TREATMENT OF DEPRESSION WITH NON-PHARMACOLOGIC INTERVENTIONS

How to help patients with depression who are reluctant to take medication

• If we treated medical illness like we treat mental illness.
SO

• I am not antimedication
• But some things can help that are not meds
• Those things are likely to help the people who are seen in a non-psychiatrist office
Overview
• Preliminary history and labs for depression
• How to diagnosis MDD and when to refer
• Non-medication Treatment options
  • Nutraceuticals
  • Exercise
  • Mindfulness Based Stress Reduction
  • Brain Stimulation
  • Light Therapy

Diagnosing Depression; things to keep in mind
• Measures and screening help immensely
  • PHQ 2: Frequency of feeling 1. lack of enjoyment and 2. feeling down
• Think in terms of impact on work, school and social functioning
• If there are visits that are creating frustration, anxiety or confusion, consider depression
• Pain causes depression and Depression causes pain
• Stigma is real and often people have bought into it. “Oh, no I’m not depressed.” Education helps.
Major Depression DSM V Criteria

• Either depressed mood OR anhedonia/loss of interest
• And 4 or more of the following:
  • Appetite or weight changes
  • Sleep disruption
  • Psychomotor agitation or retardation
  • Fatigue
  • Worthlessness or inappropriate guilt
  • Executive dysfuntion
  • Thoughts of death or suicidal thoughts

• PHQ 9 (or others) is helpful

When and how to refer to a psychiatrist

• Deal with stigma directly. If you sense they might fear being judged, acknowledge that there IS stigma, but that if 20% of people have depression in their lifetime, then any given person either has had depression or has been close to someone who had depression. I tell people we are still in the dark ages to some degree, but it has gotten a lot better and that famous people have come forward revealing their history with depression. Help patients see that you have their best interest at heart by referring them.
• Failure of 2 antidepressants
• Suicidal thinking or self-harm or anything that makes you think it is severe.
• Adolescents and children, unless you have the time to follow up frequently and educate parents on how to deal with emerging SI.
• Comorbidities such as trauma history or substance abuse
• ANY mixed features
**DSM Mixed Features specifier**

- Full criteria for a major depressive episode and **at least 3** of the following (hypo) manic symptoms during the majority of days of the current or most recent depressive episode:
  - Elevated, expansive mood
  - Inflated self-esteem or grandiosity
  - More talkative than usual or pressure to keep talking
  - Flight of ideas or subjective experience that thoughts are racing
  - Increase in energy or goal-directed activity
  - Increased or excessive involvement in activities that have a high potential for painful consequences.
  - Decreased need for sleep.
  - May be part of Unipolar depression, Bipolar II or bipolar I depression.

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**The case for meds**

- They very frequently work
- They change lives allowing increases in functioning and fulfillment
- They have revolutionized treatment of depression and other psychiatric disorders.
- They are generally better than alcohol and marijuana
Why people are reluctant to be on meds

- It may alter self-image due to feeling they have a mental illness (though therapy will attempt to alleviate this)
- Side effects when they occur.
- People often just don't want to be on them and prefer more “natural methods.”
- Sometimes they don’t feel quite themselves or feel a subtle difference that they don’t like even if there is not defined side effect.
- Inconvenience
- Awareness that depression is complex and they want to improve their health overall in hopes their depression will remit.

What I have seen from working with depressed patients for 25 years.

- Routines help
- Social support helps
- Patients do much better when they fully integrate that depression is an illness and they often need help seeing that.
- Strong religious beliefs, whatever the form, can help if there is not judgment of the person for having trouble functioning or for their sexual orientation in which case it can cause depression
History

Family history especially of bipolar depression, anxiety, substance abuse and ADHD
Substance Abuse especially alcohol
Memory loss in the elderly, mini-mental state
Anxiety and focus symptoms
Mixed episode symptoms
Recent losses and their effect

Lab work up

CBC
TSH
Vitamin D
Chem 12, though this can be skipped if there is low index of suspicion
MTHFR polymorphism

A note on Genetic testing
Nutraceuticals
• Omega-3 fatty acids
• L-methyl folate
• Vitamin D
• Probiotics

Omega 3 Fatty Acids
• Moderate Effect sizes were replicated for adjunctive Omega-3 fatty acids but only EPA or eicosapentaenoic acid, 1-2 gm/day
• No difference with DHA or docosahexaenoic acid
L-methylfolate

• L-methylfolate is a main substate of production of the three monoamines: dopamin, serotonin and norepinephrine, the lack of which is implicated in depression.

• Genetic testing for MTHFR polymorphisms can be done through a typical lab.

• Genetic mutation in the MTHFR enzyme prevents folate being changed to L-methylfolate.

• With low functioning MTHFR, less available monoamines.

• Clinically seems to be related to childhood anxiety.

• Usually has been used as an adjunct.

• Clinically there is some difference when people with double allele mutations use L-methylfolate: calmer, less restless, “more content.”

