

Herbal Medicine for Mental Health

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Disclosures

- Nothing to disclose concerning financial or personal relationships.
- Pinewood Springs Mental Health & Wellness
- Opened March 2020
- 60 Licensed Beds, Adult
- PHP/IOP Adult & Adolescent



Objectives

- Describe increasing interest in herbal medicine
- Describe recommended approach when considering herbal medicines
- Discuss current evidence and role of herbal medicine for psychiatric diagnoses

Definitions

Traditional Medicine:

“Knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, explicable or not, used in the maintenance of health and the prevention, diagnosis, improvement, and treatment of physical and mental illness”

Complementary/Alternative Medicine:

“Broad set of health care practices that are not part of that country’s own tradition or conventional medicine and are not fully integrated into the dominant health-care system”

Traditional Medicine

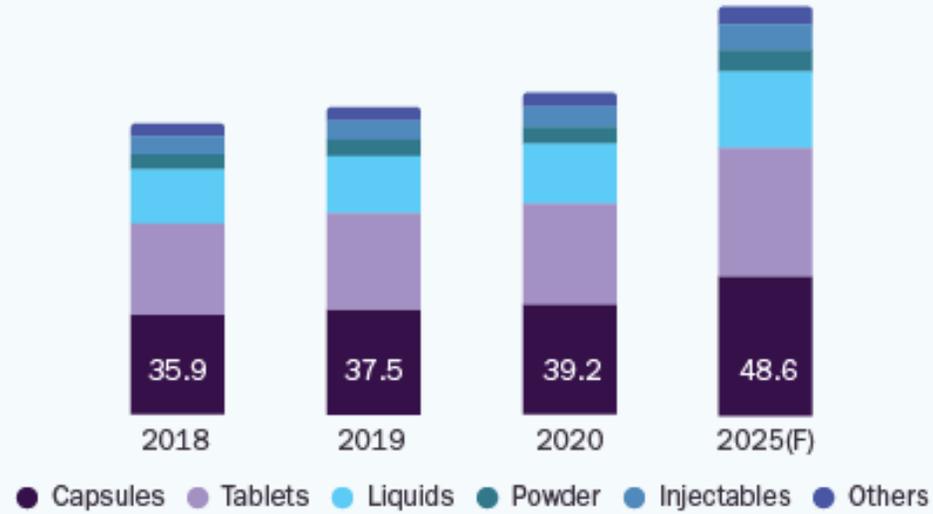
- 88% of all countries use traditional medicine
 - Herbs, acupuncture, yoga, etc
- Integral resource
 - Mainstay for those with limited access to conventional medicine
- Valuable cultural element

World Health Organization. <https://www.who.int/initiatives/who-global-centre-for-traditional-medicine>

Clement A. Functional Medicine: what it is and whether it's right for you. AJC. <<https://www.ajc.com/pulse/functional-medicine-what-it-is-and-whether-its-right-for-you/KRODUANLSZDSXL5SMAEGM3J34Y/>>

Vitamin & Dietary Supplements Market

size, by type, 2018 - 2025 (USD Billion)

