Natural Therapies for Depression

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Objectives (by the end of this session, you will be able to…):

1. Describe the scientific evidence about the effectiveness, side effects and potential drug interactions for St. Johns wort.
2. Describe the benefits and risks of using calcium, vitamin D, fish oil, s-adenosylmethionine, chromium, B vitamins and tryptophan as complementary therapies for depression.
3. Describe the importance of a healthy lifestyle, including exercise, social support and reasonable exposure to sunshine in treating patients with depression.
4. Use an ethical framework to guide discussions about therapeutic options for patients with depression.
Depression Case

A 17 year old girl who is depressed, has had a drop in grades, recently broken up with her boyfriend and less interested in participating in band, has stopped taking her SSRI after hearing about black box warnings.

Her only medications are oral contraceptives.

She wants to know if St. Johns wort might help (the news reports are very confusing). How can you advise her?
Depression – emotion, symptom, syndrome

- Clinical depression: a persistent state of unhappiness or misery that interferes with pleasure or productivity.
- Manifestations: moodiness, anger or irritability; anhedonia; sadness; social isolation; changes in sleep and appetite; somatic complaints (H/A, belly ache); dropping grades

"I have no friends."
"Life is boring."
"There is nothing I can do to make things better" or
"I wish I were dead."
Depression Differential Diagnosis and Co-morbidity

- Temporary sadness; reactive depression
- Anxiety, Schizophrenia, ADHD, Eating disorder, Substance abuse
- Child abuse/sexual abuse
- Endocrine: Hypothyroidism, DM, Addison’s, PMS
- Anemia
- Medications: anticonvulsants, OCPs, steroids, barbiturates
- Infection: EBV, HIV
- Trauma: post-head trauma
- Sleeping problems (insufficient sleep)
- Chronic fatigue, chronic pain
Epidemiology:

- Depressive disorders are common, chronic, costly
- WHO identified major depression as 4th leading cause of worldwide disease in 1990, causing more disability than heart disease; starts in childhood/adolescence
- Prevalence: 2% before puberty; 5%- 8% after puberty
- Age
  - Before puberty females: males, 1:1
  - After puberty, females:males, 2:1
- 3rd leading cause of death in adolescence is suicide
- Etiology: genetic, environmental, cultural
Screening for Depression

The U.S. Preventive Services Task Force (USPSTF) “

 recommends screening adults for depression in clinical practices that have systems in place to assure accurate diagnosis, effective treatment, and follow-up.”

However, the USPSTF: “concludes the evidence is insufficient to recommend for or against routine screening of children or adolescents for depression.”

AHRQ 2002 http://www.ahrq.gov/clinic/3rduspstf/depression/depressrr.htm
Screening Tools

- Zung Self-Assessment Depression Scale
- Beck Depression Inventory
- General Health Questionnaire, GHQ
- Center for Epidemiologic Study Depression Scale, CES-D
- Ask two questions:
  - "Over the past 2 weeks, have you felt down, depressed, or hopeless?"
  - "Over the past 2 weeks, have you felt little interest or pleasure in doing things?"
- “There is little evidence to recommend one screening method over another, so clinicians can choose the method that best fits their personal preference, the patient population served, and the practice setting.” USPSTF
# Ethical framework for Therapies

## Effective

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Cohen M. *Pediatrics*, 2005
Conventional Treatment

• Medication
  – TCA, SSRIs; new agents not noticeably better than old treatments (USPSTF)
• Psychosocial and psychotherapeutic; Behavioral therapies
• AHRQ/USPSTF (on treating ADULTS):
  – “Approximately 11 patients identified as depressed as a result of screening would need to be treated to produce 1 additional remission. If depression (incl. major depression, dysthymia, and minor depression) is present in 10% of patients, then 110 patients would need to be screened to produce one additional remission after 6 to 12 months of treatment.”
  – The potential harms of screening: false-positive results; inconvenience, cost and stigma of further diagnostic work-up; adverse effects/costs/stigma of treating false-positive patients
Medications

- **Tricyclic antidepressants:**
  - imipramine (not for kids < 6), doxepin (not for kids < 12 yo), amitryptiline (not for kids < 12)

- **Tetracyclic antidepressant:**
  - mirtazepine (Remeron; not for kids)

- **Monoamine oxidase inhibitors:**
  - phenelzine (not for < 16 yo); rasagiline (not approved for pediatrics);

