Treating the whole person with schizophrenia.

an Integrative Medicine approach

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• Disclaimer:
  • Supplements – not subject to FDA approval

• Disclosures of Financial Interest: none

• Position:
  • Professor of Psychiatry, UNC Chapel Hill
  • Medical Director of OASIS, 1st episode psychosis clinic

• Training:
  • Integrative Medicine Fellowship, University of Arizona
  • Masters in Pharmacology, University of Toronto
Learning Objectives

• Understand the modalities included in Integrative Medicine

• Better understand how frequently patients use complementary and alternative practices

• Identify CAM therapies in schizophrenia for which evidence is promising, and those for which it is lacking

• Evaluate ways to incorporate Integrative Medicine treatments into clinical practice

• Learn of available resources to evaluate the effectiveness and safety of integrative practices and products.
What is Integrative Psychiatry?
What’s in a name?

• Conventional Medicine

• Complementary - a non mainstream practice used together with conventional treatments.

• Alternative – a non mainstream practice used in place of conventional treatments.
Integrative Medicine

Conventional + Complementary
## Types of Complementary Health Approaches

| Mind & Body Practices | Natural Products |
Types of Complementary Health Approaches

Mind & Body Practices
- Yoga
- Meditation
- Breathing exercises
- Massage
- Chiropractic
- Acupuncture

Natural Products
Types of Complementary Health Approaches

Mind & Body Practices
- Yoga
- Meditation
- Breathing exercises
- Massage
- Chiropractic
- Acupuncture

Natural Products
- Herbs
- Vitamins
- Minerals
- Probiotics
- Dietary Supplements
Types of Complementary Health Approaches

Mind & Body Practices

Natural Products Practices

Alternative Whole System Approaches

- Traditional Chinese Medicine
- Ayurveda
- Traditional Healers
- Homeopathy
- Naturopathy
• Integrative Medicine
  • Incorporate nonmainstream therapies
  • Emphasis on prevention & management of chronic disease.
  • Increased emphasis on safety of a treatment.
  • Importance of the strength of the relationship between the doctor and patient.
Clarification

Integrative Medicine

Integrated Care
Use of CAM in General Population

- National Health Interview Survey
  - National Center for Health Statistics, part of the CDC, annual survey
  - CAM supplement every 5 years
  - 2012: information for 90,000 Americans
Use of CAM in General Population: 2012

- Use in the previous 12 months
  - 33 % of adults
  - 12 % of children

- Greater use in
  - Women
  - higher education and SES
  - those with chronic illness
  - those with multiple comorbidities
10 most common complementary health approaches among adults—2012

- Natural Products*: 17.7%
- Deep Breathing: 10.9%
- Yoga, Tai Chi, or Qi Gong: 10.1%
- Chiropractic or Osteopathic Manipulation: 8.4%
- Meditation: 8.0%
- Massage: 6.9%
- Special Diets: 3.0%
- Homeopathy: 2.2%
- Progressive Relaxation: 2.1%
- Guided Imagery: 1.7%

*Dietary supplements other than vitamins and minerals.

Use of CAM among those with mental illness

- In national surveys, 40 to 50% of those with self-reported depression or anxiety disorders used CAM.

- 63% of psychiatric inpatients reported using a CAM therapy in the past year.

- 68% of patients with psychotic illness reported use of CAM in past 6 months.

Most don’t disclose CAM use!
Why do people use CAM?

• Improve overall health & prevent illness
• Incomplete benefits from conventional treatments
• Decrease stress
• Sleep better
Why practice Integrative Psychiatry?

- Our patients are already using CAM
- Mental illnesses are usually chronic disorders with multiple comorbidities greatly impacted by lifestyle.
- Limited success with very expensive prescription medications with serious side effects
- Growing body of evidence for complementary practices
  - National Center for Complementary & Integrative Health
Conventional Psychiatry

- Medications
- Therapy
- other
Integrative Psychiatry

Diet, Exercise, Lifestyle

Supplements

Stress management, Therapy

Medications
Blue Zone Project

• There are five communities in the world where the population lives decades longer than average. And not only are they living longer, they’re living better – more active, greater vitality, and more engaged late into life.

