TREATMENT RESISTANT DEPRESSION

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DISCLOSURES: SEAN BARRETT, DO

- I do not have any financial relationships with ineligible companies to disclose.
- I will be discussing off-label use of a commercial product.

OBJECTIVES

- Define Treatment-Resistant Depression (TRD).
- Identify multiple pharmacological treatment options for TRD.
- Identify multiple non-pharmacological treatment options for TRD.

COMMON DEPRESSIVE DISORDERS

- Major Depression Disorder
- Persistent Depressive Disorder (dysthymia)
- Adjustment Disorder with Depression
- Bipolar Disorder
- Schizoaffective Disorder
- Depressive Disorder due to Substances
- Depressive Disorder due to Medical Condition

MAJOR DEPRESSION: DIAGNOSTIC CRITERIA

- Depressed mood plus five or more symptoms for 2+ weeks (SIGECAPS).
- Symptoms cause distress or impairment in functioning.
- Not caused by medical illness, substances, or other psychiatric. illness

MAJOR DEPRESSION: FRONTLINE TREATMENT OPTIONS

- Antidepressants + Psychotherapy
- SSRI/SNRI
- Atypical antidepressants
- MAOI, Tricyclic

MAJOR DEPRESSIVE DISORDER IN THE ELDERLY

- Often goes undetected and is more resistant to treatment.
- Depression is not a normal consequence of aging.
- Suicide rates are twice as high in the elderly.
- Treat with the same agents, but start with smaller dose and effect may take more time.

"TREATMENT RESISTANT DEPRESSION" (TRD) DEFINED

- Must meet criteria for major depressive episode.
- Two trials of optimally dosed antidepressant monotherapies that do not respond satisfactorily.
  - Combination of antidepressants is common, but efficacy is unclear
- Up to 1/3 of adults experience TRD.

WHAT CAUSES TRD?

- Risk factors:
  - Advanced age, female gender, medical illness.
- Inflammation in the brain:
  - Antidepressants effect neurotransmitters, not inflammation.
- Genetics
- Neurobiology

STRATEGIES FOR TRD

- Pharmacologic
- Devices
- Psychotherapy
- Other

PHARMACOLOGIC

- Combining antidepressants
- Adding lithium
- Adding antipsychotics
- Adding thyroid hormones
- Adding stimulants
- Ketamine

COMBINATIONS OF ANTIDEPRESSANTS

- Use medications with different mechanisms of action.
- SSRI/SNRI + Atypical antidepressants:
  - Mirtazapine (Remeron) + Venlafaxine (Effexor)
  - Bupropion (Wellbutrin) + SSRI
- SSRI/SNRI + Tricyclic antidepressants.
- Do NOT combine MAOIs with other antidepressants.

ADDING LITHIUM

- Initial dosing is 300 to 600 mg/day in 1 to 2 divided doses.
  - Increase based on response and tolerability every 1 to 5 days.
- May take up to 6 weeks to see effects.
- Monitoring
  - Response occurs with serum concentrations between 0.6 and 1.2 mEq/L.
  - BUN, Creatinine, Serum electrolytes, TSH, ECG.

ADDING ANTIPSYCHOTICS

- Second-generation antipsychotics commonly used:
  - Aripiprazole (Abilify), quetiapine (Seroquel), and risperidone (Risperdal).
- Less common:
  - Olanzapine (Zyprexa), ziprasidone (Geodon), and cariprazine (Vraylar).
- Black box warning in the elderly who have dementia.
- Monitoring:
  - QT prolongation, Extrapyramidal side effects (EPS).

ADDING THYROID HORMONES

- More data available to support T3.
- Initial: 25 mcg/day.
  - May be increased to 50 mcg/day after ~1 week based on response and tolerability
- T3 plus a tricyclic antidepressant can be started simultaneously at the beginning of treatment to accelerate response.
- Monitoring:
  - Free T_3, free T_4, and TSH

ADDING STIMULANTS

- Methylphenidate may improve outcomes in the elderly:
  - Initial: 2.5 to 5 mg once daily.
  - Increase dose based on response and tolerability in increments of 2.5 to 5 mg every 1 to 4 days up to 40 mg/day in divided doses.
- Other stimulants used for TRD in adults:
  - Lisdexamfetamine (Vyvanse), dextroamphetamine, modafinil (Provigil), pramipexole (Mirapex), atomoxetine (Strattera).
- Be sure to consider cardiovascular and other co-morbid conditions.

KETAMINE

- Produces a cataleptic-like state in which the patient is dissociated from the surrounding environment by direct action on the cortex and limbic system. Ketamine is a noncompetitive NMDA receptor antagonist that blocks glutamate.

- Esketamine FDA approved and applied intranasal in outpatient setting with very specific parameters.

- Intravenous ketamine, short-term use (1-4 weeks), administered in facilities equipped to provide advanced cardiac life support.
  - Should be evaluated by an internist or anesthesiologist to ensure patients are medically stable.

MEDICATION HAZARDS IN THE ELDERLY

- Older adults may be more sensitive to side effects and should always be given lower doses.

