Evidence-based uses of natural products to treat psychiatric disorders

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APA creates Caucus on CAM and integratiive approaches

- Organizing meeting May 04 APA Annual Meeting
- Approved by APA Board of Trustees 7/04
- Website for planning CAM/IM research agenda, education, advocacy, liaison 8/04
- Press releases announce Caucus 9/04-
- Open to all APA member psychiatrists
- list-serve for other mental health professionals
- **http://APACAM.org**

Overview

- Defining complementary and alternative medicine (CAM)
- "Evidence" in biomedicine and CAM
- Many kinds of CAM treatments used in mental health care
- CAM biological treatments—a review of the evidence
- Integrative treatments combine conventional and CAM approaches

Many conventional treatments are used—limited effectiveness when used alone

- Conventional treatments of dysthymia are "probably effective" CSR 15 DBRCT
- Conventional treatments of major depressive disorder (imi 200mg or equivalent) reduce sx severity by 53% CSR 33 DBRCT (probably less—"file drawer effect"
- At least 30% of depressed patients do not respond to defined Rx protocols

Defining CAM

- Complementary approaches do *not* violate the orthodox conceptual framework
- Alternative approaches depart from accepted medical theories
- Scientific and political issues influence perceptions of CAM
- Medicine is constantly evolving—definitions of CAM continue to change

Some examples of CAM treatments

- *Complementary* treatments include herbal medicines and other natural products
- *Alternative* treatments include energy medicine, acupuncture (but *not* Chinese herbal treatments), and homeopathy
- Future research findings will *validate some* CAM treatments and *refute others* (ie, from a biomedical perspective)

The *meanings* of evidence

- Biomedicine uses empirical evidence from controlled studies to *validate* a claimed mechanism or *verify* reported effects
- Complementary and alternative systems of medicine use *both* empirical and non-empirical evidence

Evidence in biomedicine

- Standards of evidence in *Evidence-based Medicine* (EBM)
- Hierarchy of evidence in EBM
  - Systematic reviews of RDBCTs
  - Large well-designed RDBCTs
  - Open (non-blinded) studies
  - Anecdotal reports
  - Expert consensus

Biomedical treatments of mental illness—what we use today

- Biological treatments
  - Synthetic drugs
  - Hormones
  - Some vitamins and amino acids (or precursors
- Classical forms of energy or information
  - ECT and TMS
  - Vagal nerve stimulation
  - Bright light exposure
- Psychotherapy
  - CBT, insight, existential, etc.

Evidence in CAM

- Empirical approaches use EBM methods
  - Systematic reviews of RDBCTs
  - Well designed RDBCTs
  - Non-blinded studies
  - Anecdotal reports
  - **Expert consensus**
- Non-empirical approaches use
  - Healer's expert skill
  - Intuition of individual healer
  - **Expert consensus**

CAM approaches to mental illness

- Based on both empirical and non-empirical evidence
- Patient-centered instead of Treatment-centered
- Healer's intuition plays important role
- Treatments from diverse systems of medicine
- Efficacy claims supported by many *kinds* of evidence

Categories of CAM treatments

- Life style—exercise stress management
- ***Biological treatments—herbals, other natural products***
- Mind-body practices and mindfulness—Yoga, meditation
- Validated energy-information modalities—bright light, EEG biofeedback
- Non-validated energy-information Rx—healing touch, Reiki, QiGong

Life style

- Exercise
  - Anxiety, depressed mood and BAD
- Nutrition
  - Depressed mood, possibly BAD, psychosis and some cognitive problems
- Stress reduction
  - Anxiety, BAD and psychosis

CAM biological treatments

- Western herbal medicines are important but there are *many* CAM biological treatments
- Non-Western herbs, vitamins, minerals, amino acids (and precursors), fatty acids, hormones and *maybe* homeopathy
- Combinations of CAM biological Rx and conventional biomedical Rx

Mind-body practices

- Relaxation training
  - anxiety
- Yoga
  - Anxiety and depressed mood
- Taijichuan
  - General improvements in mental health
- Meditation
  - anxiety

