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:
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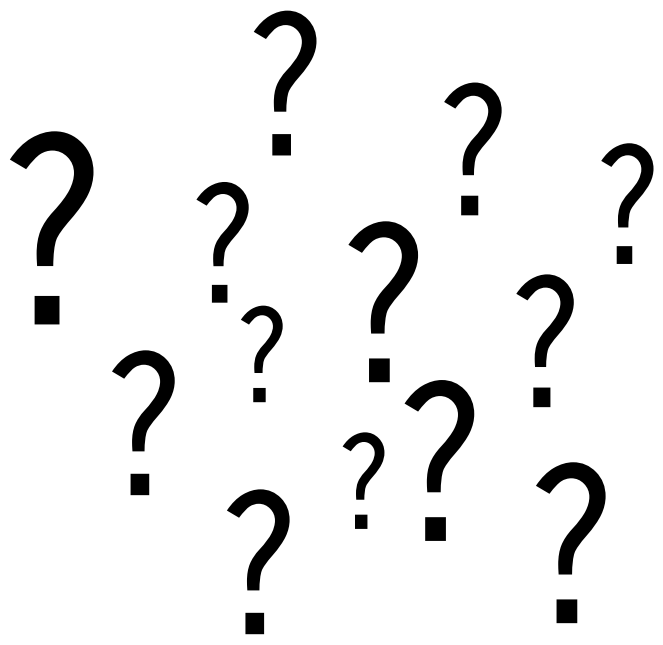
  - Medical Director of OASIS, 1st episode psychosis clinic
- Training:
  - Integrative Medicine Fellowship, University of Arizona
  - Masters in Pharmacology, University of Toronto

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?

