Wait- There's Evidence for That? Integrative Medicine Treatments for Depression

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Goals and Objectives

- Upon completion, participants will be able to:
  - Identify evidence-based clinical care guidelines that provide recommendations on complementary and alternative treatments for depression.
  - Counsel patients on the level of evidence for multiple complementary and alternative agents for use in the treatment of depression.
  - Name at least one herbal supplement and one non-pharmacological integrative medical intervention that has evidence in the treatment of depression.

Session Structure

- Pre-Test (5 Minutes)
- Case Studies (50 Minutes)
- Conclusion/Integration of Knowledge/Questions (15 Minutes)

Pre-Test

- Which complementary and alternative medication has the longest track record of use and the highest level of evidence in effectively treating mild-to-moderate depression?

Pre-Test

- Name at least TWO non-medication, non-psychotherapy based treatments for depression that have scientific evidence of efficacy.

Pre-Test

- Which of the following is true regarding S-adenosyl methionine (SAM-e) in the treatment of depression?

Pre-Test

- A 45 yo woman has a history of depression and wants to avoid SSRIs and SNRIs due to sexual side effects. Her PHQ-9 score today is 15 with no suicidal ideation. She also is not interested in 'telling people all of my problems' and refuses therapy. Which of the following treatments has the best evidence for treating her depressive symptoms as a monotherapy?

Pre-Test

- What are the limitations in the use of omega-3 fatty acids in the treatment of depression (multiple correct answers - list any that you think are relevant)?

RESOURCES

- Michigan Medicine Depression Guidelines
- CANMAT Depression Guidelines
- Natural Meds Database
- Carlat Report

Case Studies

Case Study One

- Mr. Y is a 45-year-old who has experienced depressed mood of mild-to-moderate severity since his late 30s.
- Symptoms have responded to SSRIs but he continues to feel not like himself and states that he feels as if his depression has recently gotten worse due to the pandemic.
- He was frustrated with his loss of libido on his SSRI and wants to avoid any new medications or increase in current SSRI dosage due to possibility of side effects.

Case Study One

- FH: negative for psychiatric illness
- He denies any personal history of substance abuse, episodes of racing thoughts, lack of need for sleep, suicidal thoughts or impulsive behavior.
- His PHQ-9 today is 17.

He asks you if there is a supplement he can use to help further with his depression? He additionally states that he wants something that will work quicker than his SSRI did to take effect.

Case Study One Summary

- Diagnosis – Chronic Major Depression
- Treatment – SSRI
- Current situation – not currently feeling like himself, increased stress due to pandemic, does not want to change dosage or add on another medication due to side effects
- He would like a quick acting supplement that will help his depression

Case Study One: Discussion

- Comfort with supplements or other modalities for depression treatment?
- What supplements have people tried?
- What is a supplement that can be added on to his current SSRI regimen?
- Quick acting?
- Evidence for these supplements?

SAM-e Learning Points

- S-Adenosyl methionine
- LOE – A
- MOA thought to be: increased brain levels of serotonin, dopamine, and norepinephrine whose synthesis requires SAMe together with B-12 and folate
- Multiple studies show improvement in depression scales, and cognitive function in SSRI non responders when SAM-e is used as an adjunct
- Often patients will take B12 and folate supplements with SAM-e as well
- Rapid onset of action and few side effects

SAM-e Learning Points

- Adjunctive treatment with SSRI; weight neutral and no sexual side effects
- SAMe is generally prescribed starting with 200mg/day before breakfast, then titrating to 400-600 mg before breakfast and again before lunch based upon therapeutic effect and adverse effects up to 800-1600mg/day in three divided doses
- Studies are limited therefore monotherapy is not recommended
- Contraindication: patients with bipolar disorder (can lead to mania)
- Side effects: moderate arousal or anxiety is sometimes reported when SAMe is being titrated to a therapeutic dose (resolve within a few weeks), GI upset, decreased appetite, dry mouth, insomnia, and headache
- Limiting factor = cost

Case Study One

- Mr. Y comes in for follow up in 6 weeks duration.
- He states that he is doing really well and feels as if his mind is cleared on his regimen of SSRI and SAM-e.
- His repeat PHQ-9 is now 6 and he wishes to continue on this regimen.