- TCAs:
  - Ataxia, impaired psychomotor functioning, orthostatic hypotension, and syncope leading to falls.
  - QT prolongation.
  - Anticholinergic.
  - SIADH and hyponatremia are possible – monitor sodium.

- Lithium
  - Lower optimal serum concentrations (0.4 – 0.8 mEq/L)
  - Higher risk of hypothyroidism, lithium toxicity, tremor, longer half-life, cognitive blunting.

DEVICES

- Electroconvulsive therapy (ECT)
- Transcranial magnetic stimulation (TMS)
- Vagal nerve stimulation (VNS)
- Magnetic seizure therapy (MST)
- Deep brain stimulation (DBS)

ECT

- A small electric current used to produce a generalized cerebral seizure under general anesthesia.
- Remission rates 80% in ECT vs 30% in pharmacotherapy.
- Relapse rates following remission are high, especially in patients with treatment-resistant depression.
- Adverse effects:
  - Mortality (rare), memory loss, aspiration pneumonia, fractures, dental and tongue injuries, headache, nausea.

ECT IN OLDER PATIENTS

- May be more likely to have cognitive effects, and may take longer to recover if that occurs (especially if baseline cognitive impairment).
- Can treat depression related to Parkinsonism, stroke, dementia.
- Older age may be a positive predictor of response to ECT.

TMS

- An alternating current passed through a metal coil placed against the scalp to depolarize neurons in a focal area of the cortex.

- Pros:
  - Better tolerated than ECT.
  - Does not require general anesthesia or induction of seizures.

- Cons:
  - Less efficacious than ECT.
  - May need increased voltage in elderly due to atrophy in the prefrontal cortex.

VNS

- Surgically attaching an electrode around the vagus nerve that is connected to a pulse generator implanted in the chest wall.

- Pros
  - Some observational studies suggest VNS may be beneficial for TRD.

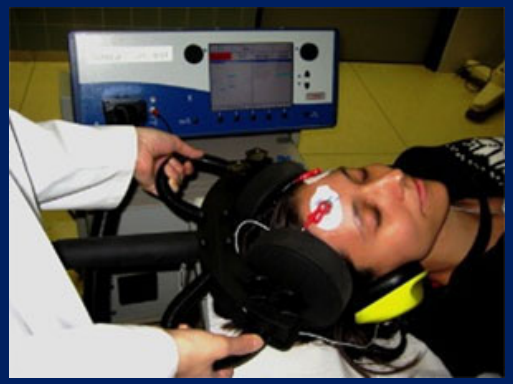
- Cons
  - Involves surgery under general anesthesia.
  - The best evidence indicates that VNS is not efficacious for TRD.

MST

- A noninvasive approach that uses a TMS device to induce a generalized seizure.

- Pros:
  - May cause less adverse effects than ECT
  - Does not utilize surgery or general anesthesia

- Cons:
  - Evidence of efficacy in TRD is weak
  - Produces a seizure

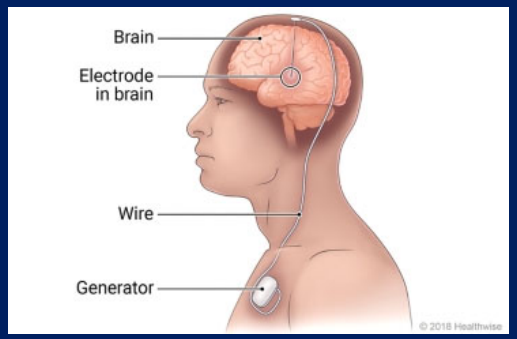


DBS

- Implanting electrodes into targeted brain regions through surgery and then tunnelling wires beneath the scalp and skin of the neck to connect the electrodes to a pulse generator below the clavicle.

- Pros:
  - Cognitive impairment may improve with deep brain stimulation.
  - Some observational studies suggest there is efficacy in patients with TRD.

- Cons:
  - Involves surgery under general anesthesia.
  - Not proven to be efficacious for TRD.



INTERVENTIONAL PSYCHIATRY IN THE ELDERLY

- ECT:
  - Research suggests impaired cognition due to depression often improves, especially in the elderly.
  - Efficacy of ECT + pharmacotherapy is improved, especially in the elderly

- Ketamine:
  - Increased blood pressure and heart heart, especially those with risk factors for coronary artery disease.

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PHARMACOGENETIC TESTING

- Cytochrome P450 enzymes responsible for the metabolism of many antidepressants have been associated with variations in serum concentrations of antidepressants due to rapid or slowed metabolism.

- Pharmacogenetic tests may be useful in the initial selection of antidepressant in TRD. They could identify rapid or poor metabolizers, which in turn could:
  - Help to prevent adverse reactions due to poor metabolism.
  - Guide the prescriber in dosing higher if patient is rapid metabolism.
  - Avoid potential problematic interactions.

- However, the testing does not inform us as to which medication will be most efficacious for that particular patient. Therefore, the clinical utility of pharmacogenomic testing remains unclear.

