PREVALENCE OF USE:
- 54% of people with severe depression and 57% of people with anxiety report using CAM medicine
- 63% of patients hospitalized for psychiatric indications used CAM therapy within last year (MDD most common)
  - 79% had not disclosed use to psychiatrist

ST. JOHN'S WORT: *Hypericum perforatum (flower)*

MECHANISM OF ACTION:
- May be hyperforin (active?), hypericin
- Inhibits reuptake of 5-HT, NA and DA
- May ↑ 5-HT receptors

SUMMARY OF EVIDENCE:
- Superior to placebo in pts with mild-mod major depression
- Similarly effective as standard anti-depressants
- Fewer side effects than standard anti-depressants
- Evidence for severe major depression is insufficient to draw conclusions

STUDY LIMITATIONS:
Variations in:
- Products
- Standardization
- Comparators (and their doses)
- Doses
- Severity of depression (more severe did less well)

DOSING:
- Most clinical trials used: 300 mg tid
  - Standardized to 0.3% hypericin/ 2-5% hyperforin
- Effect is usually seen after 10-14 days
  - Significant clinical response seen at 4-6 weeks
- Taper dose when discontinuing

SIDE EFFECTS:
- Fewer ADRs than SSRIs and less sexual dysfunction
- Common ADRs:
  - Headache, fatigue, GI upset, insomnia (take in AM)
- Serious ADRs:
  - Phototoxicity (avoid sun/use sunscreen)
  - Withdrawal syndrome (similar to SSRIs – taper)
  - Mania, hypomania (avoid in bipolar disorder)

DRUG INTERACTIONS:
- Strong inducer of P-glycoprotein & CYP450 (mainly 3A4, also 1A2, 2C19, 2C9)
  - Reduces serum levels of susceptible drugs
  - Decreases therapeutic effects
- > 45 drug interactions (18 MAJOR)
  - Immunosuppressants: cyclosporine (↓ 30-70% → transplant rejection)
  - Anti-retrovirals: reported to ↓plasma level of idinavir (57% ↓in AUC)
  - Digoxin (up to 25% decrease in AUC)
  - Opiates (methadone, oxycodone)
  - Warfarin
  - Oral contraceptives (many reports of pregnancies!)
  - SSRIs and related anti-depressants

HEALTH CANADA ALLOWABLE CLAIMS:
- Used in Herbal Medicine to:
  - Help promote healthy mood balance
  - Relieve sleep disturbances associated with mood imbalance

SAMe (S-adenosylmethionine):

WHAT IS SAMe:
- Found throughout the body
- Amino acid derivative synthesized rom ATP and methionine
- Available from meat
- Use: depression, osteoarthritis
  - Widely prescribed in Europe as an anti-depressant

SUMMARY OF EVIDENCE:
- Some positive evidence but unclear
  - More effective than placebo and comparable to TCAs
  - May have a role as an adjunct to SSRIs
- Tosylate salt is most commercially available, but **butanedisulfonate salt** has been shown to be most bioavailable
- Most common dose in trials: 800 mg po bid (mild-mod MDD)

MECHANISM OF ACTION:
- Crosses BBB and increases CSF levels
- An amino acid that acts as a universal methyl donor needed in the synthesis of monoamine transmitters (DA, NA and 5-HT) and membrane phospholipids
  - Increased 5-HT turnover
  - Increased NA and DA levels
  - Alter cellular membrane fluidity helps with facilitation of signal transduction across membrane

SAFETY:
- Headache, insomnia, jitters (take in AM)
- Significantly lower arousal dysfunction than those given adjunctive placebo
- Serious ADRs:
  - Hypomania (in patients with bipolar disorder)
  - SSRIs and MAOIs (theoretical)

KAVA KAVA:

WHAT IS KAVA KAVA?
- Rhizome & roots and stem of *Piper methysticum*
- Kavalactones (main psychoactive constituent)
  - Standardized to 30-70%
- Used as a ceremonial drink in the Pacific Islands to induce relaxation and decrease anxiety

SUMMARY OF EVIDENCE:
- Not fast acting (like BDZ) – may take 2 months for full effect
- Product standardized to 70% kavalactones >> anxiolytic effect
- Studies show it performs better than placebo

MECHANSIM OF ACTION:
- Anxiolytic mechanism largely unknown; possibly:
  - Facilitating GABA transmission by increase # of GABA binding sites
  - Inhibiting uptake of NA and DA
- Non-habit forming

SAFETY CONCERNS:
- Hepatotoxicity (was banned in Canada in 2002, re-introduced recently)
  - Interactions with CNS depressants, alcohol
  - AVOID in patients with liver disease
- May affect ability to drive

OMEGA-3 FISH OILS:

WHY MIGHT FISH OILS HELP WITH DEPRESSION?

- Epidemiologic studies show a correlation between n-3 FA intake in the diet and a low incidence of depression
- PUFAs are responsible for 20% of brain's dry weight and 33% of all fats in the CNS

MECHANISM OF ACTION IN DEPRESSION:

- Change membrane structure and function
  - Cell communication
  - Inflammatory processes (less PGE_2)
  - Neurotransmitter activities

SAFETY:

- Well tolerated at doses up to 3 g/day
- Low incidence: diarrhea, nausea, GI disturbance
- Fishy aftertaste, belching
  - Take with meals or freeze capsules before taking
- May increase risk of bleeding at higher doses (≥ 3 g/day)
  - Case reports of bleeding with warfarin

DRUG INTERACTIONS:

- Hypotensive agents: can decrease BP (additive effects)
- Anticoagulants, antiplatelet agents: can inhibit platelet aggregation (MINOR interaction)
- Lab tests: high doses increase LDL by 5-10%

SUMMARY OF EVIDENCE:

- Different MOA, different conclusions
  - EPA, not DHA may be effective in depression
  - Ratio of EPA:DHA is important (> 60% better)
- Requires well-designed, large RCTs
- Monotherapy:
  - Effective vs. placebo (small benefit)
  - 1 g EPA as effective as fluoxetine (20 mg)
- Adjunct to SSRI: conflicting study results
  - 4 small studies show effective when EPA > 60%
- Effective doses of EPA 200 – 2200 mg/day
  - Caution: doses ≥ 3 g/day can inhibit platelet aggregation

LIMITATIONS TO STUDIES:

- Different participants/comorbidities
- Varied interventions: ALA or EPA or DHA or combo
- Varied doses
- Concealment issues: risk of fish taste/smell
- Small studies (3 larger studies found negligible results)
- Different length in studies
- Possible publication bias