Case Study One

- Mr. Y comes in for follow up appointment 3 months later.
- He states that he was happy with his regimen of SSRI and SAM-e.
- He states that his mood was significantly improved leading to a new relationship. He states that since he was on a supplement, he figured he could wean himself from his SSRI to avoid potential libido difficulties.

Case Study One

- Mr. Y has been without his SSRI for about a month now and he is starting to feel depressive symptoms again.
- He is not at his lowest and his PHQ-9 is 12. He states that the SAM-e on its own is not helping enough and he would really like to avoid starting on a SSRI.
- **He is wondering if there is another supplement that he can use? He states that he does not want to try a botanical supplement since he has many environmental allergies and is nervous about being on a plant based supplement.**

Case Study One: Discussion

- Is there a supplement that can be started at this time that can be used as monotherapy for Mr. Y?

Acetyl-L Carnitine

- MOA: increase epigenetic induction of mGlu-2 receptors
- Can be used as monotherapy
- Second line agent to treat depression
- Studies (Nasca et al. 2018) have shown low level of Acetyl-L Carnitine in people who suffer from depression. The worse the depression, the lower the level of Acetyl-L Carnitine
- Treatment – 3g/day

Acetyl-L Carnitine

- Low side effect profile – mostly GI side effects
- 3 RCT showing similar efficacy to SSRI
- Meta-analysis in 2018 in psychosomatic medicine journal looked at 12 RCT and determined that ALC supplementation significantly decreases depressive symptoms compared with placebo/no intervention
- Studies were all small and therefore, more work is needed
- Other benefits: Has been studied for analgesia and pain control in patients with fibromyalgia and elderly with nerve pain.

Case Study One

- Mr. Y returns to you in 6 weeks for follow up.
- He states that although he is not 100% better he is happy with the current regimen of SAM-e and Acetyl L carnitine.
- His relationship is going well and he is happy to not have to deal with any side effects that would affect his relationship.
- His PHQ-9 is now 7 and he denies any suicidal ideation.

Case Study One

- He states that although he is happy with his supplements, he has recently lost his job.
- He would like to still avoid SSRIs however, is wondering if he can use something other than SAM-e, since a 30 day supply costs him >100$?

Case Study One: Discussion

- Cheaper alternative of supplement?

Omega-3 Fatty Acids – Fish Oil

- Can be used as monotherapy or adjunct to SSRI in treatment resistant SSRI
- Mild to moderate depression
- Meta-analysis of 15 trials involving 916 subjects suggests that omega-3 fatty acid supplementation with EPA greater or equal to 60 percent of total EPA and DHA showed the highest benefit against primary depression
- Dosage - 600-1200 mg EPA and 400-800 mg DHA per day. Up to 3-9g/day (1-2g DHA and 1-2 g EPA)

Case Study Conclusion

- Mr. Y thanks you for being open to alternative therapies and suggesting supplements that will help with his depression. He states that he will switch to fish oil and follow up in 2 months
- At his 2 month visit his PHQ-9 is stable at 7 and he is currently happy with his situation. He thanks you for helping him save money and for helping him with his health

Case Study Two

- Mr. Xavier is a 32 year-old man with a history of moderately-severe major depression. He has been on no medications for the past 5 years.
- He has been having more depressive symptoms over the past 6 months. You saw him in a PCP visit 4 months ago, and he had a PHQ-9 score of 18. He did not want to start medications at that time, and was open to psychotherapy.
- He has been doing CBT for the past 3 months.
- Today he is feeling improved but not back to his normal self, with a PHQ-9 score of 11.

Case Study Two Summary

- Dx – Major Depressive Disorder, Recurrent
- Tx – CBT for 3 months
- Current Situation: Not at baseline, PHQ-9 11, no suicidality.
- He would like further recommendations on treatment but vehemently does NOT want an SSRI/SNRI or other prescription medication.
- He asks, “What has the best evidence for treating my depression, like a supplement or something like that”?