- **SSRI’s:**
  - fluoxetine (Prozac); citalopram (Celexa, not for kids < 18); escitalopram (Lexapro, not for kids < 18)

- **SNRI’s:**
  - atomoxetine (Strattera); venlaxafine (not approved for kids); duloxetine, nefazodone, reboxetine (not for kids)

- **Catecholamine RI:**
  - bupropion (Wellbutrin; not approved for < 18 yo)
Old agents: TCA Side Effects

- Tachycardia, dry mouth, dry skin, dilated pupils, ataxia, nystagmus, hyper-reflexia, cardiac arrhythmias, seizures, coma
- Doses of 10-20 mg/kg (one to two pills) have the potential for serious toxicity and fatalities in toddlers (generally unintentional ingestions)

Amitryptiline (Micromedex)

Serious Adverse Effects:

- Agranulocytosis
- Cardiac dysrhythmia
- Decreased liver function
- Drug-induced eosinophilia
- Jaundice
- Myocardial infarction
- Pancytopenia
- Seizure
- Suicide
- Thrombocytopenia

- Aplastic anemia
- Cerebrovascular accident
- Depression, worsening
- Hypertension
- Leukopenia
- Orthostatic hypotension
- Purpuric disorder
- Suicidal thoughts
- Syncope
FDA Public Health Advisory
Suicidality in Children and Adolescents Being Treated With Antidepressant Medications, October 15, 2004

According to a 1/5/04 statement by FDA’s Dr. Thomas Laughren:

“12 / 15 studies involving children with major depressive disorder …, showed no efficacy when comparing the drug to a placebo.” …

“The overall success rate for positive studies of 20% (3/15) is clearly a concern."
FDA approved SSRIs for depressed children

• As of 2004, “the FDA has approved only Prozac for use in children with MDD”
• Prozac, Zoloft and Luvox have been FDA approved for use in children diagnosed with OCD
• Use of medications
  – In 2002, there were over 10 million anti-depressant prescriptions for children ages 1-17 years in the US
  – 2.2 /10 million were for Paxil, an anti-depressant with no approval for any indication in children. Paxil was the second most prescribed anti-depressant in the US pediatric population, despite the lack of any FDA approval for use in children.
Side effects of SSRI medications

- GI upset
- Headache; sleep disorders (somnolence or insomnia)
- Sexual side effects (impotence, probs with ejaculation)
- Dizziness, Fatigue, Sweating
- Neonatal withdrawal syndrome
- Adverse drug interactions
- Serotonergic syndrome (HTN, tachycardia, mania)
- Suicidal ideation
  - Review of 22 RCT pediatric with 9 antidepressant drugs.
  - 2298 patients with active drug; 1952 with placebo
  - Serious suicidal adverse events:
    78/2298 versus 54/1952
    Incidence rate ratio 1.89 (95% CI, 1.18-3.04)

Mosholder AD. *J Child Adolesc Psychopharmacol*. 2006
After careful review of SSRI data,

Only the U.S. FDA and the U.K. Medicine and Health Care Products Regulatory Agency maintain that an acceptable risk/benefit relationship exists for fluoxetine.

The European Medicines Agency concluded that the SSRIs should not be used in the treatment of depression in children and adolescents.

Kratochvil CJ. *J Child Adolesc Psychopharmacol.* 2006
THE ELEMENTARY-SCHOOL LUNCHROOM updated

TRADE YOU SOME CHEETOS AND A RITALIN FOR YOUR CUPCAKE AND A ZOLOFT.

HILARY B. PRICE 3.21 www.rhymeswithorange.com
Tends in placebo response

• Response to placebo is more positive in recent studies

TB Walsh. *JAMA*, 2002
Proportion of Patients Assigned to Placebo, TCAs, and SSRIs Who Showed a 50% or Greater Improvement in Hamilton Rating Scale For Depression Score by Year of Publication
Behavioral Approaches

“From an evidence-based perspective, cognitive-behavioral therapy is currently the treatment of choice for anxiety and depressive disorders in children and adolescents.”