Validated energy-information Treatments

- Bright light exposure
- Biofeedback (especially EEG biofeedback)
- ECT and transcranial magnetic stimulation (TMS)
- Cranio-electrotherapy Stimulation (Alpha-stim)
- Vagal nerve stimulation
- Magnetic field therapy

Energy-information treatments that are not (yet) validated by biomedicine

- **QiGong**
  - General improvements in "well-being"
- **Healing Touch** and **Reiki**
  - Anxiety and possibly depressed mood
- **Prayer**
  - General improvements in "well-being"
  - Many controlled studies show efficacy
- Other forms of *directed intention*

CAM biological treatments of psychiatric disorders

- **Herbal medicines**
  - Western
  - Non-Western (TCM, Ayurveda, others)
- **Non-herbal natural products**
  - Vitamins and minerals
  - Amino acids and AA precursors
  - Fatty acids
  - hormones

Western Herbal Medicines

- **St. John's Wort**
  - Depressed mood, possibly anxiety
- **Valerian**
  - insomnia
- **Kava-kava**
  - Generalized anxiety
- **Ginkgo**
  - Early or mild dementia, *possibly* age-related cognitive decline

U.S. Psychiatric Congress 04 photos

Lake

St. John's Wort (*Hypericum perforatum*)

- Continuing controversy over efficacy
- 2002 NIH-NCCAM study concluded *lack* of anti-depressant effect but *equivalent* to Zoloft
- Mechanism complex—inhibits re-uptake of serotonin, dopamine and NE, *possibly* mild MAOI activity, IL-6 inhibition (decreases CRH)
- Meta-analyses suggest efficacy above placebo and comparable efficacy to conventional anti-depressantss

St. John's Wort

- 23 double-blind placebo-controlled studies
- 13 against placebo (55% vs 22% improved)
- 3 against TCAs (64% vs 59% improved)
- Caveat: outcomes likely biased by *inappropriate* dosing of both St. John's Wort and conventional anti-depressants

St. John's Wort—meta-analysis

- BMG meta-analysis of 23 double-blind studies found *no significant difference* between St. John's Wort and TCAs in mild-moderate depression (Linde et al 1996)
- Onset of anti-depressant effect somewhat longer with St. John's Wort
- Methodological differences and design flaws precluded generalizing findings

St. John's Wort—meta-analysis

- More rigorous inclusion criteria limited meta-analysis to 9 studies (Ernst et al)
- Flawed studies excluded from analysis
- St. John's Wort *conclusively* superior to placebo and equivalent to conventional anti-depressants

St. John's Wort

- Possible benefit in Seasonal Affective Disorder (SAD)
- Increased efficacy when combined with bright light
- Note: findings are *preliminary*

Witte et al. Fortschr Med 28:404, 1995; Martinez et al J. Ger Psych Neurol 75:515, 1994

St. John's Wort

- Infrequent side effects at usual doses include nausea, insomnia, fatigue, loose stools, light sensitivity and rash (side effect incidence at higher doses *similar* to SSRIs)
- Concerns about risk of serotonin syndrome not substantiated (little MAOI activity)
- Hyperforin *not* Hypericin is probably the active ingredient—but there are *many* bioactive constituents

St. John's Wort in severe depressed mood

- Possible efficacy in severe depressed mood
- Requires higher dosing (1800mg/day vs. 900mg for moderate depressed mood)
- Few studies, patient selection bias, limited data, not yet compared to *appropriate* SSRI doses for severe depressed mood

Vorbach, E. et al Pharmacopsychiatr 30(S):81-85, 1997; NIH study)

St. John's Wort in severe depressed mood

- Previous studies compared sub-therapeutic doses of St. John's Wort to therapeutic doses of imipramine
- Response rates to St. John's Wort lower than placebo suggesting patient selection bias and/or negative researcher/patient expectations