• As a single agent: In patients that had at least one copy of the MTHFR polymorphism that was known to be impaired ability to reduce folate to L-methylfolate. Compared to placebo L-methylfolate group had significantly greater reduction of depression rating scores beginning at week 2. Remission rate was 42% by week by week 8.

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L-methylfolate dosing

• Dosing is 7.5-15 mg and is available on line for the cheapest price through Methylpro.com

• Supplementing has been done through a trade brand, Deplin which is very expensive and is the only prescription product of L-methylfolate.

• OTC forms of it are in miniscule amounts requiring about 10-30 pills to get an adequate amount if there is a genetic polymorphism.
Vitamin D

- Multiple studies have associated depression and low vitamin D levels
- Evidence for augmentation effectiveness when patients with depression are vitamin D deficient.

Probiotics

- Study: Humans both non-depressed and depressed were recruited and their feces were fed to sterile mice. The mice receiving feces that were collected and amalgamated from 5 depressed humans.
- Good gut health is associated with lower inflammation levels and therefore possibly reduced levels of depression.
- One study evaluated CRP level in CSF and that correlated with level of depression and increase glutamate activity in basal ganglia which decreased connectivity from basal ganglia to areas of the brain associated with initiating action. So there is evidence that reward circuits are interrupted with inflammation. Clinically the degree of inflammation was correlated with the degree of anhedonia, or lack of motivation.
Research on Exercise

- Overwhelming research with regular $p < .01$ or better in studies
- Intensity, time and frequency not a significant factor in comparing different studies and when studies compare these variables
- Lowest “dosage” evaluated that impacted outcomes in people with MDD was 20 minutes of moderate intensity exercise (achieving 60-80% of max heart rate)
- Exercise is regularly shown to be as effective or more effective than medications or psychotherapy

Study published in Psychosomatic Medicine in 2000 by Babyak, Blumenthal, Herman et al.

- A. Three treatment Arms, $N=156$ moderately depressed men and women
  1. Sertraline with psychiatric medication f/u at 2, 4, 10, 14, 16 weeks
  2. Exercise 30 min 3 times a week for 16 weeks
  3. Combination: both medication and psychiatric treatment
- B. Results:
  - 1. Medication worked more quickly to reduce symptoms of depression
  - 2. No significant differences between groups at 16 weeks
  - 3. At 10 month follow-up Exercise group had lower rates of depression than the medication or combination group. $p = 0.28$ whether or not anyone was still exercising. $p < 0.1$
Effects of Exercise on Depression

- Meta-analysis of research studies with a variety of sample populations
- Effect size was -0.53, indicating exercise reduced depression by one half of a standard deviation compared to control groups
- Subgroups that used clinical populations (hemodialysis patients, post-MI) the reported ES was larger at -0.94.

Meta-analysis of 30 studies

*Participants in the studies had MDD only
*Effect size was -0.72
*Length of the exercise program was the only program characteristic that moderated the effect, with 9 week or greater programs having the greatest effect.
*Age, gender and severity of depression were not significant moderators
Just as beneficial as psychotherapy, medication and other behavioral interventions

****Comparison of exercise program characteristics yielded insignificant results between groups, indicating that exercise need not be lengthy or intense and that fitness gains are not necessary for patients to experience positive benefits.****
Proposed mechanisms for exercise-relief of depression relationship

A. Thermogenic
B. Endorphin
   • 1. Elevations in endorphins have not been directly linked to decrease in depression
   • 2. “Runner’s high” is not blocked by naloxone
C. Distraction Hypothesis
D. Self-Efficacy Hypothesis
E. Anti-inflammation Hypothesis

Advice for helping patients exercise

Use a Journal or monitor with an app or pedometer.

Encourage, Sympathize and take a long view

Learn Motivational Interviewing or deepen skills with it.

Start slow: 20 min 3 times a week has been shown to make a difference, so start there. If that seems overwhelming, recommend 10 min. 3 times a week.

cheatsheet
Meditation

• A note about Jon Kabat-Zinn and the conferences with the Dalai Lama
• Has been shown to significantly
  • 1. Change brain morphology
  • 2. Improve depression
  • 3. Decrease chronic pain
  • 4. Improve Anxiety
  • 5. Enhance Immune function
  • 6. Increase brain waves associated with sense of happiness or wellbeing
  • 7. Increase empathy

Meta-analysis of MBSR stress reduction and Health Benefits

• 20 Studies were used after eliminating 44 because the quality of the research did not meet criteria.
• Studies covered a wide spectrum of clinical populations: eg: depression, anxiety, pain, cancer, and heart disease.
• Effect on various symptoms of stress, wellbeing, sadness and functioning
• Effect sizes were about 0.5 with p<0.0001

• VA population study: 8 week standard MBSR: Significant effects on depression and anxiety in 74 Veterans with depression and anxiety and pain. No effect on pain or medical illness.
Effect on brain morphology, immune system and EEG

Immune system:
Meditators showed a greater rise in antibodies in response to a flu vaccine compared to controls.

