Integrative Management of Depressed Mood—emerging approaches

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APA creates Caucus on CAM/integration

- Organizing meeting May 04 APA
- Approved by APA Board of Trustees 7/04
- Website for planning CAM/IM research agenda, education, advocacy, liaison
- Press release
- Only psychiatrists
- http://APACAM.org

Overview

- Depressed mood—defining the problem
- Biomedical treatments—what works
- "Evidence" in biomedicine and CAM
- CAM treatments—what is being used
- Integrative strategies
- Case vignettes

Depressed Mood—available treatments are *not* adequate

- Depressed mood is the leading cause of death in U.S. between adolescence and middle-age (suicide, medical and psychiatric co-morbidity)
- 15% of the population will eventually experience a major depressive episode
- 15% of severely depressed patients eventually commit suicide
- Two thirds of depressed patients never receive adequate treatment (no treatment, ineffective or poor response)

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.

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

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

Many CAM Rx are used—few effective when used alone

- St. John's Wort probably effective for mild to moderate cases, not severe
- Omega-3 FAs probably enhance mood when added to conventional drugs, but not alone
- Aerobic exercise probably effective—motivation
- Bright light exposure probably effective in SAD, not unipolar
- AAT probably effective in some cases, probably better as adjunct Rx

No single best treatment

- Individual variation in response to conventional treatments and CAM Rx related to complex underlying causes
- Individual differences in treatment preferences, affordability, etc.
- Local differences in availability of conventional or CAM Rx

Conventional biomedical approaches to mental illness

- Based on empirical evidence only
- Treatment-centered and focused on disorders (DSM-IV)
- Objective criteria determine diagnosis and treatment plan
- Treatments from biomedicine only
- Efficacy claims supported by *biomedical* evidence only

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

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**

Many evidence-based approaches possible in integrative medicine

- Physician (or CAM practitioner) and patient select the most appropriate available *combination* of treatments in view of biomedical standards of evidence
- Integrative medicine is patient-centered
- In contrast, conventional biomedicine is treatment-centered
- Both approaches are symptom-focused

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

Exercise

- Aerobic exercise equivalent to conventional antidepressants
- Best effect when combined with bright light exposure
- Motivation is key
- Elderly or impaired patients should first consult physician

Nutrition

- High fish intake may correlate with lower prevalence of MDD
- Contradictory findings of epidemiologic studies and few prospective trials
- Unclear differences between Omega-3 supplements and diet

Stress reduction

- Many studies on Yoga, Kriya sudarshan (Art of Living)
- Yogic breathing and VNS may have common pathway (sympathetic/parasympathetic re-balancing)
- Slight risk of hypomania in BAD, rare serious AEs

Mind-body practices

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

Therapies based on forms of energy or information validated by Western science

- Bright light exposure
- Music and patterned sound
- 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 Western science

- **QiGong**
  - General improvements in "well-being"
- **Healing Touch** and **Reiki**
  - Anxiety and possibly depressed mood (Shore ATM 6-04)
- **Prayer**
  - General improvements in "well-being"
  - Many controlled studies show efficacy
- Other forms of *directed intention*

CAM biological treatments

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

CAM biological treatments of depressed mood

- **Herbal medicines**
  - Western (especially St. John's Wort)
  - Non-Western (TCM, Ayurveda, others)
- **Non-herbal natural products**
  - Vitamins and minerals
  - Amino acids and AA precursors
  - Omega-3 Fatty acids
  - hormones

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

- BMJ 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 preclude 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)

Non-herbal natural products helpful in depressed mood

- Vitamins and minerals
  - B, C, Magnesium, Calcium
- Amino acids and AA precursors
  - SAMe, tyrosine, L-tryptophan, 5-HTP
- Fatty acids and phospholipids
  - Omega-3s (especially DHA)
- 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

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

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)

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

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
- Empirical data *and* Healer's intuition equally important
- Judicious combining of treatments from conventional, complementary and alternative medicine
- Goal is to improve outcomes, increase compliance, reduce AEs, encourage patient participation

Integrative treatments of depressed mood—what the evidence shows

- B-vitamins (folate) and antidepressants
- Omega-3 FAs and antidepressants
- Bright light exposure and SSRIs in SAD
- 5-HTP and antidepressants
- Dim light exposure and unipolar depression
- Yoga and SSRIs and psychotherapy
- EEG biofeedback and CBT and SSRIs
- Relaxation or mind-body practice and SSRIs
- Reiki and psychotherapy

Moderate depressed mood—Intake

- 38 yo married employed woman
- Chronic work stress, relationship problems
- No significant medical or psychiatric Hx
- Increasing alcohol use X 2 months
- Tired, poor sleep, appetite loss and poor nutrition, dysthymic mood X 2 months, NOT suicidal
- No previous conventional or CAM psychiatric Rx

Moderate depressed mood—Initial treatment plan

- Interview confirms moderate severity and absence of SI
- Patient has insight into work stresses, alcohol abuse, and dynamic relationship issues (psychotherapy)
- Review nutrition—foods rich in B-vitamins and Omega-3s
- Denies previous EtOH abuse hx; now drinks 2 glasses of wine at night
- Review stress management—daily am exercise or stress reduction practice (guided imagery)

Moderate depressed mood—Initial treatment plan (cont'd)

- Patient does not wish to take conventional antidepressant—
- Appropriate management does not call for conventional antidepressants *at this time*
- Present evidence-based choices: review comparative efficacy of conventional and CAM Rx
- Recommend Valerian 600mg/hs and trial on St. John's Wort (300mg/day advancing to 300mg TID) after reviewing risks, AEs, and obtaining consent
- Discuss AE risk when using SJW (GI distress, photosensitivity, interactions with coumadin, heparin, OCP, immunosuppressive agents, etc.)