Vorbach E., et al Pharmacopsychiatr. 30(S):81-85, 1997

St. John's Wort compared to SSRIs

- Equal efficacy and fewer side effects compared to Prozac in mild-moderate depressed mood. N=240 (Schrader)
- *Equally ineffective* compared with Zoloft and placebo in moderate to severe depressed mood. (sub-therapeutic dosing) N=340

St. John's Wort—limitations of studies

- Absence of standardized preparations
- Controversy over "active ingredient"
- Methodologically flawed designs (patient selection, symptom rating, outcomes measures, data analysis)
- Systematic reviews difficult to perform and controversial because of the above issues

St. John's Wort—concerns

- Nursing mothers—lethargic infants
- Rare cases of mania in bipolar patients
- Induces liver enzymes (CyP450)
- Lowers serum levels of many drugs
  - Digoxin (heart failure)
  - Cyclosporine (transplant rejection)
  - Anti-HIV drugs (progression of HIV sx)
  - Oral contraceptives (pregnancy)
  - Warfarin and coumadin (Stroke risk)

Kava (*Piper methysticum*)

- Ceremonial drink, analgesic and aphrodisiac in South Pacific
- Effective in "stress" and anxiety
- Alpha-pyrones have synergistic effect on skeletal muscles (anti-spasticity) and amygdala (calming)
- meta-analysis suggested efficacy above placebo—more studies needed (Lehmann et al.)
- Recent controversy over liver toxicity

Kava—concerns

- Several cases of liver toxicity reported in U.S. and Europe
- Letter of warning and consumer advisory issued by F.D.A.
- Probably related to batch contamination (?acetone)
- Avoid or use selected quality preparations until toxicity issue resolved

Kava—side effects

- Few reports of adverse effects when used appropriately
- 1.5% of 3,000 German patients reported mild side effects (GI, skin rash, headache, light sensitivity; rare tremor, restlessness)
- "kava intoxication" associated with rare pulmonary hypertension with EKG changes, dyspnea, decreased platelets, movement disorders

Valerian (*Valeriana officianalis*)

- Systematic reviews show efficacy in insomnia (Krystal and Ressler 2002)
- 600-900mg causes sedation through binding to central GABA-A receptors (mechanism similar to benzodiazepines)
- Soporific effect increases over time—maximum efficacy in two weeks
- Not habit-forming, "hangover" or cognitive slowing effects not observed

Ginkgo (*Ginkgo biloba*)

- Controlled studies show improvement in mild-moderate sx of memory loss, depression and disorientation in AD and vascular dementia
- Improvements in cognitive functioning start after 6 weeks at therapeutic dose (120mg BID) using standardized preparations (Egb 761)

Ginkgo—two mechanisms of action

- Suppression of platelet-activating factor (PAF) reduces capillary damage, decreased glutamate release following neuronal injury (terpenoids)
- Free radical scavenging reduces oxidative damage of nerve cell membranes resulting in improved membrane dopamine transport and reduced serotonin receptor density (flavonoids)

Ginkgo

- Controlled studies show consistent reversal of EEG-associated changes in AD and vascular dementia after several months of Rx in mild-moderate cases
- EEG changes—enhanced alpha and decreased slow-wave activity (some preparations better than others)
- Animal trials suggest neuroprotective effect of prolonged use following focal CNS ischemia

Ginkgo—other uses

- Improves erectile dysfunction. Open study, N=50 (Sohn and Sikora) (probably related to improved blood flow from PAF)
- May improve SSRI-induced sexual dysfunction in both men and women. Open study, 240mg/day N=63. (Cohen and Bartlik)
- *May* enhance memory or cognition in non-demented adults (conflicting findings)

Vinpocetine (*Vinca minor*)

- Semisynthetic alkaloid from periwinkle
- Neuroprotective effects include
  - Reduces resistance in CNS blood vessels
  - Inhibits destructive cascade resulting from intra-cellular Ca release following CNS injury
  - Increases cyclic GMP levels in blood vessel walls
- Double blind studies consistently show improved cognitive functioning following CVA (Bonoczk et al)