• These five pockets are called Blue Zones.
clues from 3 Blue Zone sites

Loma Linda, USA
- healthy social circles
- eat nuts

Okinawa, Japan
- whole grains
- culturally isolated
- faith
- no alcohol
- soy
- turmeric
- ‘no rush’ lifestyle

Sardinia, Italy
- fava beans
- red wine
- family movement
- plant based diet
- no smoking
- sunshine
- gardening
- empowered women

www.bluezones.com
### Health/Longevity Predicting Traits

#### Blue Zone
- Community/social engagement/family involvement
- Constant moderate physical activity
- Plant-based diet
- No smoking

#### Schizophrenia pts
- Small social networks
- Sedentary behavior
- Poor nutrition
- High rates of smoking
Life Expectancy

- **Blue Zone**
- **US**
- **schizophrenia**

**Men**

**Women**
Healthiest Diets

• Mediterranean and Dash Diets
  • Plant based, whole grains
  • olive oil and nuts as healthy sources of fat
  • More fish, less meat
  • Moderate dairy
  • Moderate alcohol

• Reduces risk for heart disease, diabetes, obesity, many cancers, Parkinson’s disease, Alzheimer’s disease
Exercise Recommendations

- Strength training ≥ twice per week
- Moderate activity - 150 min/wk
  Or
- Vigorous activity - 75 min/wk
  (HHS, AHA, ACSP)

2018 CDC report
  - 23% American adults meet guidelines
Exercise benefits

- Heart disease & stroke
- Type 2 Diabetes
- Obesity
- Anxiety
- Depression
- Insomnia
Exercise benefits for Schizophrenia

- Weight management & cardiovascular fitness
  (review of 23 studies)

- Symptom improvement
  - PANSS total, + & – symptoms, depression, anxiety
  - social functioning and quality of life
    (2016 meta-analysis of 29 RC trials – a variety of types of exercise)

- Consistent improvements in
  - global cognition, working memory, social cognition & attention (review of 10 RC trials)
What type of Exercise?

- Aerobic
- Yoga
- Strength training
- Group exercise
- Instructor led
- Walking
Dietary Supplements

• Vitamin or mineral
• Herb or other phytochemical
• Amino acid

Nutraceuticals

• Concentrated bioactive substance

Not FDA regulated but governed by the Dietary Supplement Health and Education Act of 1994
Concerns Regarding Dietary Supplements

• Effectiveness

• Quality concerns
  • adulteration, claimed ingredient at claimed dosages?

• Interactions
  • between supplements and prescription drugs.

• Adverse effects

• Cost
Omega 3 fatty acids (ie fish oil)

- **Rationale**
  - anti-inflammatory
  - influences serotonin release
  - improves serotonin R function

- Prodomal / high risk subjects
- First episode patients
- Chronic patients
Omega-3 for prevention of progression to psychosis in those at high risk.

- Amminger et al., 2010 & 2015 – 1.2 g/d fish oil for 3 months significantly decreased progression to psychosis

- McGorry et al., 2017 – 1.4 g/d fish oil for 6 months was not beneficial

However
- Everyone received Cognitive Based Case management
- High use of antidepressants (62%)
- Lower than expected progression to psychosis in both groups
Omega 3 fatty acids

Ongoing RDBPC prodromal/high risk studies

1. NAPLS, completed but not published yet

2. Study ongoing in Pakistan – omega 3 vs minocycline

3. PURPOSE study – multisite study in Europe
Omega 3 fatty acids
First episode psychosis patients

- 3 RDBPC trials

- Findings
  - earlier treatment response,
  - more patients reaching ≥ 50% improvement,
  - lower depression,
  - less EPS

- No benefit to prevent relapse in FEP off antipsychotics
Omega 3 fatty acids
Chronic schizophrenia patients

- 7 augmentation trials
  - Mild improvement in PANSS + symptoms
  - Worse PANSS score - use during an acute psychotic relapse
  - Worse cognition
  - No benefits for TD, EPS, blood sugar, lipids
Omega 3 fatty acids

• Unipolar MDD
  • > 35 randomized clinical trials
  • EPA more effective than DHA
  • Doses 1 g/d as adjunct to antidepressant

• Bipolar depression
  • 2 of 5 RCT showed decrease in depression
  • 1 to 2 g/d EPA+DHA, with low risk for stimulating cycling
Omega 3 fatty acids

- In those with established CV disease
  - ↓ triglycerides, LDL, total cholesterol
  - ↓ markers of atherosclerosis risk
  - ↓ markers of inflammation
- Decreases pain from arthritis
- Improves dry eyes
- Improves psoriasis
Omega 3 fatty acid

• Safety
  • safe and well tolerated at doses up to 6 g/d
  • Rare increases in bleeding time, usually in pts on blood thinner
  • Check the expiration date as rancid fish oil is pro-inflammatory

• Cost: 50 ¢ to $2 per day
Vitamin D

• Rationale
  • Deficiency in utero and early years is a risk factor for developing a psychotic disorder
  • Lower levels in people with schizophrenia vs control subjects, found in FEP & chronic
  • Lower levels associated with worse cognition & negative symptoms in FEP subjects
  • Deficiency in general population associated with CVD and all cause mortality
Vitamin D

- Supplementation in chronic schizophrenia pts
  - At 8 wks - NSD on + or – sx (2 studies)
  - Significant improvements in cognition (1 of these studies)