Case Study Two - DISCUSSION

- What are options for treating his depression?
- What has the best evidence as a supplement?
- Any idea on the level of evidence for these treatments?
- Do you have any personal experience with any of these effective treatments?

St. John's Wort Learning Points

- Herbal name: Hypericum perforatum
  - From a perennial plant used for hundreds of years
- Acts on serotonin receptors, inhibits monoamines
- Dose range wide: 500-1800 mg/day
- Prolonged onset of action like SSRI – 4-12 weeks
- Systemic reviews showing comparable to antidepressants and superior to placebo for mild-to-moderate depression
  - Mixed reviews for more severe depression
- May have lower level of adverse effects
  - GI symptoms, headache, rash, dry mouth, photosensitivity
  - Avoid other serotonergic meds

Case Study Two:

- Mr. Xavier decides to start St. John's Wort since it has the most evidence for efficacy.
- He continues therapy and St. John's Wort for the next 3 months and is feeling better but still not quite his normal self.
  - His PHQ-9 is now 8, improved from 18 pre-treatment
- He is happy with current therapy but his insurance is running out and will have to stop it. He would like other treatments that are 'natural'. His wife read about Saffron and wanted to see if you knew anything about this?

Case Study Two: Discussion

- Saffron (Crocus Sativus)
  - Anybody have any experience?
- Any experience with other herbal supplements if not Saffron?

Saffron

- Herbal name: Crocus sativus
- Usual dose: 20-30 mg/day
- Duration tested: 6-8 weeks
- Level of evidence
  - One meta-analysis
  - 3 systemic reviews
- Recommended use in mild-to-moderate depression as mono-therapy or add-on (adjunct) treatment
- Mild adverse effects
  - Anxiety, increased appetite, nausea, headaches

Case Study Two

- Mr. Xavier prices saffron and decides he doesn’t want to buy two supplements.
- He is wondering if there is anything he can do to help him improve his mood given that he is feeling almost back to normal.
- Do you have any ideas for anything free he can do to boost his mood?

Exercise

- Mechanism of action – increasing endorphins, psychological factors
- Evidence for both aerobic and anerobic exercise helping.
- Amount?
  - At least 30 minutes of moderate-intensity
  - At least 3 days a week
  - For at least 9 weeks
- Meta-analyses and systemic reviews show efficacy
- Monotherapy or adjunct for mild-to-moderate depression
  - Less evidence in moderate-to-severe due to lower quality trials
  - Long-term data less clear
  - May prevent depression

Case Study Two: Conclusion

- Mr. Xavier does need to lose some weight, and would like to start walking again with his partner. He agrees to start a walking regiment of 30 minutes a day 4 days a week (will do Monday/Wednesday/Friday/Saturday in AM before work).
- He continues St. John's Wort and has stopped therapy.
- You see him 2 months later and he is feeling great, with a PHQ-9 score of 4. He thanks you for helping guide him through the last few months!

Conclusion/Discussion

Things Without Evidence

- Aromatherapy – not harmful but not statistically significant (few RCTs)
  - Shamsunisha Y, Arunesh A, Pandiaraja M, Venugopal V, Poonguzhali S, Kuppusamy M. Aromatherapy for Postpartum Depression: A Systematic Review and Meta-Analysis. J Family Reprod Health. 2023 Mar;17(1):1-7

Example of Carlat Report

A CARLAT PSYCHIATRY REFERENCE TABLE

Herbs in Depression: Dosing		
Curcumin 95% curcuminoids	Start 500 mg/day, raise to 1000 mg/day after 1 week (max 2000 mg/day)	NuVitality ($7), Root2 C3 Complex ($13), Doctor's Best ($25), A1Vitality ($25)
Saffron Safranal 2%–3%	Start 15 mg/day, raise to 15 mg BID after 1 week	Swanson ($11), Paradise Herbs Saffr-Tone ($21), Life Extension Optimized ($24, dosed as 88.25 mg BID)
St. John's wort Hypericin 0.3%	Start 300 mg/day, raise by 300 mg every 1–2 weeks to target of 600–1200 mg/day divided BID (typical dose 900 mg/day)	Shaklee MoodLift Complex ($30)*, Douglas Labs Max-V ($32), MediHerb 1.8 g ($54)