Non-Western herbal medicines

- Ayurveda
  - Ashwagandha
  - Mentat
  - Bramyadiyoga
- Chinese medicine
  - Huperzine-A
  - Bu lai cas
  - Qian Jin Yi Fang
- Japanese traditional medicine (Kampo)
  - Kami-untan-to
- Other systems of medicine (Siberia)
  - Rhodiola rosea (Golden root)

Japanese traditional medicine (Kampo)

- Kami-untan-to (KUT)
- Age-related memory loss and dementia
- Mechanism of action
  - Stimulates nerve growth factor (NGF) production
  - Resulting in increased ChAT production (synthetic enzyme for Ach)
  - Increases available acetylcholine
- Animal studies promising

Ayurveda

- **Ashwagandha**
  - Memory enhancement and age-related cognitive decline
  - Probably functions as cholinesterase inhibitor
  - Possibly useful in avoiding opiate dependence in pain patients
  - Promising animal studies
- **Mentat**
  - Age-related memory decline
  - Compound herbal formula
  - Probably affects cholinergic neurons
  - Promising animal studies
- **Brahmyadiyoga**
  - Limited data *suggest* anti-psychotic efficacy
  - Compound herbal formula
  - Mechanism may involve D-2 antagonism

Chinese herbal medicines

- **Huperzine A (Huperzia)**
  - Inhibits acetylcholinesterase (same mechanism as contemporary Western drugs)
  - Limited data suggest comparable efficacy
  - Few side effects
- **Bu lai cas**
  - Strong free radical scavenger (like Ginkgo)
  - Used in China to treat dementia
  - Animal studies promising

Siberia

- Rhodiola rosea (Golden root)
  - Adaptogen in Russian and Scandinavian folk medicine. Taken daily as a tea.
  - Believed to increase longevity
  - Russian studies recently declassified (Cosmonauts and Olympic athletes used to enhance stamina)
  - Effects include cognitive enhancement, calming, and improved mental performance over long periods
  - Mechanism likely involves improved efficiency of CNS energy metabolism, increases serotonin, dopamine and Norepinephrine
  - Caution: may cause mania in bipolar patients

Non-herbal natural products

- Vitamins and minerals
  - B, C, E, Magnesium, Calcium
- Amino acids and AA precursors
  - SAMe, tyrosine, L-tryptophan, 5-HTP
- Fatty acids and phospholipids
  - Omega-3s (EPA and DHA), PS
- Hormones
  - DHEA, phytoestrogens

B vitamins

- **Thiamin (B-1)**
  - Improved cognitive fx in AD or age-related decline
  - Potentiates effects of Ach in memory and learning
- **Folate**
  - Deficient in depression and anxiety
  - Supplementation boosts SSRI effect
- **Pyridoxine (B-6)**
  - Deficient in depression
  - Enzyme co-factor for conversion of L-tryptophan to serotonin and L-tyrosine to NE
  - Effective in depression when GI pathology
- **Cyanocobalamin (B-12)**
  - Depressed patients respond dramatically when deficient