- Supplementation in general population
  - Decrease in all cause mortality & cancer mortality (Cochrane reviews 2014)

- Safety: wide margin of safety
- Cost: low < 25 ¢ per day
Vitamin B6

• Rationale
  • Important in DNA synthesis & methylation, homocysteine metabolism
  • Antioxidant & free radical scavenger,
  • Important in dopamine, serotonin & GABA metabolism
Vitamin B6

• Supplementation
  • ↓ antipsychotic related TD (3 studies)
  • ↓ akathisia - Equal to propranolol 40 mg/d (1 study)
  • Dose at least 300 mg/d, and up to 600 mg bid
  • benefits often begin by week 3

• Side effects: very rare & very mild

• Cost: 25 to 80 ¢ per day
N-Acetylcysteine

• Rationale
  • Provides the rate-limiting precursor in synthesis of glutathione (GSH)
    • GSH is #1 antioxidant & free radical scavenger in the brain
    • GSH dysregulation at the gene, protein and functional levels leads to NMDA receptor hypo function
    • GSH is lower in those with schizophrenia
  
  • Antioxidant - pro-neurogenesis & anti-inflammatory
RDBPC trials of NAC in Schizophrenia

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>wks</th>
<th>dose</th>
<th>Outcome: significant improvements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>g/d</td>
</tr>
<tr>
<td>Berk 2008</td>
<td>140</td>
<td>24</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Farokhnia 2013</td>
<td>42</td>
<td>8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Rapado-Castro 2015</td>
<td>121</td>
<td>24</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Rossell 2016</td>
<td>140</td>
<td>24</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Rapado-Castro 2017</td>
<td>58</td>
<td>24</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Conus 2018</td>
<td>61</td>
<td>24</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

Safety: NSD from placebo  Cost: ~ 50 ¢ per day
L-Theanine trials in Schizophrenia

• Theanine: component of green & black tea

• Rationale
  • Up-regulates inhibitory neurotransmitters
  • Modulates 5HTP and DA
  • Increases BDNF
  • Neuroprotective following cerebral infarct & TBI
L-Theanine trials in Schizophrenia

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>duration</th>
<th>dose</th>
<th>Outcome- improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kardashev 2018 RDBPC</td>
<td>40</td>
<td>8</td>
<td>400 mg + 50 mg pregnenolone</td>
<td>✗</td>
</tr>
<tr>
<td>Ritsner 2011 RDBPC</td>
<td>40</td>
<td>8</td>
<td>400 mg</td>
<td>✗</td>
</tr>
</tbody>
</table>

- Safety: NSD vs placebo
- Cost: ~ 40 ¢ per day
Ginkgo Biloba

- Rationale
  - Antioxidant
  - Free radical scavenger
  - Improves mitochondrial respiration
  - May increase cerebral blood flow
Ginkgo Biloba

- Results as adjunct for chronic schizophrenia
  - Significant improvement in negative & total PANSS sx
  - Dose of 240 to 360 mg/d (in bid to tid dosing)
    (8 RDBPC trials, 1,033 patients)

- Safety: side effects NSD vs placebo, but some reports of post-op bleeding

- Cost: 20 to 80 ¢ per day
Cannabidiol and Schizophrenia

• Rationale
  • Anandamide is an endogenous cannabinoid that activates the CB1 receptor in the brain – mood, cognition, pain
  • CBD is an inhibitor of reuptake & breakdown of anandamide
  • CBD cognitive & psychotic symptoms of THC in healthy volunteers

• FDA – CBD is a schedule 1 drug & not a supplement
## Cannabidiol and Schizophrenia

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Duration</th>
<th>Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leweke et al 2012</td>
<td>42</td>
<td>4 wks</td>
<td>800 mg</td>
<td>PANSS +, PANSS total, -, &amp; general</td>
</tr>
<tr>
<td>DBR active control (amilsulpiride)</td>
<td></td>
<td></td>
<td></td>
<td>Less EPS, wt gain, prolactin</td>
</tr>
<tr>
<td>Leweke et al 2014</td>
<td>29</td>
<td>4 wks</td>
<td>600 mg</td>
<td>PANSS +</td>
</tr>
<tr>
<td>RDBPC crossover</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McGuire et al 2017</td>
<td>88</td>
<td>6 wks</td>
<td>1000 mg</td>
<td>PANSS +, CGI</td>
</tr>
<tr>
<td>RDBPC</td>
<td></td>
<td></td>
<td></td>
<td>NSD on cognition</td>
</tr>
<tr>
<td>Boggs et al 2018</td>
<td>36</td>
<td>6 wks</td>
<td>600 mg</td>
<td>NSD on PANSS or cognition</td>
</tr>
</tbody>
</table>

**Safety:** generally NSD, perhaps greater sedation

**Cost:** $60 to $100 per day

6 ongoing CBD in Schizophrenia studies --
Mind Body Medicine & Schizophrenia

• Review of 42 clinical trials (Helgason and Sarris 2013)