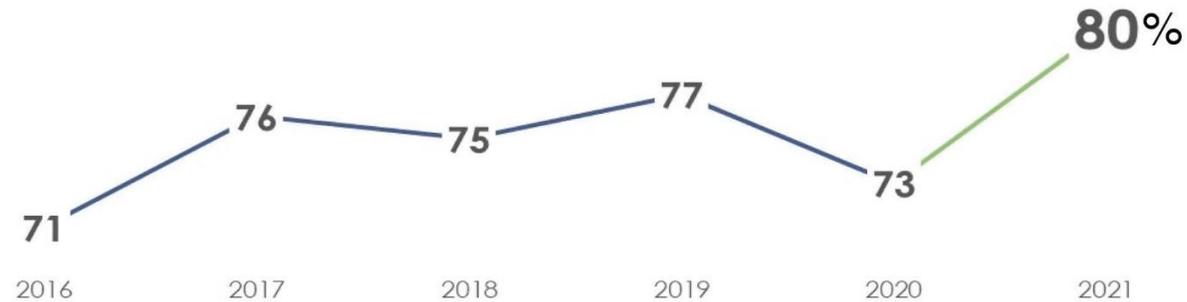


4.4%

Global Market CAGR,
2020 - 2025

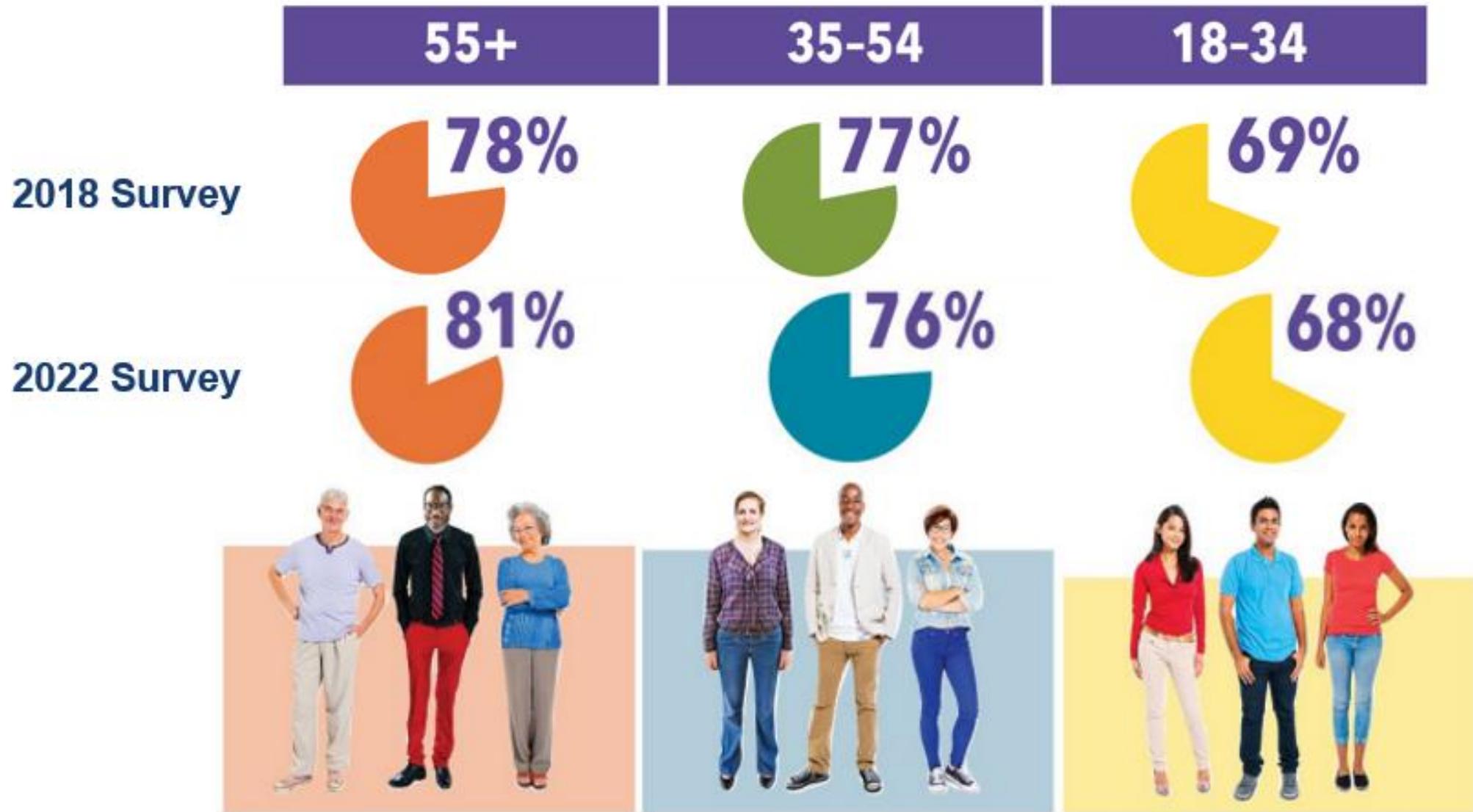
Source:
www.grandviewresearch.com

Four out of five Americans use dietary supplements.



2021 CRN Consumer Survey on Dietary Supplements

PERCENTAGE OF U.S. ADULTS TAKING DIETARY SUPPLEMENTS IN EACH AGE GROUP:



Council for Responsible Nutrition

2022 CRN Consumer Survey on Dietary Supplements: www.crnusa.org/CRNConsumerSurvey

Dietary Supplements

- Multi-route OTCs and “health food” products (i.e., teas)
- No premarketing data and no regulations
 - *“This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.”*
- Labeling requirements
 - Statement of identity (“Dietary Supplement”)
 - Quantity of contents (# pills)
 - Nutrition labeling
 - Ingredient list
 - Manufacturer, packer, distributor details

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Dietary Supplements



1. Contains ingredients listed on label, in accurate declared potency and amounts
2. Does not contain harmful levels of specified contaminants
3. Will breakdown and release into the body
4. Has been made according to FDA's Good Manufacturing Practices using sanitary and well-controlled procedures



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Herbals & Alternatives for: Depressive Disorders

St. John's
Wort

L-
methylfolate

SAM-e

5-HTP

Omega-3

St. John's Wort

- Blocks cortisol secretion
- Weakly inhibits monoamine oxidase
- Inhibits serotonin, norepinephrine, dopamine reuptake

- Dose: 300mg PO TID



St. John's Wort

- Efficacy demonstrated in mild-moderate depression
- Meta-analysis: 23 randomized trials, 1757 outpatients
 - Superior to placebo
 - Effective when used alone (20/23 trials) or in combo with other herbs (3/23)
 - Comparable to prescription antidepressants
 - Lower side effects and dropout rates
- Cochrane Review: 27 trials, 2291 patients
 - Superior to placebo
 - Unclear compared to prescription medications

St. John's Wort

- **Conflicting Evidence**

- Large-scale, multicenter, double-blind case report tabulation
- 200 patients across 11 US academic medical centers
 - No different than placebo
 - Not effective for Major Depressive Disorder

St. John's Wort

- Photodermatitis
- Hypersensitivity
- GI upset
- Dizziness
- Dry Mouth
- Sedation
- Restlessness
- Constipation
- **Case reports of mania/hypomania**
- **Serotonin Syndrome**

