

Treating the whole person
with schizophrenia.

an Integrative Medicine
approach

Karen Graham MD

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NCPA

- 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?

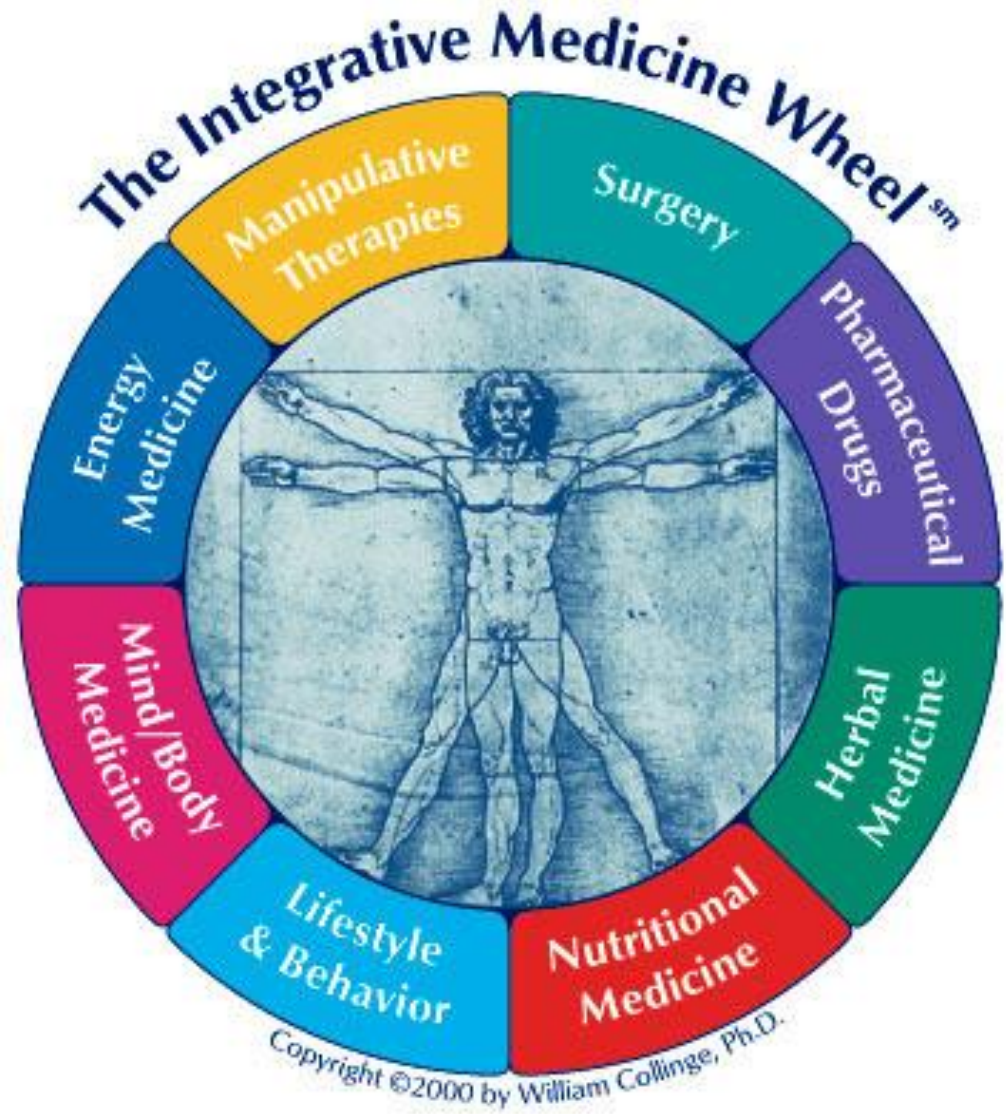


National Center for
Complementary and
Integrative Health

- 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

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Natural Products

- Herbs
- Vitamins
- Minerals
- Probiotics

