Integrative Treatments in Perinatal Mental Health: An Evidence Based Approach

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Disclosure: Past 12 months

• Advisory board/consulting: Takeda, Lundbeck, Johnson and Johnson, Otsuka, Genentech, JDS therapeutics
• Honoraria for medical editing: DSM Nutritionals, GOED newsletter
Complementary and Alternative Medicine (CAM)

- Defined as “a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine (NCCAM, 2002)”
- The American Psychiatric Association developed a task force to assess CAM in psychiatry
  - Evidence Base and Safety for CAM treatments in Major Depressive Disorder

Why Focus on CAM?

- Use of CAM treatments has increased over past several decades
- Approximately 40% of adults in the U.S. use at least one CAM therapy annually
  - CAM use among children approximately 12%, or about 1 in 9 children; Children are five times more likely to use CAM if a parent/other relative uses CAM.
- Americans spend over $33 Billion annually out of pocket on CAM therapies

Barnes et al., 2008; Eisenberg et al., 1998; Nahin et al., 2007
CAM: the Most Commonly Used by US Adults

- Natural nonvitamin/nonmineral products (18%)
  - Most common: fish oil/omega 3/DHA, glucosamine, echinacea, flaxseed oil or pills, and ginseng
- Deep breathing exercises (12.7 %)
- Meditation (9.4 %)
- Chiropractic or osteopathic manipulation (8.6 %)
- Massage (8.3 %)
- Yoga (6.1 %)

Barnes et al., 2008

CAM: Associations with Likelihood of Use

Use greatest among:
- Women (42.8%, compared to men 33.5%)
- Ages 30-69 (30-39 years: 40%, 40-49 years: 40%, 50-59 years: 44%, 60-69 years: 41%)
- Higher levels of education (Masters, doctorate or professional: 55%)
- Higher income (poor: 28.9 percent, near poor: 30.9 percent, not poor: 43.3 percent)

Barnes et al., 2008
Prevalence of CAM Use

• Use in psychiatry:
  – One study showed use by 63% of inpatients
  – MDD most common indication
  – Over half of those with Major Depressive Disorder (MDD) and/or other depressive disorders use CAM treatments
  – Most patients did NOT disclose use of CAM to their psychiatrist

Tindle et al., 2005; Elkins et al, 2005; Kessler et al., 2001;

Considerations in Evaluating the Evidence Base

• CAM treatments are popular and appealing to patients
  – Internet and other sources may inflate perception of data base
  – Patient preference and accessibility sometimes precludes full evaluation, risk/benefit discussions in optimal medical decision-making process
  – Psychiatrists often not well educated about CAM; may be uncomfortable discussing
Considerations in Evaluating the Evidence Base

- Few CAM treatments have been systematically studied for clear psychiatric indications with adequate outcome measures.
- Control conditions: finding appropriate control conditions can be challenging (i.e., exercise).
- Some treatments have long-standing use in other cultures; may have literature available in other languages – cultural biases, language access issues.

The APA CAM Task Force Process: Highlights:
Selected CAM treatments for MDD

- Omega-3 fatty acids
- St. John’s Wort
- S-adenosyl-methionine (SAMe)
- Folate
- Light therapy
- Acupuncture
- Exercise
- Mindfulness based psychotherapies

APA Task Force Report, JCP, 2010
**Wish List: Treatment of Depression in Pregnancy & Postpartum**

- Efficacy
- Safety in pregnancy
- Safety in breastfeeding
- Something that babies and mothers need anyway
- No carbs!
- Tastes like chocolate

**Omega-3 Fatty Acids in Pregnancy and Postpartum**
**Omega-3 fatty acids**

- Studied as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (not the plant source alpha-linolenic acid)
- Some but not all meta-analyses show benefit over placebo for unipolar and bipolar depression
  - Substantial heterogeneity
  - Few studies demonstrate benefit as monotherapy
- Role in neurocognitive development

Parket et al., 2006; Freeman et al., 2006; Su et al., 2008; Nemets et al., 2007, McNamara and Carolson, 2006