• supportive evidence was found for
  • mindfulness techniques
  • music therapy
  • meditation
  • yoga
  • breathing exercises
  • general relaxation training
Mindfulness and Schizophrenia

- 11 Randomized controlled trials
  - Improved anxiety, insomnia
  - Acceptable to patients

- Mindfulness for AH
  - 4 cross sectional studies
    - Greater mindfulness & acceptance of voices associated with less distress, depression, anxiety, less compliance to voice commands, and improved QOL
  - 3 controlled trials (underpowered pilot studies)
    - 2 of 3 showed benefit of mild effect size
# Recap

## Types of CAM

<table>
<thead>
<tr>
<th>Mind &amp; Body Practices</th>
<th>Natural Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Yoga</td>
<td>• Herbs</td>
</tr>
<tr>
<td>• Meditation</td>
<td>• Vitamins</td>
</tr>
<tr>
<td>• Breathing exercises</td>
<td>• Minerals</td>
</tr>
<tr>
<td>• Massage</td>
<td>• Probiotics</td>
</tr>
<tr>
<td>• Chiropractic</td>
<td>• Supplements</td>
</tr>
<tr>
<td>• Acupuncture</td>
<td></td>
</tr>
</tbody>
</table>
Case 2: Using IM in practice

- Jenny is a 24 year old student with schizophrenia
  - has + sx well controlled with aripiprazole 15 mg daily
  - but with low mood, moderate anxiety, and insomnia
  - BMI is 29, and she eats out for many meals
  - walks to and from classes but no other physical activity
  - likes school but finds it difficult & stressful
  - main way to relax is watching TV by herself
IM Recommendations

- **Weight management**
  - Exercise, nutrition/diet counseling, mindful eating, metformin

- **Cognition**
  - Aerobic exercise, NAC, Vitamin D, stimulant

- **Insomnia**
  - Morning exercise, sleep hygiene, melatonin, CBT-Insomnia, Progressive muscle relaxation, trazodone

- **Anxiety**
  - Daily yoga, slow paced breathing, mindfulness, theanine, less coffee/more green tea, Mediterranean diet, join a social group on campus, SSRI, buspirone, hydroxyzine, etc.
Integrative Psychiatry Resources

• Book
  • Complementary and Integrative Treatments in Psychiatric Practice by P Gerbarg, PR Muskin & RP Brown. 2018 APA Press

• Internet sites
  • https://nccih.nih.gov (NIH)
  • www.intpsychiatry.com
  • www.consumerlab.com
  • www.naturaldatabase.com
  • www.azcim.org
Thank you ...
References

Statistics of CAM usage in general population in the US.

Use of CAM among those with mental illness.

Blue Zones/longevity
www.bluezones.com
Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. Lancet Psychiatry. 2017 Apr;4(4):295-301.

Anti-inflammatory Diet
www.drweil.com/diet
**Exercise and Schizophrenia**


**Falkai, P; Malchow, B; Schmitt, A.** Aerobic exercise and its effects on cognition in schizophrenia. Curr Opin Psychiatry 2017;30(3):171-175.


Omega 3

Amminger GP, et al., Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry 2010; 67: 146-154


Behdani et al., 2018: RCT of 4 g/d w-3 FA vs placebo for 3 months. n=56 pts on clozapine + Depakote, SD in wt, waist circumference, BMI. However NSD wrt lipids, FBS, or hs-CRP.


Bentsen H, Osnes K, Refsum H, A RPC trial of an omega-3 fatty acid and vitamins E+C in schizophrenia Transl Psychiatry 2013 Dec 17;3:e335.


Includes; Fenton et al., Am J psychiatry 2001, 158:2071-2074 & Emsley et al., Am J psychiatry 2002 159:1596


**Vitamin D**


**Vitamin B6**

NAC


Rapado-Castro M, Berk M, Venugopal K, et al., Towards stage specific treatments: effects of duration of illness on therapeutic response to adjunctive treatment with N-acetyl cysteine in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2015 Mar 3;57:69-75.

L-theanine


CBD


Leweke FM, Hellmich M, Pahlisch F et al., Modulation of the endocannabinoid system as a potential new target in the treatment of schizophrenia. Schizophrenia Res. 2014 April:153, (S1): s47,  PANSS + improvement of 2.4 points. This is in a group of anti-psychotic naïve FEP subjects

Mind Body Medicine and Schizophrenia


Strauss C, Thomas N, Hayward M. Can we respond mindfully to distressing voices? A systemic review of evidence for engagement, acceptability, effectiveness and mechanisms of change for mindfulness based interventions for people distressed by hearing voices. Front Psychol. 2015 Aug 14;6:1154

Ashwagandha