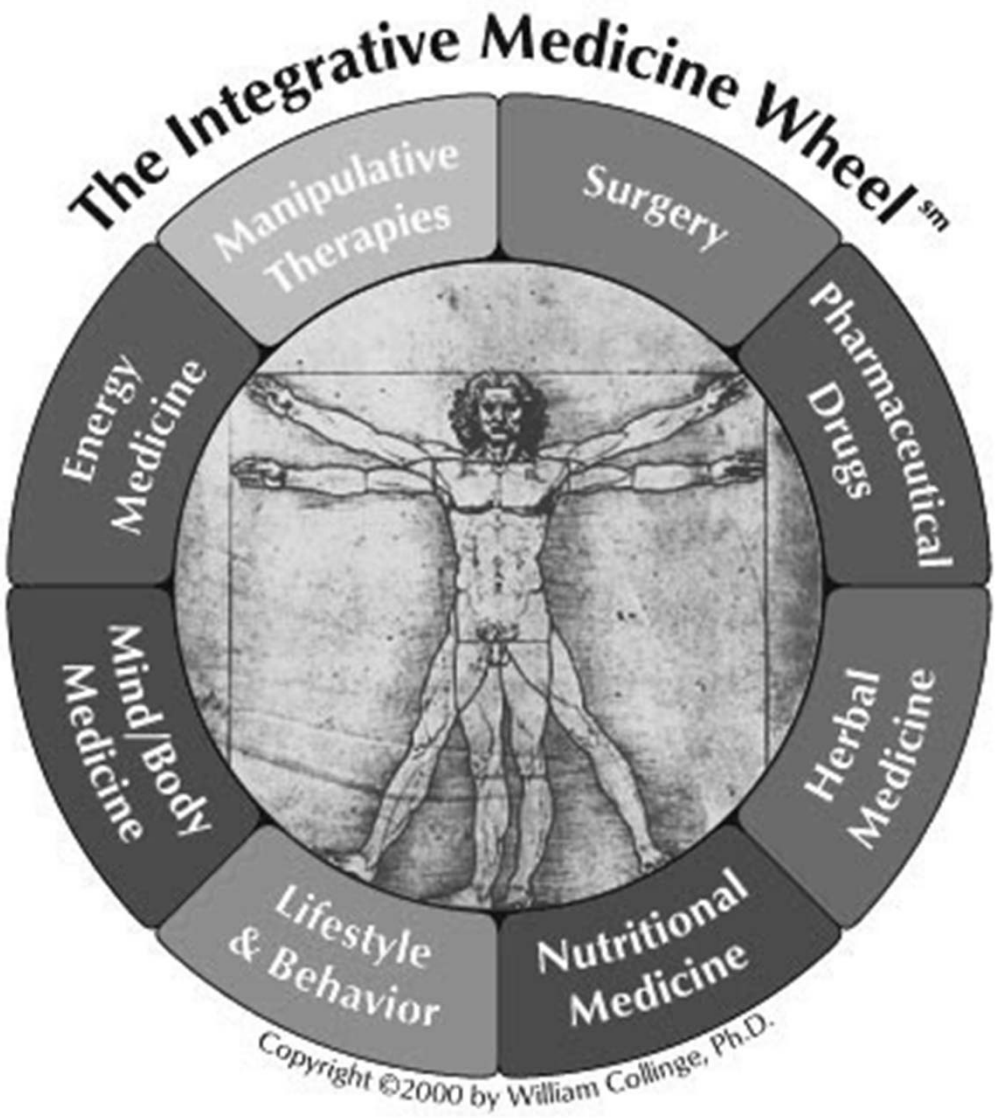


What's in a name?

- 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

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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

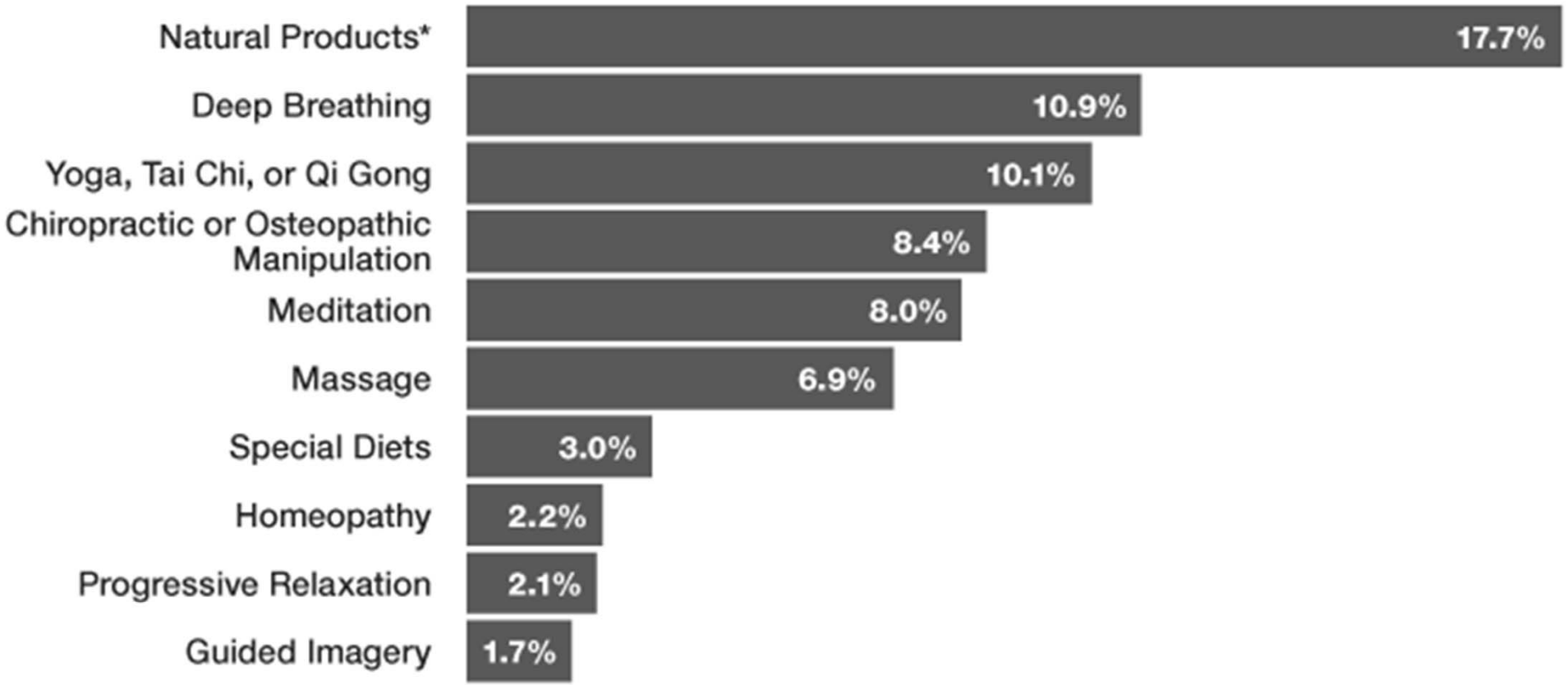
Use of CAM in General Population

- 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!