**Monthly price for typical dose*

From the Article:
"Herbal Therapies for Depressionc"
with **Scott Mendelson, MD, PhD**
The Carlat Psychiatry Report, Volume 21, Number 3, March 2023
www.thecarlatreport.com

Table from Michigan Medicine Depression Clinical Care Guidelines

Table 6. Other Modalities and Integrative Treatments for Mild to Moderate Depression

Treatment	Monotherapy or Adjunctive	Order of Use	Dosing Range	Notes	LOE[a]
Substantial Evidence					
Exercise					
Mild to moderate depression	Monotherapy	First-line	30 minutes of moderate exercise at least three times per week for 9 weeks		A
Moderate to severe depression	Adjunctive	Second-line	(as above)		A
Light Therapy					
Mild to moderate seasonal or winter depression	Monotherapy	First-line	10,000 Lux light within 2 feet, angled toward face, for 30 minutes daily for up to 6 weeks, preferably in morning		A
Mild to moderate non-seasonal depression	Monotherapy or Adjunctive	Second-line	(as above)		B
St. John's Wort	Monotherapy	First-line	500–1800 mg/day	Most evidence for efficacy. Similar action to SSRIs. Documented evidence as second-line adjunctive treatment for moderate to severe MDD.	A
Limited Evidence					
Other natural products and medications[b]					
Omega-3 Fatty Acids	Monotherapy or Adjunctive	Second-line	3–9 g/day (1-2 g EPA + 1-2 g DHA per day)	Helpful in elderly with mild to moderate depression[i] [A] Adjunct with SSRI helps depression, anxiety, and sleep[ii] [B]	A
Acetyl-L-carnitine	Monotherapy	Second-line	3 g/day	Low side effect profile. 3 RCTs show comparable efficacy to antidepressants.	A
S-Adenosyl methionine (SAM-e)	Adjunctive	Second-line	800–1600 mg/day	Overall studies are low quality, limiting use as a monotherapy	A
Methylfolate	Adjunctive	Second-line	15–30 mg/day	Folic acid itself does not separate from placebo.	A
Other treatments[c]					
Yoga	Monotherapy or Adjunctive	Second-line	No standard protocol	Data are mixed and many studies have methodological issues. No major risks of yoga.	A
Acupuncture	Adjunctive	Second-line	No standard protocol	Studies are difficult to compare given lack of standard protocol. Risks include mild bleeding, bruising, headache, and infection.	B

[a] Level of evidence: A = Systematic review of randomized controlled trials; B = randomized controlled trials; C = systematic review on non-randomized controlled trials, non-randomized controlled trials, group observation studies; D = Individual observation descriptive study, E = expert opinion.

[b] Vitamin D at 1500 IU daily [IIB], crocus sativus (saffron) at 20–30 mg/day [IIB], DHEA at 30–450 mg/day [IIA], and lavandula 2–4.5 mL/day (1:2 tincture) [IIB] show little to no benefit with lower quality studies compared to other complementary and alternative treatments. Their use is usually safe.

Treatment	Monotherapy or Adjunctive	Order of Use	Dosing Range	Notes	LOE [a]
Substantial Evidence					
Exercise					
Mild to moderate depression	Monotherapy	First-line	30 minutes of moderate exercise at least three times per week for 9 weeks		A
Moderate to severe depression	Adjunctive	Second-line	(as above)		A
Light Therapy					
Mild to moderate seasonal or winter depression	Monotherapy	First-line	10,000 Lux light within 2 feet, angled toward face, for 30 minutes daily for up to 6 weeks, preferably in morning		A
Mild to moderate non-seasonal depression	Monotherapy or Adjunctive	Second-line	(as above)		B
St. John's Wort	Monotherapy	First-line	500–1800 mg/day	Most evidence for efficacy. Similar action to SSRIs. Documented evidence as second-line adjunctive treatment for moderate to severe MDD.	A