Dietary Supplements

Types of Complementary Health Approaches

Mind & Body
Practices

Natural Products

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



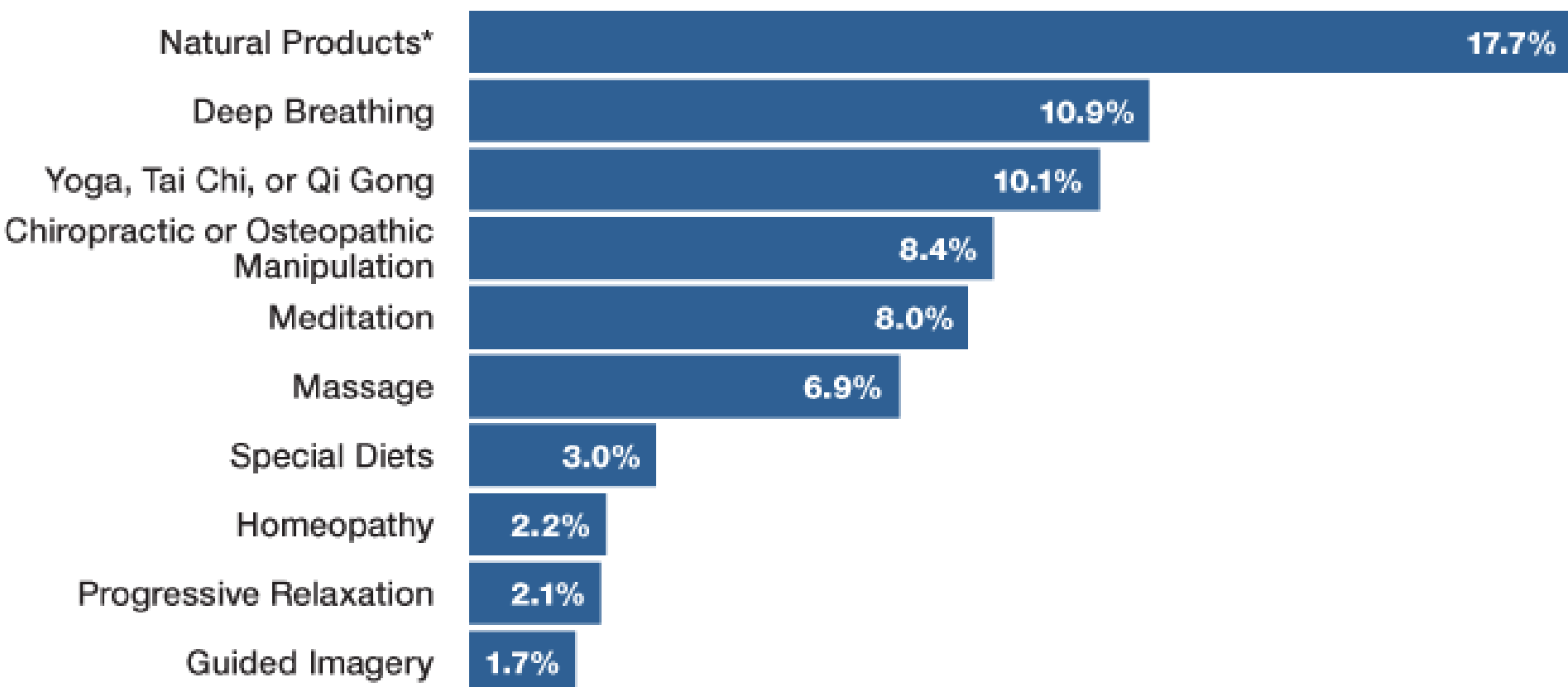
- National Health Interview Survey
 - National Center for Health Statistics, part of the CDC, annual survey
 - CAM supplement every 5 years
 - **2012**: information for 90,000 Americans

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



*Dietary supplements other than vitamins and minerals.