Serotonin Syndrome

- Toxicity typically from 2+ serotonergic/serotonin modulating agents
- 60% cases present within 6 hours post dose change or med addition
- 25% cases present after 24 hours
- Reported with overdose of single agents

St. John's Wort

- Induces CYP2D6, 2C19, 3A4, 1A2, PGP
- Decreases efficacy of many medications, not limited to:
 - Oral contraceptives
 - Digoxin
 - Warfarin
 - Antiretrovirals
 - Cyclosporine
- Should be stopped 2 weeks prior to surgery
 - Associated with cardiac complications and prolonged sedation (anesthesia)

Folate (B9) → L-methylfolate

- Folate: essential vitamin found in food (folic acid: synthetic form)
- Correlation between low folate levels and Major Depressive Disorder
 - Associated with treatment resistance
- May be considered as adjunct with an antidepressant



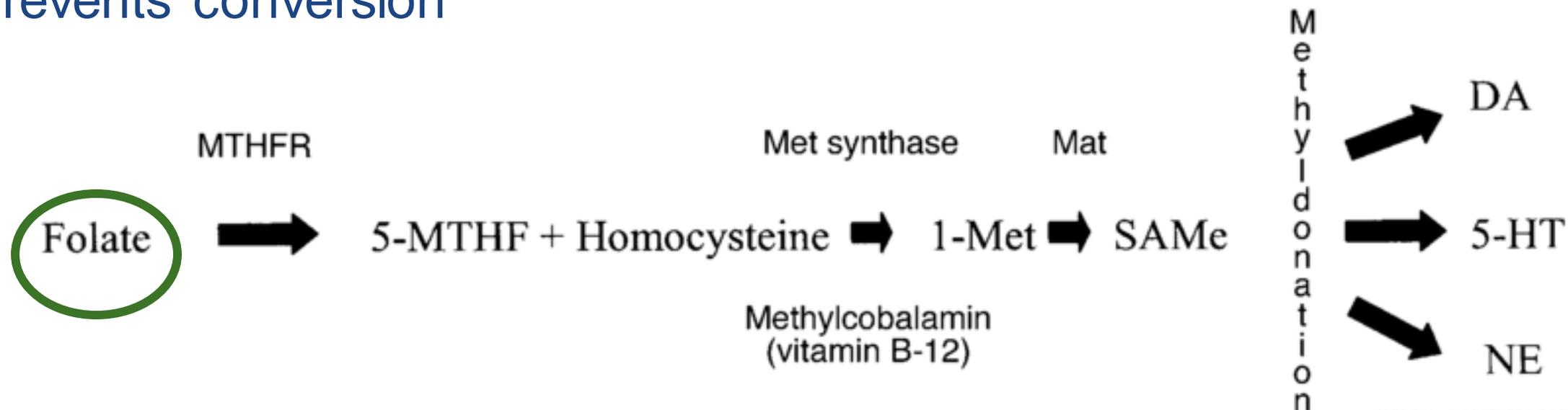
Farah A. The role of L-methylfolate in depressive disorders. *CNS Spectr.* 2009;14(1 suppl 2):2-7

Ginsberg et al. L-methylfolate plus SSRI or SNRI from treatment initiation compared to SSRI or SNRI monotherapy in a major depressive episode. *Innov Clin Neurosci.* 2011;8(1):19-28

<https://experiencelife.lifetime.life/wp-content/uploads/2021/03/Folate-image-1280x720.jpg>

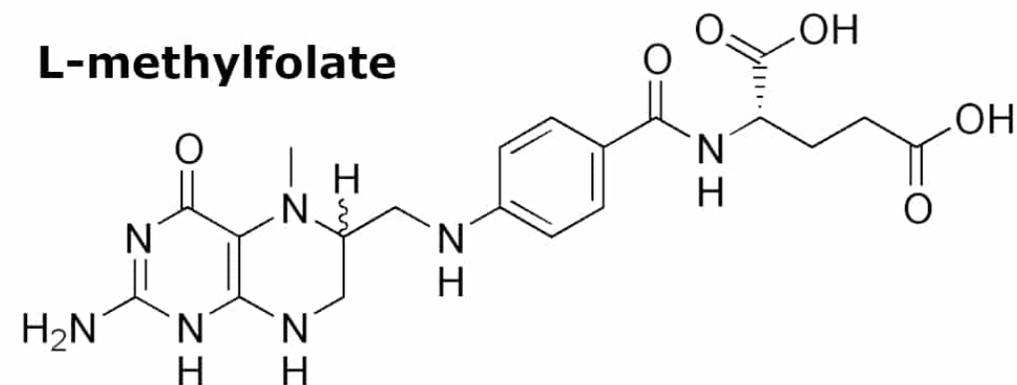
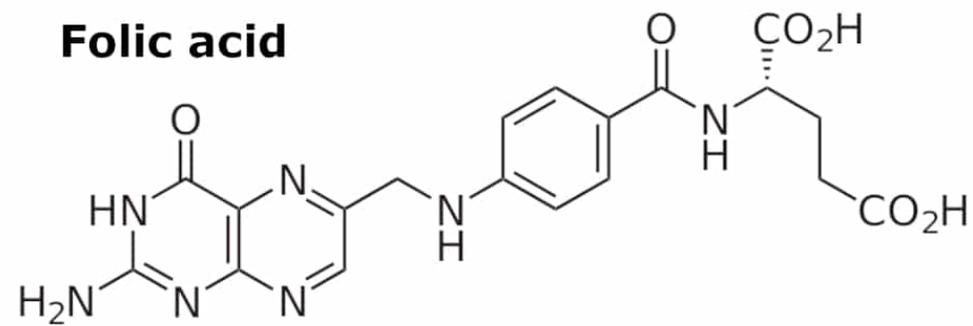
Folate (B9) → L-methylfolate