Compton SN. *JAm Acad Child Adolesc Psychiatry*. 2004
CAM is common in Depression

• Depression is one of the top 10 diagnoses for which patients seek CAM therapies
• Commonly used among depressed adolescents
• Fewer than 30% of depressed teens tell docs they are using CAM therapies
• Clinicians need to ask!
Integrative Approach

- Lifestyle
- Biochemical
- Biomechanical
- Bioenergetic
Lifestyle

- Sunshine
- Sleep
- Exercise; structure/supervision
- Mind-Body Therapies
  - CBT - above
  - Biofeedback?
  - Meditation?
- Environment; less TV; most social support
- Nutrition (low glycemic index?)
Sunshine, circadian rhythms and sleep

Desynchronization of internal rhythms plays an important role in the pathophysiology of depressive disorders. This has stimulated the idea that resetting normal circadian rhythms may have antidepressant potential.

“Winter depression was first modeled on regulation of animal behaviour by seasonal changes in daylength, and led to application of light as the first successful chronobiological treatment in psychiatry.”

Sunshine

• Known association between inadequate sunshine and depression – SAD
• Frequent indoor tanners are often depressed and seeking relief; watch for rebound depression if they stop
• Vitamin D deficiency and depression?
  – Vitamin D receptors exist in the brain
  – Low level of serum 25-hydroxyvitamin D and high PTH are significantly associated with a high depression score (Jorde, 2005)
  – 25-hydroxyvitamin D3 and 1,25-dihydroxvitamin D3 levels are significantly lower in psychiatric patients than in normal controls (Schneider, 2000)
  – RCT of 44 Australian patients (none, 400 IU versus 800 IU vitamin D) vitamin D3 significantly enhanced positive affect (Landsdowne, 1998)
• How much? 10 – 15 minute daily of exposure to hands and face in spring, summer fall; wintertime? Latitude?
Light therapy

• Proven effective for seasonal affective disorder in adults (Terman M Evid Based Ment Health, 2006)
• Strong evidence of helpfulness of bright light for non-seasonal depression; meta-analysis of studies from 1987-2001: (effect size=0.53, 95% CI=0.18 to 0.89, similar to medications)
• Recent RCT of 29 women with non-seasonal depression; light therapy for 28 days significantly better than control, (McEnany GW, 2005)
• Benefits onset within 2 days in some studies; effective in institutionalized elderly and community; effective in summer and winter
• No pediatric studies?
• Side effects: hypomania, autonomic hyperactivation (Terman M, 2005)
Light Therapy for Depression

Plus 3 studies not included in this review, comparing dim light to bright light.

Sleep

- Regular time; Routine
- Hot bath; cool room; dark room
- Massage before bed
- Lavender, chamomile, melatonin?
- Music, calm, orderly, quiet
- NO TV IN BEDROOM
- NO vigorous exercise right before bed
- GET MORE versus intentional sleep reduction/deprivation (in those with excessive sleep)
Exercise

- Depressed mood and fatigue are common in individuals deprived of usual exercise activities, and may be partially mediated by reduced fitness levels.
- These findings may explain mood changes in response to short-term exercise withdrawal such as injuries and recovery from medical procedures (and illnesses such as mono).
- Changes over time in kids exercise/gym/playground time
- No studies on exercise therapy for depression in pediatrics; positive effects in adults with nearly all kinds of exercise studied, including yoga and tai chi
- Common sense precautions!

Berlin AA. *Psychosomatic Med*, 2006
Exercise as Therapy – Yes in adults

Lawlor DA. *BMJ* 2001
Yoga for depression

• Five RCTs in adults, each of which used different forms of yoga; severity ranged from mild to severe.
• All trials reported positive findings, but methodological details were often missing or inconsistent
• No adverse effects were reported with the exception of fatigue and breathlessness in participants in one study.

Pilkington K. *J Affective Disord*, 2005
Biofeedback, Hypnosis, Guided Imagery

- Helpful for headaches, pain, anxiety
- Insufficient data for depression
Meditation

- Meditation training leads to significant increases in left-sided anterior activation, a pattern previously associated with positive affect, in the meditators compared with the nonmeditators.
- No RCTs specifically on depression, though positive effects on anxiety.
- No pediatric studies.
- Walking meditation? Other kinds?