Vitamin C

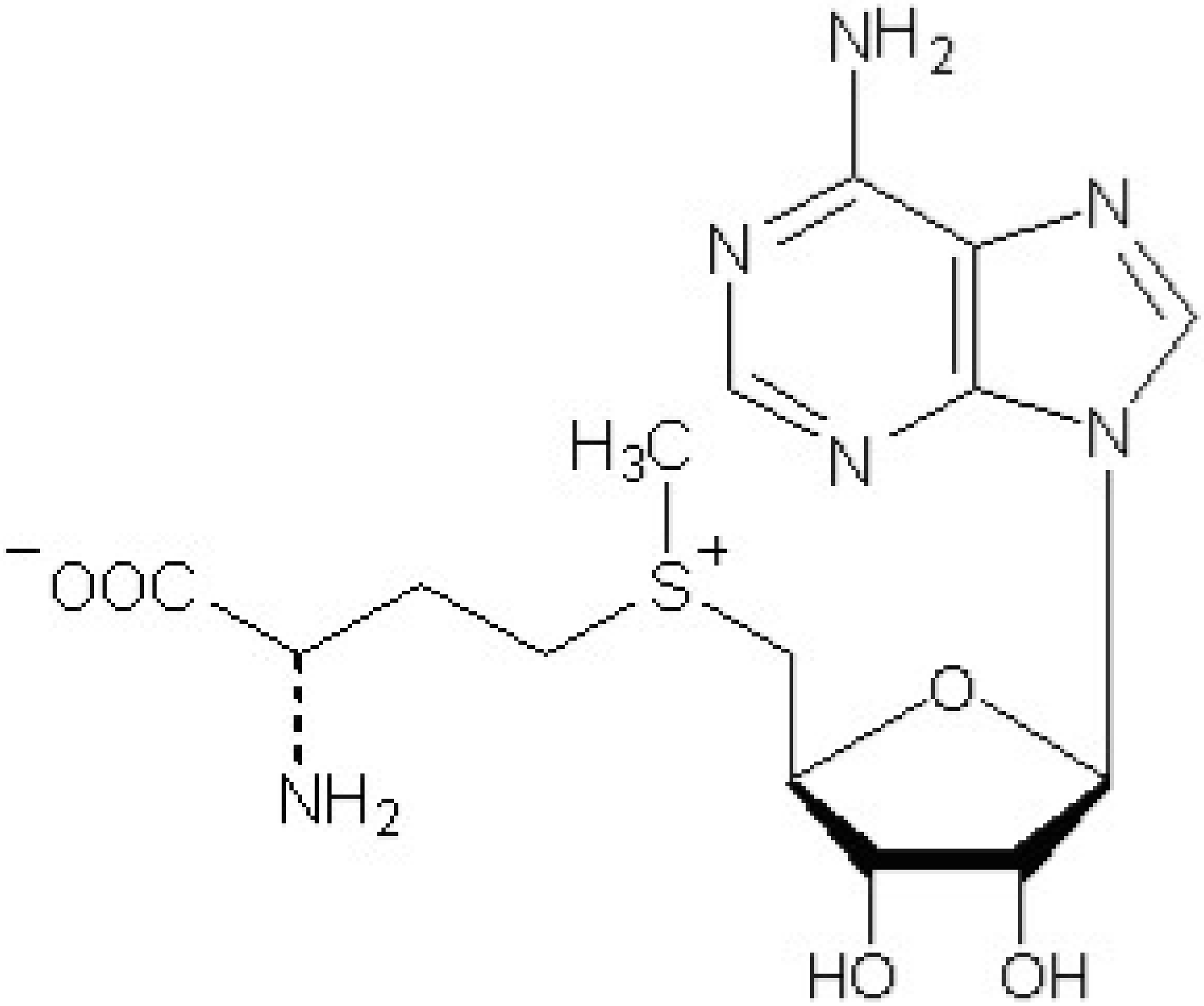
- Case reports suggest response in depressed patients with low CSF serotonin
- Double-blind study showed improved mood in chronically depressed hospitalized patients
- Possibly slowed progression in early AD
- Case reports in autism

Vitamin E

- Strong anti-oxidant (increased efficacy when combined with tocotrienols)
- Improved efficacy when combined with vitamin C
- Mixed tocopherols have enhanced anti-oxidative potential
- RDBCT data *suggest* improvements in TD
- *May* delay progression in early or moderate AD
- *May* lessen drug-induced parkinsonism, EPS

Magnesium and Calcium

- **Magnesium**
  - Effective in PMS 360mg/day starting on day 15 of cycle
  - Improved mood, energy, discomfort and fluid retention
- **Calcium**
  - Effective in PMS 1200mg/day
  - Benefits similar to Mg
  - Caution: GI distress, headache, nausea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Amino Acids and precursors