Source: Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the use of complementary health approaches among adults: United States, 2002-2012. National health statistics reports; no. 79. Hyattsville, MD: National Center for Health Statistics. 2015.

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!

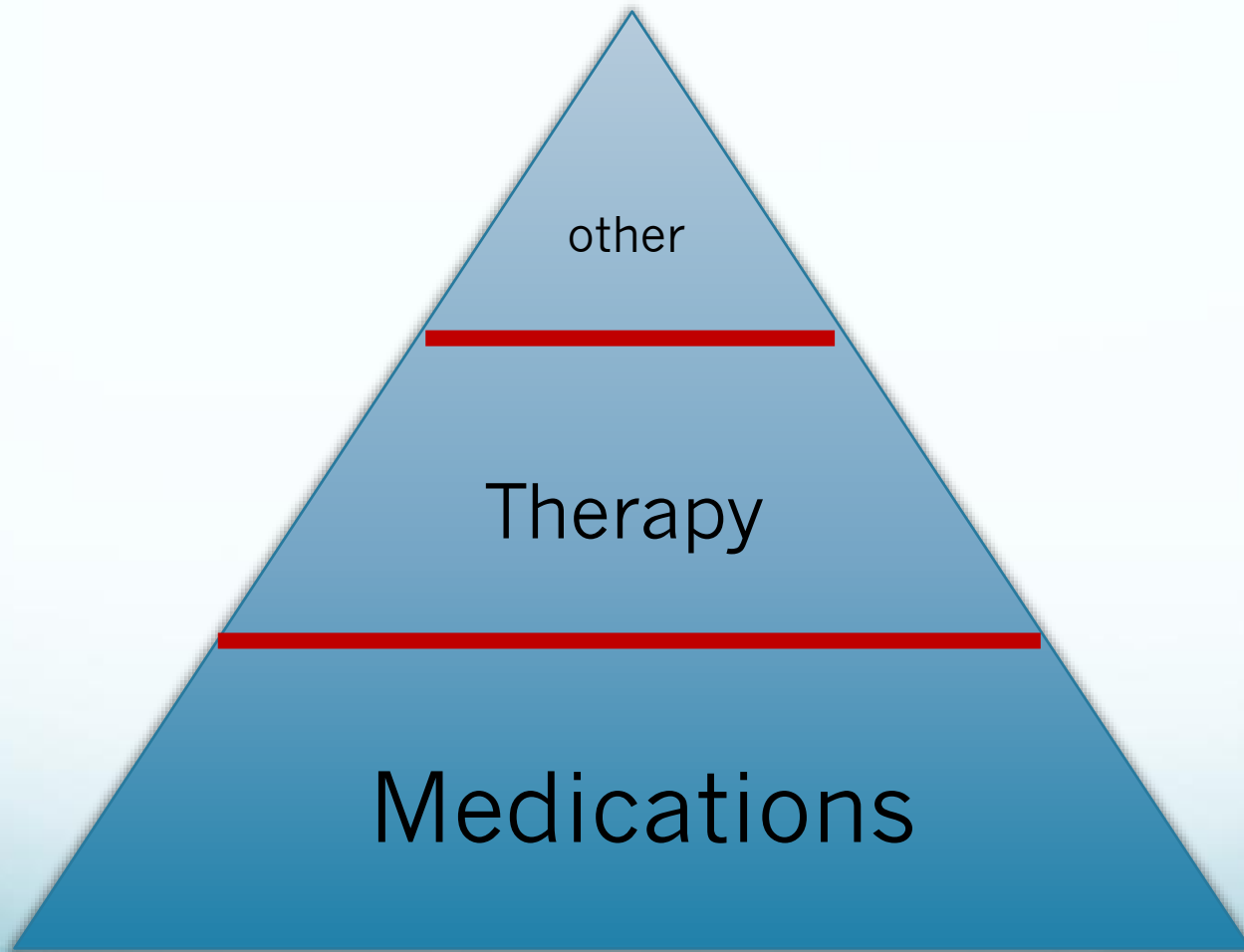
Why do people use CAM?