- Cofactor in synthesis of serotonin, dopamine, and norepinephrine
- **MTHFR** (methylene tetrahydrofolate reductase) – enzyme to convert
- C677T, T/T genotype (5-10% Caucasian population) polymorphism prevents conversion



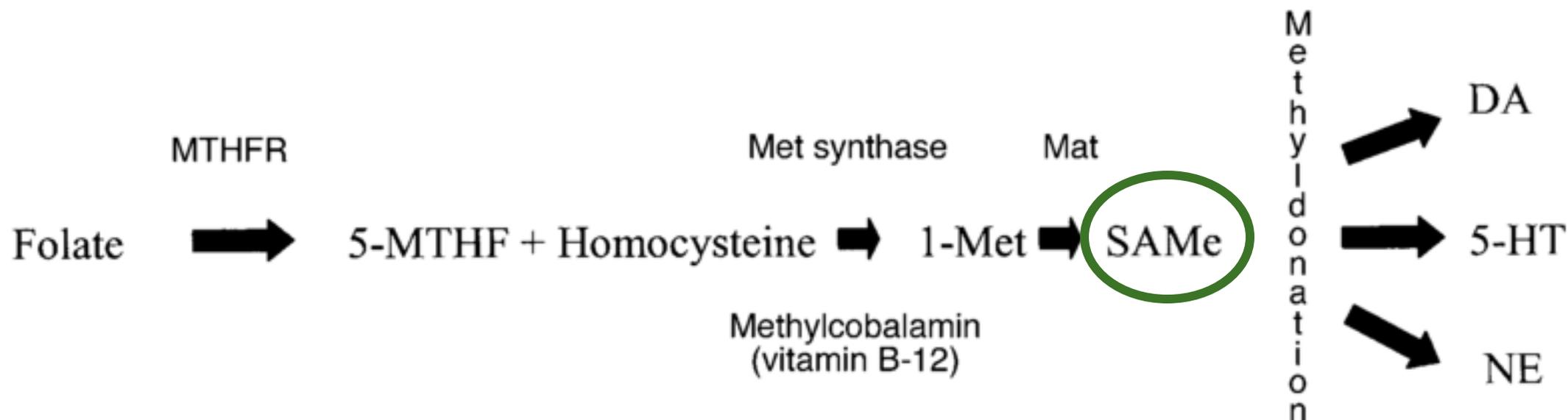
L-methylfolate (Deplin)

- Deplin: medical food
- Requires prescription
- Indicated in patients with sub-optimal L-methylfolate levels and MDD or schizophrenia
- L-methylfolate dose: 7.5mg to 15mg PO daily (\$90-240/month)
- Folate dose: 400mcg PO daily



S-Adenosyl Methionine (SAM-e)

- Endogenous compound, a precursor in neurotransmitter production
- Bypasses MTHFR polymorphisms



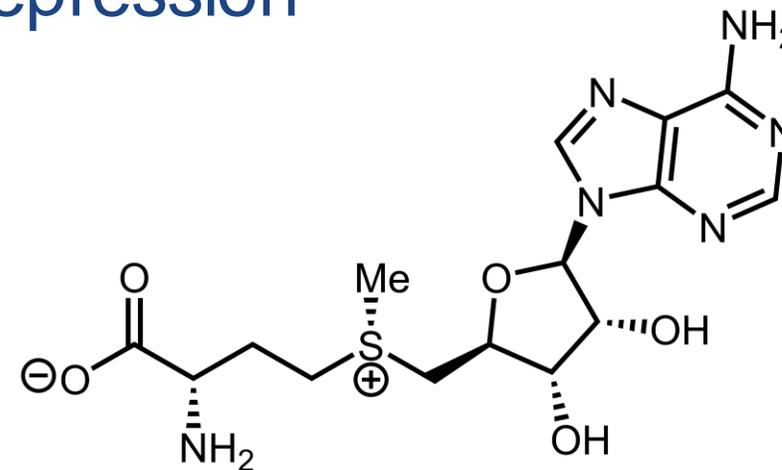
<https://archive.ahrq.gov/clinic/epcsums/samesum.htm>

<https://www.nccih.nih.gov/health/sadenosylmethionine-same-in-depth>

https://upload.wikimedia.org/wikipedia/commons/7/7c/S-adenosyl_methionine.png

S-Adenosyl Methionine (SAM-e)

- Minimal evidence, poor quality studies in depression
 - Too few participants
 - Short duration
 - IV administration
- Dose: 400-1600mg PO daily
- Cost prohibitive: \$0.50-1.00 per 400mg tab