- **SAMe**
  - Synthesized from Methionine and ATP
  - Important methyl donor—maintains membrane fluidity, neurotransmitter synthesis, energy metabolism
  - Increases glutathione production resulting in significantly increased CNS free radical scavenging
  - Accelerates recovery following ischemic CNS injury (CVA, p-concussion syndrome)
  - Mild side effects include GI distress, insomnia, loose stool, but NOT sexual dysfunction
  - Caution: can induce mania in Bipolar patients

Amino acids and precursors

- **SAMe**
  - Accepted Rx for depression, arthritis and liver disease in Europe
  - As effective as conventional antidepressants
  - Role as Methyl donor increases NE, serotonin and dopamine (antidepressant effect)
  - Improves membrane uptake of phospholipids, improving fluidity
  - In DB studies antidepressant efficacy equivalent to all TCAs and SSRIs
  - Often effective in refractory depression
  - Safe in combination with SSRIs

Amino Acids and precursors

- **L-Tyrosine**
  - Precursor of norepinephrine (NE)
  - Dramatic improvement in refractory depression *with anti-depressants* (case reports)
  - Increased response when low urinary MHPG levels (NE metabolite)

Amino Acids and precursors

L-tryptophan

- May be as effective as TCAs (Imi and Ami) in unipolar depressed mood
- Fewer conclusive studies than 5-HTP and does not cross BB barrier as readily
- Increased response with normal or *high* urinary MHPG levels (ie, normal CNS NE levels)
- More effective than bright light in SAD
- DB study effective in PMS 2gm TID
- ***Caution:*** **previous cases of EMS (probable contamination)**

Amino acids and precursors

5-HTP

- DB study findings more consistently positive than L-tryptophan
- Same biosynthetic pathway as LT and one step closer to Serotonin
- improved CNS serotonin production when used with B-6 or C
- More readily crosses BB barrier than LT
- Potentiates action of conventional antidepressants
- ***Caution:*** may induce serotonin syndrome when used with SSRI, or mania in bipolar patients

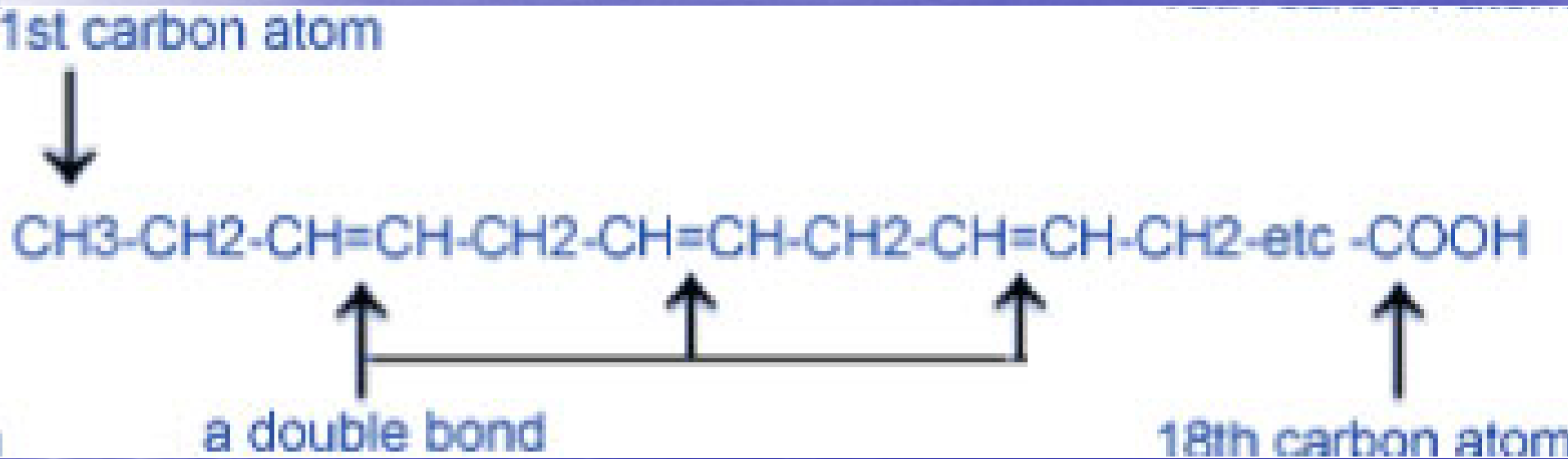
Amino Acids and precursors

Acetyl-L-carnitine (ALC)