- 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



Integrative Psychiatry



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.





LOMA LINDA
Californië

NICOYA
Costa Rica

SARDINIË
Italië

IKARIA
Griekenland

OKINAWA
Japan

**BLUE
ZONES**
www.sanova.nl

clues from 3 Blue Zone sites

Loma Linda, USA

healthy social circles
eat nuts

Sardinia, Italy

whole grains
culturally
isolated

Okinawa, Japan

faith
no alcohol
soy

family
movement
plant based diet
no smoking

fava beans
red wine

turmeric
'no rush' lifestyle

sunshine
gardening
empowered women

Health/longevity predicting traits

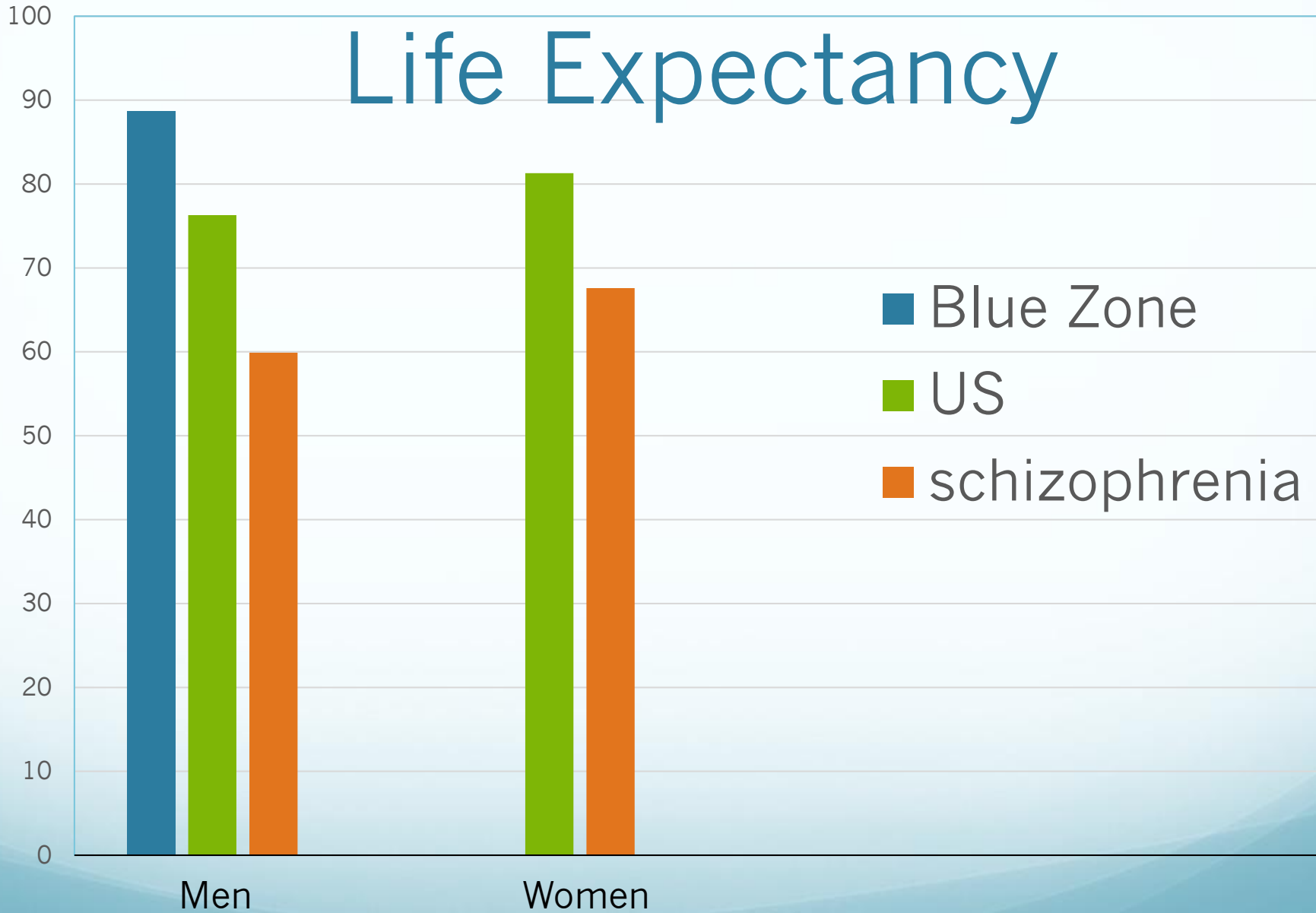
Blue Zone

- 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



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 \geq 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
- Prodromal / 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 $\geq 50\%$ 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

Trial	N	wks	dose	Outcome: significant improvements			
				g/d	PANSS positive	PANSS negative	cognition
Berk 2008	140	24	2		*		PANSS general
Farokhnia 2013	42	8	2		*		PANSS total
Rapado-Castro 2015	121	24	2	*	*	*	
Rossell 2016	140	24	1		*		Global, akathisia
Rapado-Castro 2017	58	24	2			*	
Conus 2018	61	24	2.7			*	GSH levels

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

