity**[1-6]

- Neuroplasticity describes the degree to which neurons make and reorganize synaptic connections in the brain
- Closely associated with learning, adapting, and healing from injury
- MDD is associated with synaptic dysfunction and decreased synaptic density, leading to the modern framework for a more unified model of what depression is → and how treatment works

A unifying effect of different treatment approaches is that they stimulate BDNF signaling, which enhances neuroplasticity

A common pathway for different modalities:
Antidepressant medication
Stimulation therapy (ECT, TMS)
Psychotherapy
Exercise
Meditation
Happy experiences
Psychedelic treatments

This combination is especially synergistic

Medication may be part of the treatment. When choosing a medical treatment, it's usually best to start with first-line classes[6-8]

- SSRIs
- SNRIs
- Bupropion
- Mirtazapine

SSRIs have the widest range of indications (psychiatric and medical)

First-line for depressive and anxiety disorders
Well-studied in most medical conditions (including pregnancy)
Unlikely to have “bonus” secondary effects
Side effects/problems:

- Sexual side effects ↑↑
- QTc prolongation limited to citalopram/escitalopram
- Weight gain likely varies by agent

SNRIs may be uniquely helpful for neuropathic pain[9-10]

Agent	Estimated NNT 50% improvement(for pain)
SNRIs	6.4
TCAs	3.6
Gabapentin	6.3
Other AEDs	n/a

Side effect profile similar to SSRIs but with addition of increased BP/heart rate
Higher risk of uncomfortable withdrawal on venlafaxine

Bupropion is a mild stimulant

- May improve energy, concentration, motivation
- Suppresses appetite
- Less likely to be helpful for anxiety
- Side effects/AEs: anxiety, insomnia, higher risk of seizures
- Bonus: smoking cessation

Mirtazapine helps with sleep and appetite

- Sedating effect is often dose-dependent
- Increased appetite may be good or bad depending on the individual in treatment
- May help with nausea as well

Serotonin modulators are newer and may or may not have certain advantages with respect to side effects[12-15]

Vilazodone

- May be less likely to cause weight gain and sexual side effects
- Must be taken with food

Vortioxetine

- May be less likely to cause sexual side effects (compared to paroxetine)

Case #2

TM is a 27-year-old man who says that he is depressed and anxious, and he recently visited a ketamine clinic that he learned about online. He explains that the ketamine clinic is run by an anesthesiologist, and their policy is that before they start treatment, a PCP or a psychiatrist needs to sign a form certifying that ketamine treatment is appropriate. He expects you to sign this form today, and he feels hopeful that the treatment will work.

Patients should complete at least 2-4 trials of first-line treatments before choosing an advanced therapy[16]

- “Treatment-resistant depression” usually defined as a failure to respond to **2 full therapeutic antidepressant trials**
- Frequency estimated ~30%
- Authorizations for advanced therapies typically require **4 failed trials**

Adjunctive medication may be more appropriate than a referral [17-19]

Buspirone

- Safe, but weak evidence for efficacy

Lithium

- Effective, but complicated to prescribe
- Associated with reduced suicidal ideation

Antipsychotics

- Aripiprazole preferred
- Side effect profile is biggest deterrent
- Some evidence also for quetiapine, olanzapine, risperidone, brexpiprazole

TMS is a safe and effective ambulatory procedure[20]