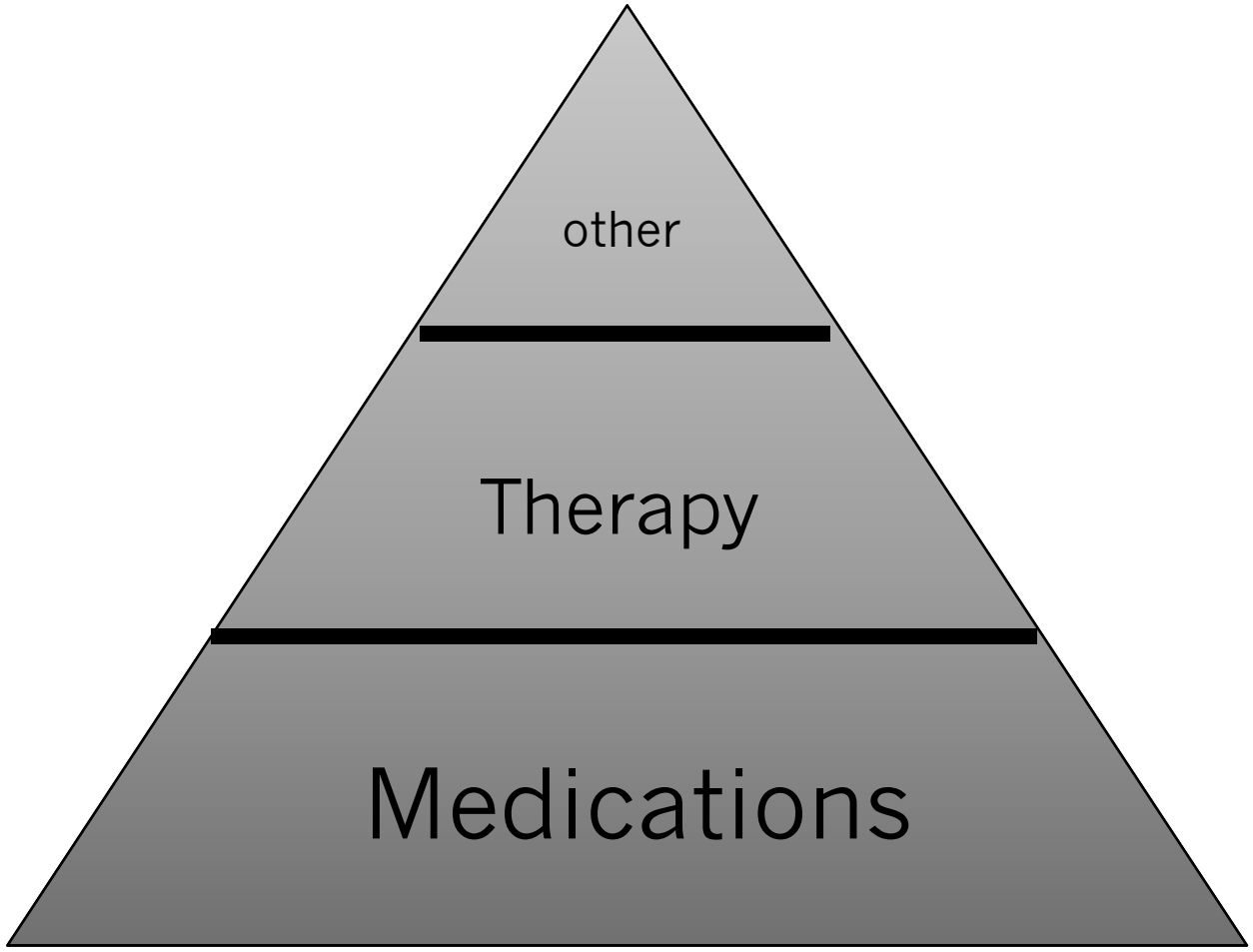
Why do people use CAM?