Davidson RJ *Psychosom Med*, 2003
Diet

- Sugar; additives/preservatives/salicylates
- Glycemic index; sugar rush, followed by crash
- Fish, fish oils
Sugar and Depression

• Poor glycemic control associated with higher depression scores (numerous studies)
• Treating depression often improves glycemic control
• Can improving glycemic control improve depression?
Lifestyle summary

• Moderate amounts of sunshine
• Exercise regularly
• Optimize sleep and improve sleep quality
• Low glycemic index diet; avoid sugar swings
Biochemical

- Medications
- Dietary Supplements
Depression: common dietary supplements and herbs

- Fish oil
- St. Johns wort (SJW)
- B vitamins, folate
- SAM-E
- MSM
- Chromium
- 5-HTP
Fish oil

- Patients with depression have often have low dietary intake and low tissue and plasma levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the fatty acids found in fish oil. (Peet. Drugs, 2005)
- Several randomized controlled trials (RCTs) have evaluated the benefits of fish oil supplements for depressed patients. (Nemets. Am J Psychiatry, 2002; Su KP, 2003)
- Doses of 1 gram daily of EPA appear to be effective in randomized, controlled clinical trials in adults. (Peet M, 2002)
- Unnecessary to go to 2 grams EPA daily (Even for bipolar depression) (Frangou S. Br J Psychiatry, 2006)
- A 2005 review suggests that fish oil appears to be an effective adjunctive therapy for major depression. (Peet M, 2005)
- No studies in pediatrics, though DHA commonly added infant formula
- Safety: fish allergies, taste, belching; very high doses, increased risk of bleeding, nosebleeds? Little risk of mercury, dioxin, PCB’s;
- Compare brands at www.consumerlabs.com
Saint Johns wort

- Most commonly used CAM therapy for depression
- Comparable to sertraline in German RCT of 241 depressed adults, once daily doses over 24 weeks (Gastpar. Pharmacopsychiatry, 2005)
- Two open label trials in adolescents showed improvement within two weeks in 25/33 and 9/11 patients (Findling, 2003; Simeon, 2005); Improvement in 2 weeks predicts long-term response; if no benefit in 2 weeks, stop
- 2005 Cochrane review: “Current evidence regarding hypericum extracts is inconsistent and confusing”; different products used in different trials, different kinds of patients; in some studies St. Johns wort is as effective as standard medications, but no more effective than placebo.
Herb-drug interactions: Saint Johns wort

Speeds elimination of many drugs, eg. digitalis, theophylline, clarithromycin, erythromycin, protease inhibitors and OCPs
SJW safety

- Side effects – drug interactions, photosensitivity, serotonergic syndrome
- Lowers serum levels of many meds
- Birth Control Pills!
- See NIH NCCAM review
- Product variability; see www.consumerlabs.com
- St. Johns wort patient handouts are available from:
  - Memorial Sloan Kettering Cancer Center
  - Swedish Medical Center in Seattle
  - University of Maryland Medical Center
  - Wake Forest University Baptist Medical Center’s Best Health internet site (www.besthealth.com)
  - Harvard Medical School-Intelihealth
B vitamins and folate (B6)

- B6 (pyridoxine)
  - Low levels of pyridoxal phosphate (PLP) are significantly associated with depressive symptoms (Hvas AM 2004)
  - A systematic review suggested that B6, 100 – 200 mg daily benefits premenstrual depression; Odds ratio ~2. (Wyatt KM. BMJ, 1999)
  - Side effects: nausea, vomiting, abdominal pain, anorexia, headache, somnolence, lower B12 levels, sensory neuropathy (typically with doses over 1000 mg daily, can occur lower)
Folate and B12

- **Folate**
  - Lower levels of folate in depressed persons
  - Low folate associated with poorer response to antidepressant meds
  - Supplemental folate can improve response to meds

- **B12**
  - Lower levels in depressed persons
• Lower levels of calcium in depressed persons
• Higher PTH in depressed persons
• Estrogen regulates calcium and PTH metabolism; sometimes dysregulates? *(Thys-Jacobs S. J Am Coll Nutr, 2000)*
• Supplementation may benefit women with PMS-related depression *(Dickerson LM. *Am Fam Physician*, 2003)*
• 1000 – 1200 mg daily
SAM-E