<https://archive.ahrq.gov/clinic/epcsums/samesum.htm>

<https://www.nccih.nih.gov/health/sadenosylmethionine-same-in-depth>

https://upload.wikimedia.org/wikipedia/commons/7/7c/S-adenosyl_methionine.png

S-Adenosyl Methionine (SAM-e)

- Side Effects

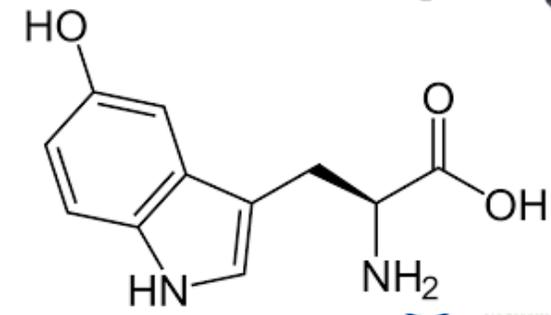
- Headache
- Dizziness
- Anxiety/nervousness
- GI related effects
- Sweating
- Insomnia
- Possible platelet aggregation blocking
- Cases of mania/hypomania

- Drug Interactions

- Antidepressants
- (St. John's Wort)
- Dextromethorphan
- Levodopa

5-Hydroxytryptophan (5-HTP)

- Derived from African *Griffonia simplicifonia* tree
- Precursor for serotonin (serotonin agonist)
- Dose: 150-800mg PO daily for 2-4 weeks
- Rated as 'possibly effective' for depression
- May be more effective than placebo
- Poor quality, few participants



5-Hydroxytryptophan (5-HTP)

- Side Effects

- GI effects
- Anxiety
- Shivering
- Heart problems
- Eosinophilia-myalgia syndrome (EMS)
 - Contaminant-related?
- Seizures
- Serotonin Syndrome

- Drug Interactions

- Antidepressants
- Carbidopa
- Narcotics
- Dextromethorphan

Omega-3 Fatty Acids

- Undefined role in treatment
- Studied as an adjunct to antidepressants
- Suggestive of benefit, though quality of evidence is low

- Essential for brain function/development
- Substrate for eicosanoid production (neuronal transmission)
- Anti-inflammatory and immunosuppressive features



Omega-3 Fatty Acids

- Available products contain eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), or a combination.
- Studied doses range from 1-9g per day
- Most benefit with 2 EPA: 1 DHA

- Side effects: GI upset, diarrhea, constipation



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Herbals & Alternatives for: Anxiety & Sleep

Lavender

Kava
Kava

Valerian
Root

Ginseng

Lavender

- Aromatic flowering plant
- Antibacterial, antifungal, sedative, and potential antidepressant activity
- May inhibit voltage-gated calcium channels
- May bind to NMDA receptors and SERT
- May modify 5HT1A receptors



Lavender

- Topical preparations
- Aromatherapy
- Oral preparations
- **Silexan/CalmAid: German product**
 - Gel-cap (80mg) taken 1-2 times daily
- Possible adjunctive with antidepressant

<https://m.media-amazon.com/images/I/81eLF4QPKqL.jpg>; <https://homegardenandhomestead.com/wp-content/uploads/2021/08/lavender-essential-oil.jpeg>



CalmAid[®]

CLINICALLY STUDIED LAVENDER

Helps reduce **tension & stress***

30 SOFTGEL

*This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease.

CalmAid[®] CLINICALLY STUDIED LAVENDER

Feel more relaxed with CalmAid, the advanced lavender oil supplement studied to help reduce feelings of **tension and stress**.*

- Once daily softgel
- Easy-to-swallow
- Safe for daily use
- Non-habit forming
- Non-drowsy

CalmAid contains Silexan[™], the orally administered lavender oil used in clinical studies.

Recommendation: Take 1 softgel once or twice daily with a glass of water, or as recommended by a healthcare professional.

Caution: Do not use in children under 12 years of age, or if pregnant or nursing. If taking any medications, consult a healthcare professional before use. In clinical studies, burping with a mild lavender aroma has been reported in a small number of users.

Supplement Facts	
Serving Size 1 Softgel	
Amount Per Serving	% DV
Silexan [™] English Lavender (Lavandula angustifolia) Essential Oil	80 mg **

**Daily Value (DV) not established.

Other Ingredients: canola oil, gelatin (softgel), glycerin, sorbitol, annatto extract color

Contains soy.

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Lavender

- Studies of lavender oil product taken by mouth suggest benefit for anxiety
 - Small size, study limitations
- Anecdotally, aromatherapy helpful for anxiety
- Side effects: GI distress (PO), skin irritation (topical)
- Not believed to have drug interactions or contribute to withdrawal symptoms at PO doses of 80-160mg

Kava Kava

- Kavapyrones modulate GABA-A receptor binding
- May potentiate MAO-B inhibition
- May inhibit voltage-gated ion channels

- Positive effects on anxiety (short term)
 - Cochrane review
 - Meta-analysis of 7 randomized controlled trials



<https://www.nccih.nih.gov/health/kava>

Vernani et al. *J Fam Pract.* 2005 Sep; 54(9): 789-90 Pittler MH, Ernst E. *Cochrane Database Syst Rev.* 2003; (1): CD 003383 Pittler MH, Ernst E. *J Clin Psychopharmacol* 2000 Fe; 20(1):84-89.