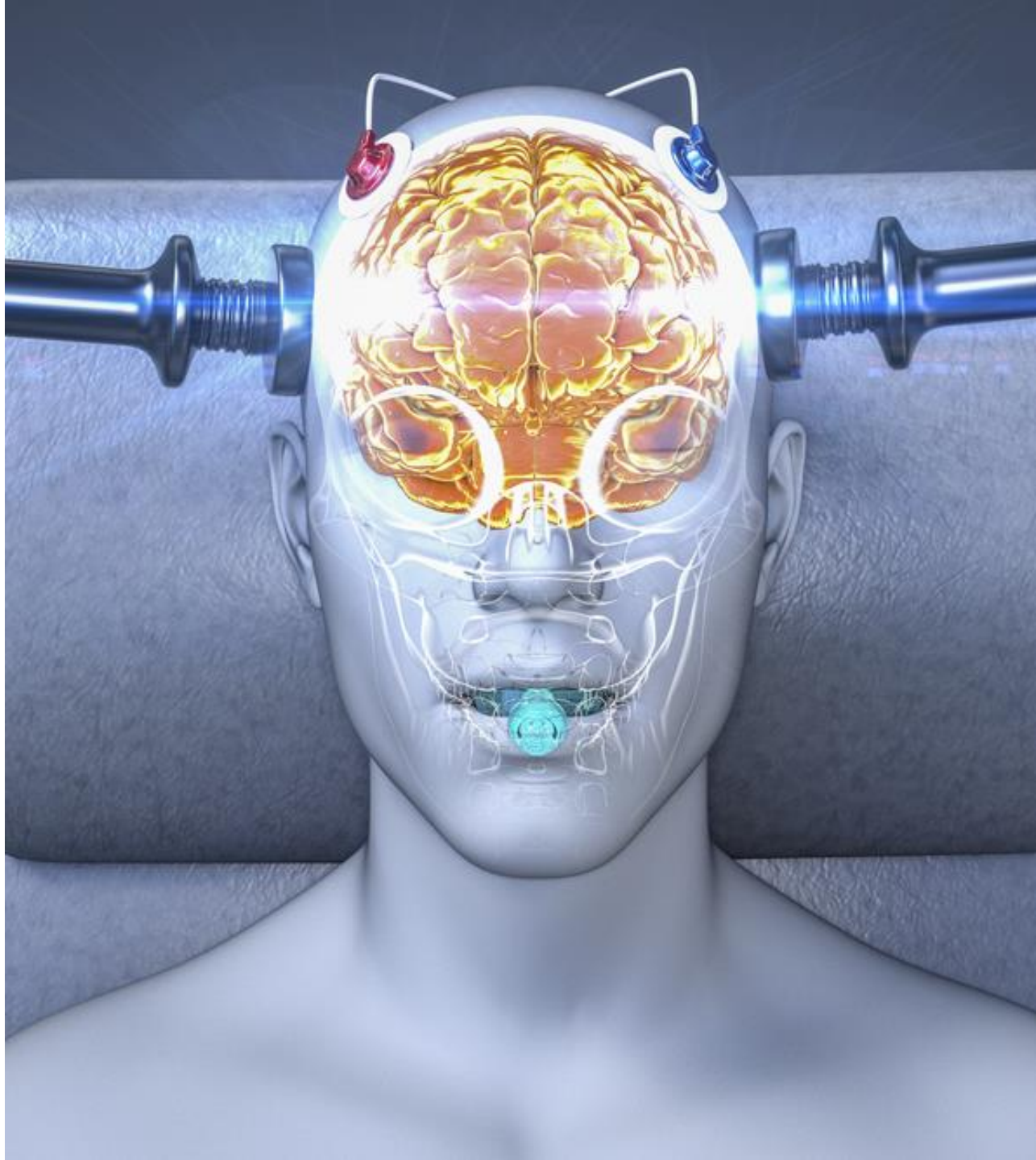
- Magnetic pulses delivered to specific brain regions through the scalp via a magnetic inductor coil
- Most common side effects are scalp discomfort and headache
- Avoid in patients with epilepsy
- Schedule may be inconvenient

Ketamine and esketamine are effective for many patients, but there are caveats[22-24]

- Single dose can alleviate depression and SI within 4 hours
- Effects last up to 1 week
- Facility should have nursing resources
- Long-term safety, efficacy, and treatment planning not well known

When to think about ECT[7,20]

- Efficacy as high as 80%
- No absolute contraindications
- Stigma is most significant barrier for many
- Clinical priorities are:
  - Highly treatment-resistant
  - Psychotic features
  - Catatonia



The research into classic psychedelic (e.g., psilocybin) treatments for depression is growing[26-27]

- ~20 trials looking at various permutations, including phase III
- Psilocybin-based treatments associated with improved:
  - Depression
  - Anxiety
  - Spiritual well-being
  - QoL
  - Pain
- Few adverse outcomes

Patients are put into a vulnerable state, and there is enormous potential for abuse in that area

- https://www.cbc.ca/news/canada/british-columbia/bc-sexual-abuse-psychedelic-therapy-1.5953480
(accessed 4/6/25)

A lot of hype ➔ $$$ opportunities[28-30]

- For-profit clinics offering psychedelic treatments have grown rapidly
- Quality and adherence to treatment guidelines likely varies
- Psychedelic treatments should be reserved for treatment-resistant cases and good psychiatric/medical candidates
- Try to steer patients with questions/interest in psychedelic treatments toward reputable clinics and providers
- Cannabis does not currently have an evidence-based role in any mood disorders or anxiety conditions

Pitfalls to avoid:

- Clinics offering only 1 kind of treatment
- Offering psychedelic treatment as first-line when other first-line treatments are available
- Offering a drug or prescription without psychotherapy
- Providing or prescribing ongoing treatment with drug
- Lack of clarity around the licensing/training of the therapist

https://apnews.com/article/psychedelic-drugs-mushrooms-startups-psilocybin-fda-e3f629f817781b096d72535e022d8b2f (accessed 4/8/25)

MOC REFLECTIVE STATEMENT (BRIEF TAKE HOME NOTES FOR REFERENCE)

1. SSRIs, SNRIs, bupropion, and mirtazapine are all reasonable first choices for treating major depressive disorder
2. First-line treatment for anxiety disorders are SSRIs (and CBT).
    1. SNRIs and mirtazapine can also be considered
    2. Bupropion is less predictable for anxiety
3. Novel treatments such as ketamine* and psilocybin* might be appropriate as part of an advanced treatment plan, but they are not first-line and should come from reputable sources

*Not FDA-approved

Brief Reference Slide

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