- AHRQ review concluded that compared to placebo, 3 weeks of treatment with SAMe was associated with a significant improvement in depression (http://www.ahrq.gov/clinic/epcsums/samesum.htm)
- SAMe was comparable to treatment with conventional antidepressant medications. (Pancheri P, 2002)
- In an open trial of 30 adults with MDD for whom antidepressant meds ineffective, 800 - 1600 mg of SAM-E X 6 weeks resulted in significant improvements in 50% and remission in 43% (Alpert, 2004)
- Benefits typically appear within two to four weeks of starting daily administration
- Problems – product variability; poorly absorbed (need enteric coating); mania in bipolar patients; interactions with SSRI meds; see consumerlabs: http://www.consumerlabs.com/results/same.asp
5-HTP and L-trp

- 5-hydroxytryptophan is immediate precursor of serotonin metabolism from dietary L-tryptophan (L-trp)
- Meta-analysis of trials involving 64 patients suggest 5-HTP and L-trp better than placebo in treating depression (Shaw K, Cochrane. 2002)
- Food sources – dairy, eggs, poultry, meat, soy, tofu, nuts; supplement doses - start at 50 mg TID; max dose 1200 mg daily
- Side effects – EMS related to contaminated lot from one manufacturer; nausea, drowsiness; may potentiate SSRI medications; decreased carbohydrate intake and weight loss?
Chromium

- Trivalent chromium is essential mineral
- Widely used CAM therapy for DM; important cofactor in glucose metabolism
- RCT of chromium picolinate (600 micrograms daily) in patients whose depression is characterized by carbohydrate craving (eg PMS) significant improvement in craving and depressive symptoms (Davidson. *Biol Psychiatry*, 2003; Docherty, 2005)
Biomechanical

• Surgery –
  – Vagal nerve stimulation?
• Cranial, spinal or joint adjustment – No
• Transcranial magnetic stimulation - ?
• ECS - ?
Physiologic effects of massage

• Increased blood flow and lymphatic drainage
• Muscle relaxation
• Stress reduction
• Balances right and left prefrontal cortex activity in those with right dominance (Jones N. Adolescence. 1999)
• Decreased levels of cortisol and increased levels of serotonin and dopamine in depressed adults (Field T. Int J Neurosci. 2005)
• In depressed pregnant women, massage, compared with progressive relaxation, led to higher dopamine and serotonin levels and lower levels of cortisol and norepinephrine (Field T. J Psychosom Obstet Gynaecol. 2004)
Massage Clinical Effects

- Decreased Anxiety
- Decreased Pain
- Enhanced growth and development in pre-term babies and in infants of depressed moms
- Little data on massage
- Who volunteers?
Bioenergetic

• Acupuncture

• Healing Touch/TT/Reiki/Qi Gung
  – one RCT of distant Reiki, weekly for 6 weeks; positive effects on depression sustained over one year (Shore AG. Altern Ther Health Med. 2004)
  – Positive effects on pain, anxiety in patients with cancer, HIV, injuries

• Prayer/Spirituality

• Homeopathy – case reports positive; few RCTs; safe
Acupuncture

- RCT of 30 patients randomized to sham or laser acupuncture: BDI scores fell from baseline by 16.1 points in the intervention group versus 6.8 points in the sham controls (P<0.001) (Acupunct Med. 2005)
- Meta-analysis: “the effect of electroacupuncture may not be significantly different from antidepressant medication, weighted mean difference -0.43 (95% CI -5.61 to 4.76)” (Mukaino Y Acupuncture Med, 2005).
- RCT 38 women with depression: acupuncture, sham, wait list; significant reduction in depression with real acup. (Allen JJB. Psycho Sci, 1998)
- No pediatric studies. Good safety profile. Rare infections, broken needles, forgotten needles, bleeding, bruising
Prayer

- Religious activities seem to benefit depression.
- Inadequate data on effect of intercessory prayer on depression
## Ethical framework for Therapies

**Effective**

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Cohen M. *Pediatrics*, 2005
You must be as tall as this sign to attack the city

NOTICE
Depression SUMMARY

• Assess risk of suicidality
• Respect patients and families; negotiate clear goals and agreements
• Support healthy lifestyle, including sunshine, sleep, low glycemic diet and exercise
• Correct deficiencies of B vitamins, Calcium, chromium
• Consider supplements of SAM-E, 5-HTP
• Offer social support
• Consider safe therapies, including massage and acupuncture and Therapeutic or Healing Touch or Reiki
• Support safe, culturally consistent therapies (eg prayer)
• Beware of potential interactions
• GIVE SUPPORT and HOPE, be PRACTICAL
• Close follow-up