Kava Kava

- Side Effects:

- **Liver damage (serious/fatal)**
- Dizziness
- Mild GI disturbances
- Temporary yellowing of skin, hair, and nails
- Long-term use by cause skin scaling (**kava dermopathy**)



<https://www.nccih.nih.gov/health/kava>

- Drug Interactions:

- Moderate inhibitor of 3A4, 2C19, and 2D6
- Synergistic effect with CNS depressants
 - Benzodiazepines
 - Barbiturates
 - Ethanol

Valerian Root

- Used as a sedative in ancient Greece/Rome
- Anxiety and sleep
- May increase gamma aminobutyric acid (GABA)
- Challenging interpretation of studies due to poor volume and methodology
- Conflicting results



Valerian Root

- Systematic review: 9 randomized, placebo-controlled, double-blind clinical trials of valerian for sleep
- All with flaws. High methodology ratings in 3/9.
- Repeated-measured design: 128 participants, two valerian formulations and placebo
- Statistically significant subjective improvements in time to fall asleep, sleep quality, nighttime awakenings

Valerian Root

- Side Effects:

- Headaches
- Excitability
- Uneasiness
- GI effects
- Dizziness
- Cardiac disturbances

- Drug Interactions:

- Mild inhibitor of 3A4 and 2C19
- Synergistic effects with CNS depressants
 - Benzodiazepines
 - Barbiturates
 - Ethanol
 - Anesthetics

Ginseng

- Endurance aid to reduce stress and fatigue
- Various species (Chinese, Panax, etc), parts used
 - Distinct chemical structures (ginsenosides)
- Long harvesting process – premature harvest may affect efficacy
- Modulates monoamine neurotransmitter system, upregulating neurotrophic factors, anti-inflammatory action
- No evidence (possible anti-inflammatory, blood sugar lowering effects)



<https://medlineplus.gov/druginfo/natural/967.html#DrugInteractions>

: https://media.istockphoto.com/id/1158312485/photo/red-fruit-of-korean-traditional-ginseng.jpg?s=612x612&w=0&k=20&c=SCfw8TmU4YSBqTL3tTflx7oRtOp4uYd0HRkSbSp4LNY=https://www.news-medical.net/image.axd?picture=2019%2F5%2Fshutterstock_734716603.jpg

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https://www.news-medical.net/image.axd?picture=2019%2F5%2Fshutterstock_734716603.jpg

Ginseng

- Side Effects

- Insomnia
- Hypertension
- Anxiety
- Euphoria
- Case report of mania

- Drug Interactions

- Weak inhibitor of 2C9 and 3A4
- Weak inducer of 2D6
- Warfarin
- Antidepressants
- Stimulants
- Antidiabetic agents



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Herbals & Alternatives for: Neurocognitive Disorders

Ginkgo
Biloba

Vitamin E

Ginkgo Biloba

- Extensive history in Chinese medicine
- Varying effects depending on varieties
- Reuptake inhibitor of serotonin, norepinephrine, and dopamine
- Antioxidant and vasoactive properties
- Dose: 240mg by mouth daily (most commonly studied via extract EGb 761)



Ginkgo Biloba

- No conclusive evidence in any health conditions
- Ginkgo Evaluation of Memory Study, National Center for Complementary and Integrative Health
 - >3,000 older adults
 - Determined does not prevent occurrence or worsening of dementia, cognitive decline, Alzheimer's Disease
- Current research indicating no benefit to memory enhancement in healthy people
- Possible, inconclusive benefits in anxiety and premenstrual syndrome

Ginkgo Biloba

- Side effects:
 - Dizziness
 - Diarrhea
 - Bleeding complications
 - Decreasing platelet aggregation
- **One study:** increased risk of stroke and transient ischemic attack
- Drug Interactions:
 - Anticoagulant medications
 - Antiplatelet medications

Vitamin E

- Dietary sources
- May support as an antioxidant
- Cochrane review found no efficacy for mild cognitive impairment or Alzheimers Disease (AD)



Vitamin E

- Side Effects:
 - Nausea
 - Diarrhea
 - Fatigue
 - Bleeding complications
 - Decreasing platelet aggregation
- Observational Studies (High Dose)
 - Increased total mortality
 - Heart failure
 - Prostate cancer
 - Hemorrhagic stroke