EEG:
- No difference in EEG between groups
- At Time 2 and 3 meditators showed significantly greater activation at the L. Central site, C3/4 compared to wait listed controls.
- L Central asymmetry is associated with positive dispositional affect

Meditation’s effect on brain morphology:
8 week MBSR study done on self referred patients interested on reducing stress
No significant disease present in the subjects:
18 men and women with 17 controls
8 weekly group meetings lasting 2.5 hours plus a 6.5 day on the 6th week
Guided meditation audio recordings to be done daily
Avg 22.6 hours engaged in active homework in the 8 weeks

L. Hippocampus, PC, and TPJ developed increased grey matter p=0.014, with no difference between groups prior to the study.
Role of the hippocampus

Hippocampus has a role in modulation of cortical arousal and responsiveness, regulation of emotion.

This may reflect the increase in emotional regulation that is shown in multiple MBSR studies.

PTSD is associated with a decrease in hippocampal volume. Smaller hippocampi are correlated with risk for stress related psychopathology.

But volume loss appears to be reversible

Temporo-Parietal junction

• Crucial to the experience of the self and when damaged can cause out of body experiences or feeling of disembodiment
• Social cognition, ability to infer intentions, desires of others.
• This region is activated when people feel compassion
Posterior Cingulate cortex

• Functions to assesses the relevance and significance of a stimulus for oneself

• Together the PCC, TPJ, and hippocampus forms a circuit that performs diverse forms of self projection. (Remembering the past, thinking about the future and conceiving the viewpoint of others.)

• These abilities allow autobiographical info to be used adaptively to enable alternative perspectives. (So important with depression.)

Major Depressive Disorder
With Seasonal Patterns

This specifier applies to recurrent major depressive disorder.

A. There has been a regular temporal relationship between the onset of major depressive episodes in major depressive disorder and a particular time of the year (e.g., in the fall and winter.

   **Note:** Do not include cases in which there is an obvious effect of seasonally related psychological stressors (e.g., regularly being unemployed every winter).

B. Full remissions (or a change from major depression to mania or hypomania) also occur at a characteristic time of the year (e.g., depression disappears in the spring).

C. In the last two years, two major depressive episodes have occurred that demonstrate the temporal seasonal relationships defined above and no nonseasonal major depressive episodes have occurred during the same period.

D. Seasonal major depressive episodes (as described above) substantially out number the nonseasonal major depressive episodes that may have occurred over the individual’s lifetime.
Light Therapy

• Equivalent or better than medications in treating SAD
• Effective light boxes: full spectrum, 10,000 lux
• Use in the morning as it can cause insomnia
• No more than 2 feet away with eyes open but not looking at the box.
• 30 min daily
• Works faster than antidepressants; clinically often seems to work within days
• FDA does not test, approve or regulate light boxes.
• Insurance used to cover them but it seems as cost effective to buy them
• A certain mail order giant sells good ones for $70 dollars and up
• Can trigger manic episodes
• Patients with Diabetes or retinal disease should be cleared by optometrist

Brain Stimulation

• ECT
• TMS
• TMS induced focal seizure
• Deep Brain Stimulation
• VNS
Transcranial Magnetic Stimulation

- An Electric Coil creates a magnetic field and the coil is placed on the patient’s head on the dorsolateral prefrontal cortex, very associated with the seat of depression.
- 20 min – 30 min procedure of repetitive stimulation to DLPFC in bursts.
- Increases BDNF, blood flow and catecholamines to the area stimulated.
- 70% of patient’s retain effects for a year.
- Few side effects, headache, scalp pain, some early fuzzy-headedness.
- FDA cleared for depression and most insurance pays for it.
- Medicare began paying for it about 2 years ago after doctors made the case that patients disabled due to depression stood a chance to do well.

Transcranial Magnetic Stimulation (TMS)

- 39 early clinical trials
- Controlled studies showed effect size of 0.62
- Almost all patients were medication resistant
- Low sham response rates, far lower than placebo in typical med trials
Later clinical trials

- Meta-analysis circa 2006-07
- N=276
- Effect size = 0.76
- Compared positively to ECT

- NIMH study, independent of industry:
  - 190 patients with treatment resistant depression
  - Remission: Active: 15%, Sham: 4%  p=0.015  (four times greater odds of remitting than sham)
  - 30% in remission in open label extension phase
  - Excellent safety

World Psychiatry Journal study Feb 2015

20 research sites in US, Canada, Germany and Israel
Deep Brain Stimulation
• Showing promise with very severe, refractory depression.
• Electrodes placed intracranially and deep structures stimulated

ECT
• New form that causes much less amnesia: FEAST: Focal electrically administered seizure therapy, which uses unidirectional current
• RUL, or right unilateral was an improvement re: affect on cognitive function
• Still the best treatment for severe, suicidal depression or depression with psychosis
• Deep Brain Stim study that got more than 10,000 responses but only 17 were eligible because most did not fit the criteria of having tried ECT.
References

References


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