Trial	N	duration	dose	Outcome- improvement		
				negative	anxiety	other
Kardashev 2018 RDBPC	40	8 wks	400 mg + 50 mg pregnenolone	*	*	
Ritsner 2011 RDBPC	40	8 wks	400 mg	*	*	general

- 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

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

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

Mind & Body Practices

- Yoga
- Meditation
- Breathing exercises
- Massage
- Chiropractic
- Acupuncture

Natural Products

- Herbs
- Vitamins
- Minerals
- Probiotics
- Supplements

Case 2: Using IM in practice

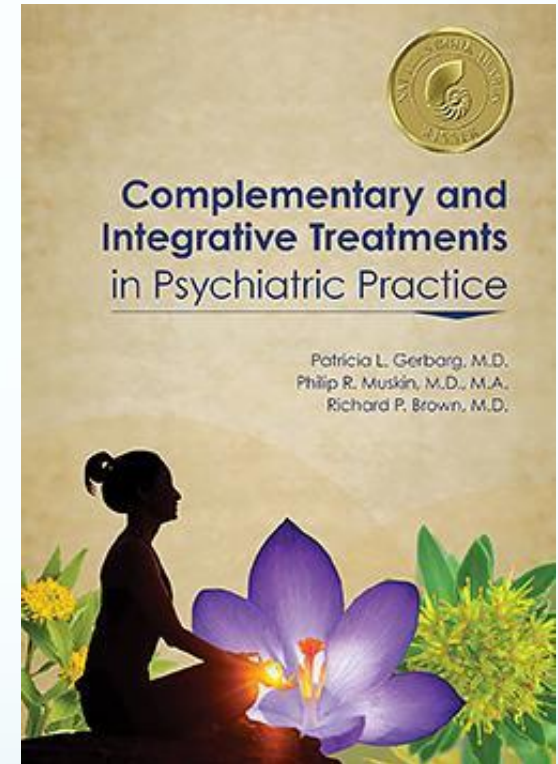
- Jenny is a 24 year old student with schizophrenia
 - has + sx well controlled with aripiprazole 15 mg daily
 - but with low mood, moderate anxiety, and insomnia
 - BMI is 29, and she eats out for many meals
 - walks to and from classes but no other physical activity
 - likes school but finds it difficult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

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<http://nccih.nih.gov/research/statistics/NHIS/2012>

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www.bluezones.com

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Anti-inflammatory Diet

www.drweil.com/diet

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