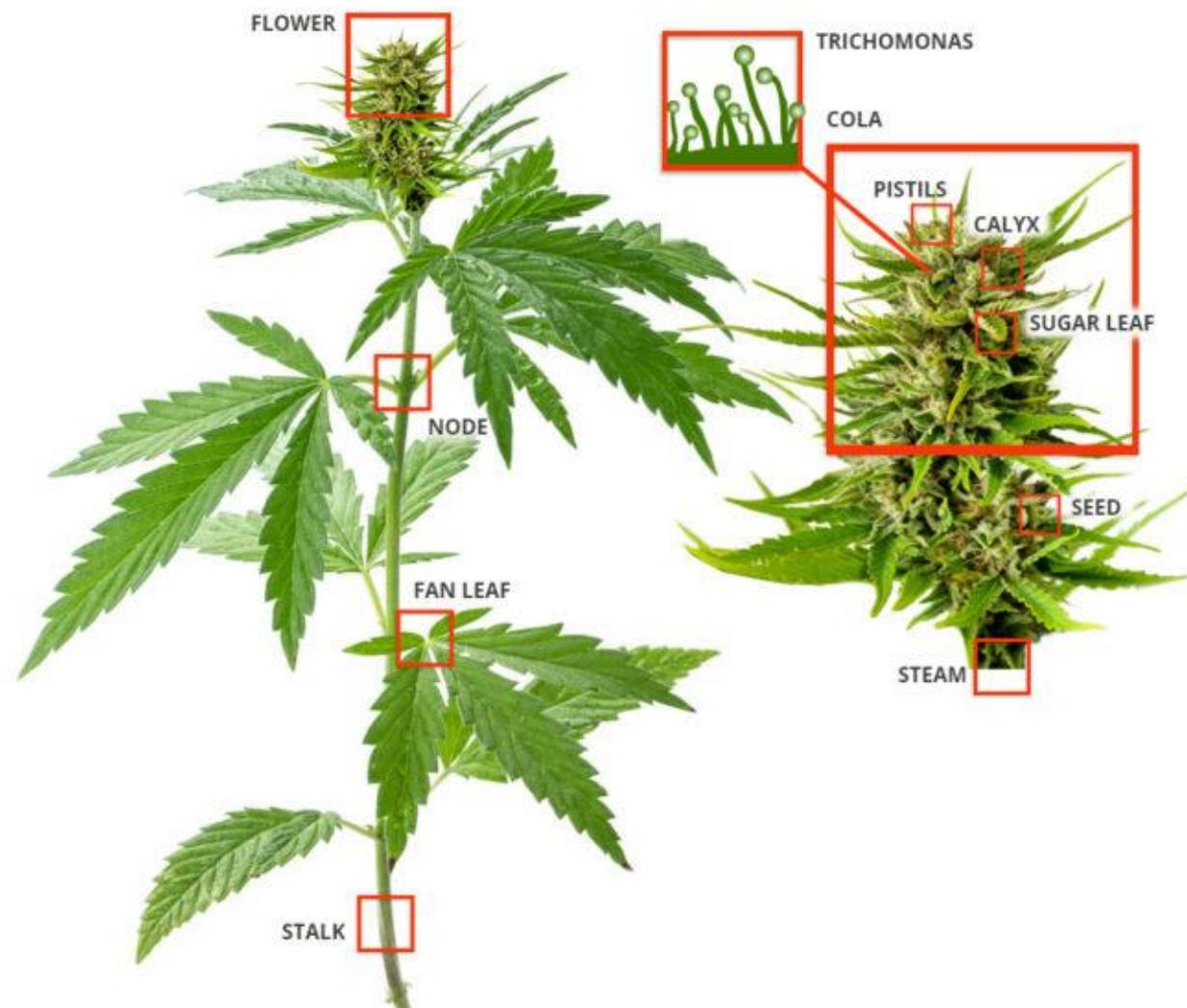


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Cannabis & Psilocybin

Cannabis

- Endocannabinoid System
- Involved in appetite, pain, mood, immune function, and neurodevelopment
- >500 active chemicals
- >80 unique cannabinoids
 - Dose dependent effects
 - Inconsistent/inaccurate labeling



Approved Products

Generic	Brand	Formulation	Approved Use
Dronabinol	Marinol [®] , Syndros [®]	oral synthetic THC	FDA approved <ul style="list-style-type: none"> • Appetite stimulation in AIDS • Chemotherapy nausea and vomiting
Nabilone	Cesamet [®]	oral THC analog	FDA approved <ul style="list-style-type: none"> • Chemotherapy nausea and vomiting
CBD	Epidiolex [®]	oral solution of CBD	FDA expanded access program <ul style="list-style-type: none"> • Intractable epilepsy
Nabiximols	Sativex [®]	mixture of THC and CBD (1:1) as oromucosal spray	Approved in Canada and 13 other countries for MS spasticity

Cannabis

Anxiety, PTSD

Cannabis

Schizophrenia, Psychosis

CBD Side Effects

- Short term:
 - Sleepiness/insomnia
 - Decreased appetite
 - Diarrhea
 - Irritability/anxiety
 - Orthostasis
 - Headache
 - Transaminase elevations (doses >600mg)
- Long term:
 - Weight loss
 - Anhedonia
 - Suicidal thoughts/behaviors

THC Side Effects

- Short term:

- Tachycardia
- Dizziness
- Disorientation
- Euphoria
- Dry mouth
- Somnolence
- Nausea/vomiting
- Fatigue
- Anxiety
- Depersonalization

- Long term:

- Cannabis use disorder (CUD)
- Hyperemesis syndrome
- Decreased sperm count
- Stroke
- Impaired cognitive functioning
- Myocardial infarction
- Insomnia
- Anxiety/Depression
- Psychosis

Cannabis

- Smoke induces 1A2
- Inhibits 2C9, 2D6, 2C19, and 3A4
- Substrate of CYP 2C9, 3A4
 - Antidepressants
 - Antipsychotics
- May increase plasma-protein displacement
 - Increases anticoagulation in patients taking warfarin