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**Placebo-controlled trials of omega-3 fatty acids in Unipolar MDD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>N</th>
<th>Omega-3</th>
<th>Length of Trial</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peet and Horrobin, 2001</td>
<td>Adjunctive therapy to antidepressant medication</td>
<td>N=70</td>
<td>EPA 1.2, or 4 g/day</td>
<td>12 weeks</td>
<td>EPA more effective than placebo (best response 1 g)</td>
</tr>
<tr>
<td>Nemets et al., 2003</td>
<td>Adjunctive therapy to antidepressant medication</td>
<td>N=20</td>
<td>EPA, 2 g/day</td>
<td>4 weeks</td>
<td>EPA more effective than placebo</td>
</tr>
<tr>
<td>Marangell et al., 2003</td>
<td>Monotherapy</td>
<td>N=36</td>
<td>DHA, 2g/day</td>
<td>6 weeks</td>
<td>DHA not more effective than placebo</td>
</tr>
<tr>
<td>Su et al., 2003</td>
<td>Adjunctive therapy to antidepressant medication</td>
<td>N=28</td>
<td>EPA + DHA, 9.6 g/day</td>
<td>8 weeks</td>
<td>EPA + DHA more effective than placebo</td>
</tr>
<tr>
<td>Silvers et al., 2005</td>
<td>Adjunctive therapy to antidepressant medication</td>
<td>N=77</td>
<td>EPA + DHA, 8 g/day</td>
<td>12 weeks</td>
<td>EPA + DHA not more effective than placebo</td>
</tr>
<tr>
<td>Nemets et al., 2006</td>
<td>Monotherapy; childhood MDD, methylphenidate allowed for comorbid ADHD</td>
<td>N=28</td>
<td>EPA + DHA, 600 mg per day</td>
<td>16 weeks</td>
<td>EPA + DHA more effective than placebo</td>
</tr>
<tr>
<td>Mischoulon et al., 2009</td>
<td>Monotherapy</td>
<td>N=57</td>
<td>EPA, 1 g per day</td>
<td>8 weeks</td>
<td>trend towards efficacy (p=0.087) for EPA compared to placebo</td>
</tr>
<tr>
<td>Grenyer et al., 2007</td>
<td>Adjunctive therapy to antidepressant medication</td>
<td>N=83</td>
<td>DHA+ EPA (DHA&gt;EPA)</td>
<td>16 weeks</td>
<td>No difference between omega-3 or placebo</td>
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</tbody>
</table>
### Treatment Studies of Omega-3 Fatty Acids for Perinatal Depression

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>N</th>
<th>Omega-3 dose</th>
<th>Length of Trial</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freeman et al., 2006 b</td>
<td>Open-label, flexible-dose for MDD in pregnancy</td>
<td>12</td>
<td>EPA and DHA, flexible-dose; mean final dose 1.9 g/d</td>
<td>mean participation 8.3 weeks</td>
<td>40.9% mean decrease in depressive symptoms on the EPDS</td>
</tr>
<tr>
<td>Freeman et al., 2006 c</td>
<td>Randomized dose-ranging trial for postpartum MDD</td>
<td>16</td>
<td>EPA and DHA, 0.8 g, 1.4 g, or 2.8g/d</td>
<td>8 weeks</td>
<td>mean % decreases on the EPDS and HRSD 51.5% and 48.8%, respectively (no significant differences between groups)</td>
</tr>
<tr>
<td>Su et al., 2008</td>
<td>Double-blind, placebo-controlled trial for pregnant women</td>
<td>36</td>
<td>EPA and DHA, 3.4 g/day</td>
<td>8 weeks</td>
<td>significantly higher response, remission rates in omega-3 group</td>
</tr>
<tr>
<td>Freeman et al., 2008</td>
<td>Double-blind, placebo-controlled trial in pregnant and postpartum women (all received supportive psychotherapy)</td>
<td>59</td>
<td>EPA and DHA, 1.9 g/day</td>
<td>8 weeks</td>
<td>no significant difference between omega-3 fatty acids and placebo</td>
</tr>
<tr>
<td>Rees et al., 2008</td>
<td>Double-blind, placebo-controlled trial in pregnant and postpartum women</td>
<td>26</td>
<td>6 g fish oil per day; 1.6 g DHA, 0.4 g EPA(total 2.1 g omega-3 fa) (2.1 g DHA and EPA)</td>
<td>6 weeks</td>
<td>no significant difference between omega-3 fatty acids and placebo</td>
</tr>
</tbody>
</table>

### St. John’s Wort

- Herbal remedy with great popularity in Europe
- Usually studied as hypericum extract
- Some randomized controlled trials in MDD favorable, especially in mild to moderate MDD
- Less convincing in more severe MDD, and large federally funded studies in the U.S. diminished interest
  - Two U.S. large trials did not demonstrate difference between St. John’s Wort and placebo on primary outcomes
- Important drug-drug interactions

Shelton et al., 2001; Hypericum Study Group, 2002; Lecrubier et al., 2002; Linde et al., 2005; Roby et al., 2000; Mannel et al., 2004; Schwarz et al., 2003
Perinatal Considerations

- Study in pregnant women (N=33) treated with hypericum
  - Possible neonatal syndrome: newborns had increased rates of colic, drowsiness, lethargy compared to infants of matched depressed and non-depressed control mothers
  - Five were noted to experienced adverse effects, although none required medical intervention.
  - Possible neonatal syndrome described

- Breastfeeding case reports: Hyperforin and hypericin: low levels in breastmilk: Infants with nondetectable plasma levels, no adverse effects

Lee et al., 2003; Klier et al., 2002; Klier et al., 2006

Accessibility, Challenges of Study

- Example: accessibility may add to the methodological challenges of study
- Study of St. John’s Wort vs. Placebo:
  - those assigned to St. John’s Wort had variable adherence verified by metabolite blood levels
  - placebo group was found to have a surprising number of participants with notable St. John’s Wort metabolite levels (Vitiello et al., 2005)
Folate