- Strong anti-oxidant and increases energy production in mitochondria
- Many animal studies show strong neuroprotective effects—less neuronal loss following Stroke, more rapid recovery
- Enhanced cognitive performance in vascular dementia
- Slows progression in early stages of AD
- Improves depressed mood in elderly demented patients refractory to conventional Rx

Fatty Acids and phospholipids

- Fatty acids
  - Omega-3s (EPA and DHA)
  - Omega-6s (AA, others)
- Phospholipids
  - Phosphatidylserine (PS)


1st carbon atom
CH3-CH2-CH=CH-CH2-CH=CH-CH2-CH=CH-CH2-etc -COOH
a double bond
18th carbon atom

Omega-3 Fatty Acids

- **EPA (ecosapentanoic acid)**
  - High incidence of depression, AD in industrialized countries (FAs processed out of food)
  - Low levels in depression, aggression, ADHD and dementia
  - 67% greater risk of AD with low serum DHA
  - Synergistic effects with anti-depressants
- **DHA (decosahexanoic acid)**
  - Necessary for fetal brain development
  - Low serum levels=higher risk of AD
  - May improve cognition in AD or vascular dementia

Phospholipids

- **Phosphatidyl Serine (PS)**
  - 300mg/day for one month, then reduce dose
  - Moderate improvement in age-related cognitive decline (many controlled trials)
  - May help in early or mild AD
  - Does not improve cognitive fx in vascular dementia
  - Probably stabilizes nerve cell membranes
  - May stimulate dopamine production
  - Bovine derived PS more effective (?DHA)

Hormones

- **DHEA**
  - Controlled studies show improved mood and memory in intact and impaired patients
  - Note: inconsistent results in elderly
  - Surgically menopausal women may benefit most
  - ***Caution:*** Insomnia, irritability, slightly increased estrogen

hormones

- **Phytoestrogens**
  - PMS may be related to decreased serotonin caused by changing estrogen:progesterone balance
  - 40% greater risk of breast cancer with estrogen replacement (Nurses Health Study)
  - Phytoestrogens from soy (isoflavones) *protect against* breast CA
  - Phytoestrogens from Red Clover and Black Cohosh also effective in menopause and do not bind to estrogen receptors (animal studies)
  - Phytoestrogens improve physiological and affective symptoms of menopause

Integrative approaches combine CAM and conventional methods

- All effective modalities are considered
- Selected approaches based on *rigor* of evidence and *relevance* to patient needs
- Optimum integrative solutions are identified
- Realistic integrative treatment plans based on available CAM resources, patient preferences and financial constraints

Integrative approaches to mental illness

- Based on objective *and* subjective evidence from quantitative *and* qualitative methods (balance of rigor *and* relevance)
- Not exclusively patient-centered *or* treatment-centered
- Both empirical evidence *and* Healer's intuition are important
- Judicious combining of treatments from conventional, complementary and alternative medicine
- Goal is to improve outcomes, increase compliance, reduce AEs, encourage patient participation

Summing up

- Some conventional treatments work better than others
- Some CAM treatments work better than others
- Appropriate integrative approaches to depressed mood depend on history and symptom severity
- Integrative medicine identifies the best combination of treatments suited to the patient taking into account medical evidence, local availability of resources, patient preferences and financial constraints
- ***There is no best conventional, CAM or integrative treatment plan—the most suitable strategy evolves with changing symptoms and circumstances***

Concluding Remarks

- Significant and consistent findings including systematic reviews and meta-analyses suggest comparable efficacy of many natural products and conventional psychopharmacologic treatments
- Many natural products are safe in combination with conventional treatments
- Evidence-based integrative treatments will be used to improve outcomes and reduce side effects