PSYCHOTHERAPY

- Very important in all phases of treatment.

- Many obstacles exist, including:
  - The patient's fears, attitudes, and misconceptions
  - Cost
  - Transportation
  - Time constraints
  - Availability of therapists

- Telehealth has been helpful, but seniors may struggle with technology.

PSYCHOTHERAPY IN OLDER ADULTS

- Special considerations:
  - Research suggests older adults may be more open to psychotherapy than pharmacotherapy.
  - Older adults may experience better outcomes of psychotherapy when compared to adults.

- Limitations
  - Sensory impairment.
  - Physical health.
  - Difficulties with transportation.
  - CBT is effective for older adults with depression, but research is limited on other disorders such as anxiety.

PSYCHOTHERAPY TYPES

- Cognitive behavioral therapy
- Interpersonal therapy
- Problem solving therapy
- Reminiscence/life review
- Insight oriented

COGNITIVE BEHAVIORAL THERAPY

- A professionally trained provider assists the patient in identifying and correcting distorted, maladaptive beliefs.
- Includes education on relaxation exercises, exposure therapy, coping skills training, stress management, or assertiveness training.
- First line treatment for MDD alone or in combination with other interventions including medications.

INTERPERSONAL THERAPY

- A professionally trained provider addresses interpersonal difficulties that lead to psychological problems.
- Focus on the individual's interpersonal life in four problem areas:
  - Grief, interpersonal disputes, role transitions, and interpersonal skill deficits
- First line treatment for MDD alone or in combination with other interventions including medications.

PROBLEM SOLVING THERAPY

- A professionally trained provider assists patients in identifying social problems related to depression with the goal of developing rational and effecting problem-solving skills.
- Patients learn consider barriers, set achievable goals, list and evaluate the advantages and disadvantages for solutions, develop/implement an action plan, and evaluate the outcome.
- Evidenced-based treatment for minor depression.

REMINISCENCE/LIFE REVIEW

- A professionally trained provider assists the patient in reconstructing their life story and examining positive/negative experiences.
- The goal is to reduce depression, increase life satisfaction, improve self-care and self-esteem, and help older adults cope with crises, losses, and life transitions.
- Designed specifically for older adults with mild to moderate depression.

INSIGHT-ORIENTED

- Examines subconscious conflicts, repressed memories, dreams and transference.
- The patient learns new ways of thinking and tries to stop repeating the mistakes of the past.
- **Psychoanalysis** is lengthy and the therapist is less engaged. Free association and interpretation are utilized.
- **Psychodynamic** therapy is shorter and more focused. The therapist is more engaged.

NEW FRONTIERS: PSYCHEDELICS

- Psilocybin, MDMA, LSD, and others.
- Psilocybin found in “magic mushrooms” and is serotonergic.
- Growing evidence that psilocybin may be beneficial for many disorders, including depression, anxiety disorders, OCD, PTSD, and substance abuse.
- Psilocybin shown to be beneficial for depression specifically related to end-of-life and cancer.
- Usually the patient engages in psychotherapy after taking the substance.
- Reports of “micro-dosing.”

PRESCRIBING ANTIDEPRESSANTS IN NURSING HOMES

- Federal regulations in nursing home require prescribers to consider gradual dose reduction (GDR) after a certain period of time.
- Department of Inspections and Appeals (DIA) enforces the regulations.
- Pharmacy consultants monitor the documentation and sometimes send reports to prescribers.
- As a prescriber, you should NEVER reduce a psychiatric medication unless you are familiar with the patient's history.

GDR: PSYCHOPHARMACOLOGICAL MEDICATIONS

- Within first year after admission or after initiation:
  - GDR in two separate quarters with at least one month in between.
- After first year, GDR is annual (unless clinically contraindicated).
- GDR **clinically contraindicated** if
  - symptoms return or worsen after most recent reduction within facility,

    OR
  - Prescriber has documented clinical rationale stating that reductions would exacerbate condition causing impaired function or destabilization
- Prescriber must document clinical rationale at least once a year.

HOW LONG SHOULD ANTIDEPRESSANTS BE CONTINUED?

- Relapse rates for major depression are relatively high, especially for older patients and those who have had multiple relapses and early onset.
- Must consider multiple factors including history, safety, patient preference, age, seasonal, genetics, stressors, substance use, psychotherapy, etc.
- May be able to discontinue augmentation sooner, but evidence is lacking.
- Less likely to relapse after antidepressant reduction if utilizing psychotherapy.

GDR: MY PRACTICE

- Once stable, wait approximately one year before attempting reduction. Will re-attempt gradual dose reduction annually if patient motivated and no safety issues. Avoid attempted reduction in the Fall or Winter.

REASONS WHY PATIENTS FAIL TO RESPOND TO ANTIDEPRESSANTS

- Inadequate dose
- Inadequate length of treatment
- Noncompliance
- Unresolved or new stressor
- Substance abuse
- Bipolarity not recognized
- Psychosis not recognized
- Co-morbid personality disorder
- Psychotherapy not properly utilized

THE END

- Thank you!

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