- Low folate levels associated with poorer, slower response to SSRIs
- Treatment studies as adjunctive treatment showed benefit for patients on fluoxetine, especially women
  - Those who received folate vs. placebo more likely to be responders, have less side effects (0.5 mg/d)
- No evidence for monotherapy
- Low risk
  - Protective against birth defects – 0.4-1 mg recommended for women of reproductive age
- Reasonable to suggest use as an adjunctive strategy in addition to antidepressants, especially for women

Papakostas et al., 2004; Papakostas et al., 2005; Coppen and Bailey, 2000
**S-adenosyl-L-methionine (SAMe)**

- Occurs naturally in humans; needed as a methyl donor in synthesis of important compounds with implications for mood
- Agency for Healthcare Research and Quality (AHRQ) systematically assessed database for MDD, and found evidence to support further research
- Studies generally show benefit over placebo and equivalence to tricyclics
- Studied mostly as monotherapy; small study supported role as augmentation strategy

Papakostas et al., 2003; AHRQ, 2002; Mischoulon and Fava, 2002; Delle Chiaie et al., 2002; Bressa et al., 1994

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**SAMe: Perinatal Considerations**

- Placebo-controlled study of postpartum women: Cerutti et al. (1993)
  - found significant decreases in depressive symptoms with SAMe
  - Diagnoses of MDD were not established
  - Significantly greater improvement in depressive symptoms in the SAMe group compared to the placebo after 10 days
- No data are available regarding the efficacy of SAMe in antenatal depression
  - At least 8 studies have assessed SAMe for cholestasis in pregnancy. Five systematically reported tolerability and side effects, without observed side effects for mothers or babies (AHRQ, 2002)
**L-Methylfolate**

- Augmentation of 15 mg per day found substantially better than placebo in treatment resistant depression (7.5 mg not better than placebo)
- May be especially beneficial in those with a genetic deficiency in the methylene tetrahydrofolate reductase (MTHFR) gene that converts folic acid to L-methylfolate

Papakostas et al., 2012

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**Acupuncture**

- Part of Traditional Chinese Medicine
- Systematic reviews, meta-analyses fail to demonstrate consistently positive results over control conditions
- Generally low risk
- Pregnancy:
  - Caution: Some points may cause uterine stimulation
  - 2 studies showing efficacy over controls of sham acupuncture and massage

Halbreich, 2008; Leo and Ligot, 2007; Smith and Hay, 2005; Motl, 2002; Rabl et al., 2001; Manber et al., 2004; Manber et al., 2010
Other CAM Therapies for Perinatal Depression

• Massage
• Bright Light Therapy
• Exercise

Field et al., 2009; Golden et al., 2005; Epperson et al., 2004; Kripke et al., 1992; Oren et al., 2002; Corral et al., 2007; Dunn et al., 2005; Blumenthal et al., 2007; Trivedi et al., 2006; Artal and O’Toole, 2003; Heh et al., 2008
Nutrition and Women’s Mental Health

Nutrition as a Women’s Issue

• Women typically influence a household’s food intake
• Women represent the great majority of those with eating disorders
• Women have higher risk of depression
  – Growing evidence of relationship between dietary patterns and mood
• Evidence for long-term transgenerational effects of in utero nutrition
Nutrition and Depression

At least 3 large prospective cohort studies demonstrate associations between depression and patterns of nutritional intake

- Inverse association between the quality of the diet and psychological morbidity
- Suggest diets high in processed foods associated with higher rates of depression
- Diets rich in “whole foods” lower risk

Bidirectional relationship between risk of obesity and risk of depression

Jacka et al., AJP, 2010; Sánchez-Villegas et al., Arch Gen Psychiatry. 2009; Akbarly et al., Br J Psychiatry 2009; Luppino et al., Arch Gen Psychiatry 2010

Durable Future Consequences

- Long-term consequences of dietary patterns
- There have been a number of studies that demonstrate transgenerational effects of dietary composition, particularly fat content/composition
- There appears to be programming for increased risk of obesity, metabolic dysregulation; affected by offspring’s exposures and environment
- “the maternal high fat diet has a profound influence on the innate immune response of the offspring...and that this has enduring consequences for cognition and affect”

Massiera et al., J Lipid Res. 2010; Bilbo and Tsang, FASEB J 2010
Clinical and Public Policy Implications

• Clinical Considerations
  – Include nutritional habits, weight history in patient assessments
  – Talk with patients about what they eat, monitoring and advice
  – Children are dependent on others for food
  – Households may be the smallest units for targeted nutritional changes

• Educational and policy efforts
  – Education, marketing, financial subsidies
  – Move to better nutrition likely to be variable within a population
  – Example: New York City requirement of restaurants to post calorie labeling
    • Modest consumer behavior changes overall, no change in socioeconomically disadvantaged neighborhoods

Rabin RC, How Posted Calories Affect Food Orders, New York Times, November 3, 2009; Freeman, AJP 2010 (editorial); Saxena et al., World Psychiatry. 2006

Summary

• Integrative Medicine (CAM) is an important area in mental health and appealing to perinatal women
  – Women often want non-medication treatment options
  – Good quality, systematic, adequately powered controlled trials are needed; safety data needed
  – Efficacy, safety, acceptability, and accessibility are key issues