Psilocybin → Psilocin

- 5HT2A Partial Agonist
 - (“off target” 1AR, 1BR, 2CR, 5, and 7)
- Increases cortical excitability
- FDA ‘Breakthrough Therapy’ designation
 - Currently in Phase 2B and 3 trials
 - 2 different multinational trials – Major Depressive Disorder and Treatment Resistance



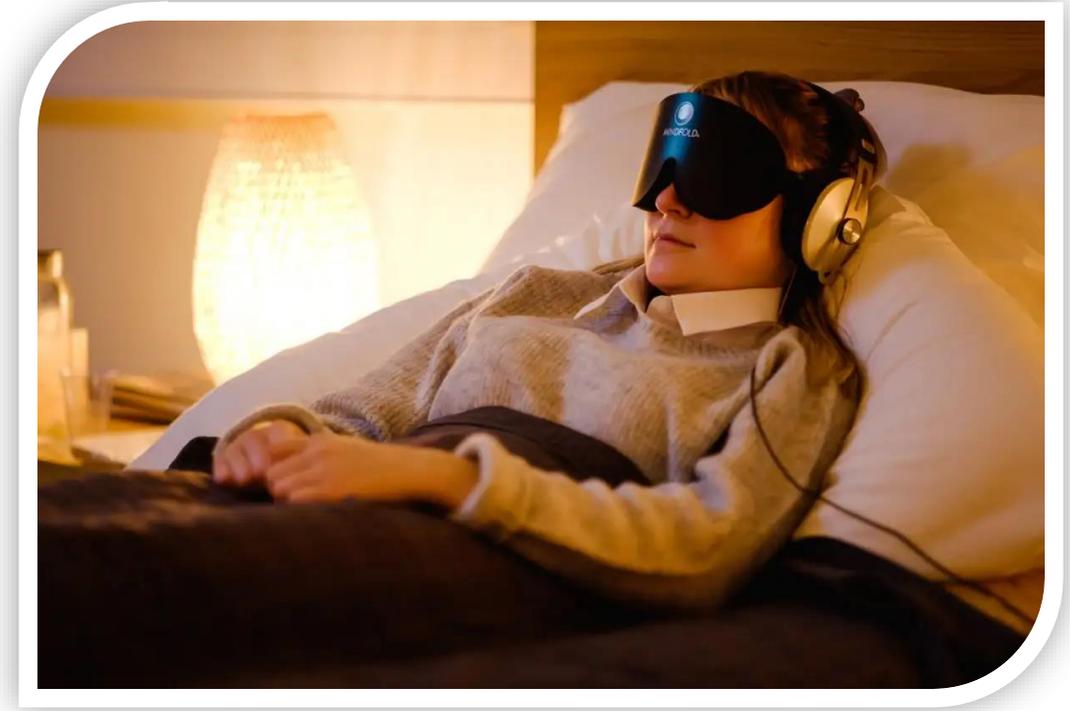
Psilocybin

- Acute effects, dose dependent (4-6 hours)

Subjective Effects	Physiological Effects	Challenging Experiences
Unity	Increased heart rate	Fear/panic – death
Bliss	Increased blood pressure	Fear/panic – insanity
Insightfulness	Drowsiness	Paranoia
Disembodiment	Dizziness/weakness	Grief
Impaired cognition/control	Blurred vision	Feeling isolated
Complex/elementary imagery	Tremors	Physiological distress
Audiovisual synesthesia	Nausea	Perceived arrhythmia
Spiritual experience	Paresthesia	
Anxiety	Impaired motor coordination	

Psilocybin

- Medical/Psychiatric Screenings
- Careful preparation, monitoring, and aftercare/integration
- Physiological Exclusions
 - ECG, BP, HR
- Psychological Exclusions
 - Personal/family history psychosis
- Hallucinogen Persisting Perception Disorder (HPPD)
 - Rare/absent in controlled settings



Barrett et al. *J Psychopharmacol* 2016;30(12):1279-1295

Cohen *J Nerv Mental Disease* 1960;13(1):30-40

McGlothlin & Arnold *Arch Gen Psychiatry* 1971;24-35-49

https://images.newscientist.com/wp-content/uploads/2021/11/10154115/PRI_209558802.jpg

Psilocybin

- Major Depressive Disorder
 - Current evidence suggests possible rapid antidepressant effects
 - May be sustained for 1 year post-treatment in patients with Major Depressive Disorder
- Substance Use Disorders
 - Possible rapid/sustained effects
 - Smoking cessation
 - Reduced drinking/abstinence in those with alcohol dependence



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Closing Considerations

Closing Considerations

- Variability in composition and potency
- Numerous interactions
- Need for discontinuation prior to procedures
- Limited to no data supporting use
 - Pregnancy & lactation
 - Adolescents
 - Severe mental illness

Advising Patients

Goals &
Expectations

Advising Patients

Current/
Historical Use

Resources

- The Office of Dietary Supplements
 - <http://ods.od.nih.gov>
- The National Center for Complementary and Alternative Medicine
 - <http://nccam.nih.gov>
- Natural Medicines Comprehensive Database
 - www.naturaldatabase.com

Herbal Medicine for Mental Health

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