Moderate Depressed mood—3 week follow-up (cont'd)

- Patient reports
  - Improved sleep with Valerian
  - Drinks one glass of wine with dinner now
  - Not motivated to exercise "…sluggish.."
  - Morning Yoga routine "helps a little.."
  - Some improvement in diet
  - Stopped SJW after 3 days because of GI distress
  - Relationship problems continue
  - Does not wish to take antidepressants
- Supportive therapy, review plan
  - Review choices; suggest SAMe 200mg advancing to 400mg BID p discussing AE risks. Folate 1mg and B-12 with SAMe

Moderate depressed mood—6 week follow-up (cont'd)

- "I'm beginning to get out of the woods…"
  - Began to "feel better" after ten days on SAMe at 400mg/am, 200mg/Noon
  - No significant AEs noted (eg, jitteriness, insomnia)
  - Has *not* taken folate or B-12 "*too many pills!*.."
  - Actively working on relationship issues and limit-setting at work
  - Continues daily Yoga practice

Moderate depressed mood—final session (cont'd)

- Mood "back to normal.." patient cancels third follow-up appointment but leaves messages saying she is continuing in psychotherapy

"…I can do this on my own…call you when I need you…."

Severe depressed mood—vignette
Intake

- 73 yo retired recently widowed male
- Severely depressed/agitated mood X 2 months following death of spouse
- Passively suicidal; denies plan
- Can't get to sleep "I'm always thinking…"
- Severe CAD on coumadin and newly dx'd HTN on antihypertensives
- X2 previous severe depressive episodes responded to conventional antidepressants; no mania history

Severe depressed mood—vignette *Intake* (cont'd)

- High risk patient—assess suicide risk, denies active plan, refuses voluntary hospitalization "..I'm not crazy.."
- Patient denies alcohol use or abuse history
- Local confidents, friends, adult daughter and grandchildren live in area
- On reviewing medication Rx history, Venlafaxine (Effexor) was effective. Patient wants to resume Effexor.

Severe depressed mood—vignette *Intake* (cont'd)

- Patient advised to try other antidepressant because of HTN and Effexor risk of elevated BP Patient has heard about AEs and reports of increased suicide risk with Paxil, other drugs, and wishes to try non-conventional alternatives
- Patient advised that conventional Rx are better than CAM Rx for severe depressed mood. Mirtazepine (Remeron) is recommended viz disturbed sleep.

Severe depressed mood—vignette *Intake* (cont'd)

- Patient has read about Omega-3 FAs for depressed mood and requests information
- Advised about case reports of bleeding with coumadin or ASA, and encouraged to work on dietary changes instead
- Advised to take folate 1mg, C 1gm and E (mixed tocopherols) 400IU
- L-theanine 200mg BID for anxiety/agitation
- Encouraged to resume daily walks with daughter
- Provided with instructions for contacting Crisis Team

Severe depressed mood—vignette One week follow-up

- Attended grief support group "but I'm not a group kind of person…."
- Denies SI or plan "I have my daughter and grandkids…"
- Somewhat brighter and significantly improved sleep with Remeron 15mg, but "it's the other way around now… eating too much…!"
- Has not taken vitamins or L-theanine "…too many ….damn pills…!"
- "my daughter is making me eat fish all the time…"
- Spending a lot of time with confident, talking about his wife and taking longer walks

Severe depressed mood—vignette One week follow-up (cont'd)

Plan

- Provide encouragement for improved diet and exercise
- Reports "more even" with daily exercise
- Has been enjoying classical music in the mornings
- Stress benefits of exercise and nutrition for depressed mood
- Asks for recommended reading—suggest book on loss and grief
- Invite patient to consider individual psychotherapy
- Encourage patient to take folate, C and E
- 5-HTP 50mg BID for appetite suppression and synergistic antidepressant effect

Severe depressed mood—vignette Two weeks later (cont'd)

- "I think this stuff is working…" continues on Remeron 15mg without AEs
- Mood is noticeably brighter. Continues to deny SI/plan
- Appetite is "almost normal.." on 5-HTP 50mg BID; denies daytime drowsiness
- Has been taking "..the vitamins some of the time…when I remember.."
- Planning to go to the SF Opera with his daughter
- Reading the recommended book on death and grieving and writing notes in the margins "..maybe we can do some of that talk therapy now…"

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 integrative treatment plan—the most suitable strategy evolves with changing symptoms and circumstances***