Table from Michigan Medicine Depression Clinical Care Guidelines (pending publication)

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Other natural products and medications [b]					
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Acetyl-L-carnitine	Monotherapy	Second-line	3 g/day	Low side effect profile. 3 RCTs show comparable efficacy to antidepressants.	A
S-Adenosyl methionine (SAM-e)	Adjunctive	Second-line	800–1600 mg/day	Overall studies are low quality, limiting use as a monotherapy	A
Methylfolate	Adjunctive	Second-line	15–30 mg/day	Folic acid itself does not separate from placebo.	A
Other treatments [c]					
Yoga	Monotherapy or Adjunctive	Second-line	No standard protocol	Data are mixed and many studies have methodological issues. No major risks of yoga.	A
Acupuncture	Adjunctive	Second-line	No standard protocol	Studies are difficult to compare given lack of standard protocol. Risks include mild bleeding, bruising, headache, and infection.	B

Table from Michigan Medicine Depression Clinical Care Guidelines (pending publication)

Complementary and Alternative Pharmacotherapy Option for Mild-to-Moderate Depression – Agents with Low Quality or Low Volume Evidence

Agent	Use	Level of Evidence	Michigan Medicine Recommendation	CANMET Recommendation	VA DOD Recommendation	Dosing Range	Notes
DHEA	Monotherapy	A	3rd Line Treatment	Recommended 3rd Line Treatment	Not Evaluated	30-450 mg/day	Converted to sex hormones Higher doses can increase breast cancer
Crocus Sativus (saffron)	Monotherapy or Adjunct Treatment	A	3rd Line Treatment	Recommended 3rd Line Treatment	Not Evaluated	20-30 mg/day	Well tolerated overall with few side effects
Lavandula	Adjunct Treatment	B	3rd Line Treatment	Recommend 3rd Line Treatment	Not evaluated	2-4.5 mL/day (alcoholic tincture 1:2) or 6-12 mL/day (1:5)	Only studied for short term (4-8 week) use
Vitamin D	Adjunct Treatment	B	3rd Line Treatment	Not Evaluated	Not Recommended	1500 IU daily	No evidence as a monotherapy Open-label study with high dose annual adjunct helping geriatric depression

Table adapted from Michigan Medicine Depression Clinical Care Guidelines (pending publication)

Pre-Test Answers

- Which complementary and alternative medication has the longest track record of use and the highest level of evidence in effectively treating mild-to-moderate depression?

St. John’s Wort

Pre-Test Answers

- Name at least TWO non-medication, non-psychotherapy based treatments for depression that have scientific evidence of efficacy.

Yoga, Exercise, Light Therapy, Acupuncture

Pre-Test Answers

- Which of the following is true regarding S-adenosyl methionine (SAM-e) in the treatment of depression?

SAM-e has the benefit of acting relatively quickly compared to other antidepressant agents.

Pre-Test Answers

- A 45 yo woman has a history of depression and wants to avoid SSRIs and SNRIs due to sexual side effects. Her PHQ-9 score today is 15 with no suicidal ideation. She also is not interested in 'telling people all of my problems' and refuses therapy. Which of the following treatments has the best evidence for treating her depressive symptoms as a monotherapy?

Acetyl-l carnitine

Pre-Test Answers

- What are the limitations in the use of omega-3 fatty acids in the treatment of depression (multiple correct answers - list any that you think are relevant)?

Dosing (DHA vs. EPA), number of capsules required to get 3-9 g/day, interaction with antiplatelets, ‘fish burps’, some studies great evidence and some poor evidence

Resources to Share

- For a fee – University of Arizona Integrative Medicine
- With PubMed Access – CANMAT Depression Guidelines
- Attached to this PowerPoint – DRAFT tables from Michigan Medicine's updated Depression Guidelines
  - Based on CANMAT and VA guidelines, along with updated literature search through 2019.
- In Process: Michigan Medicine Depression Clinical Care Guidelines (under review).