- Improve overall health & prevent illness
- Incomplete benefits from conventional treatments
- Decrease stress
- Sleep better

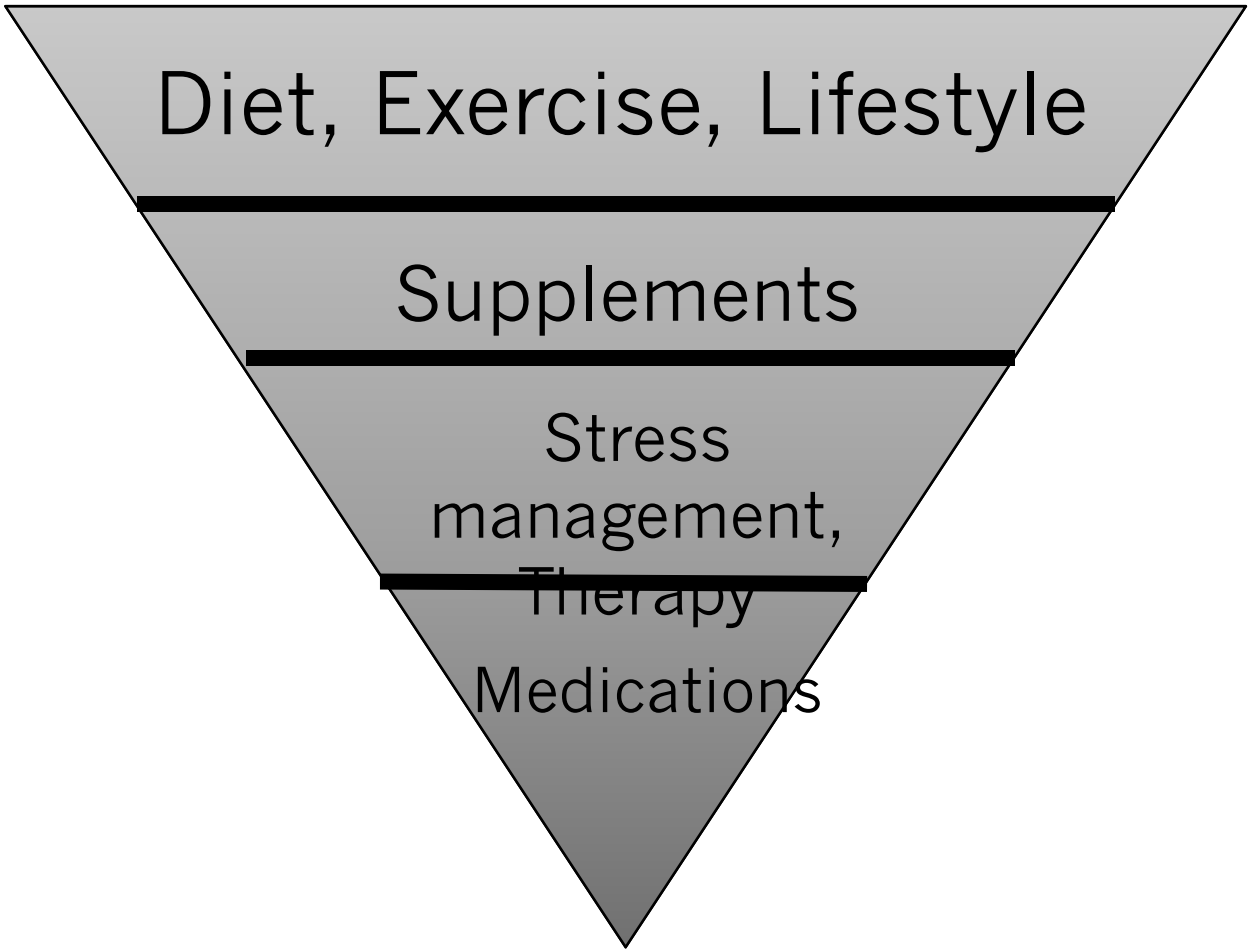
Why practice Integrative Psychiatry?

- 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



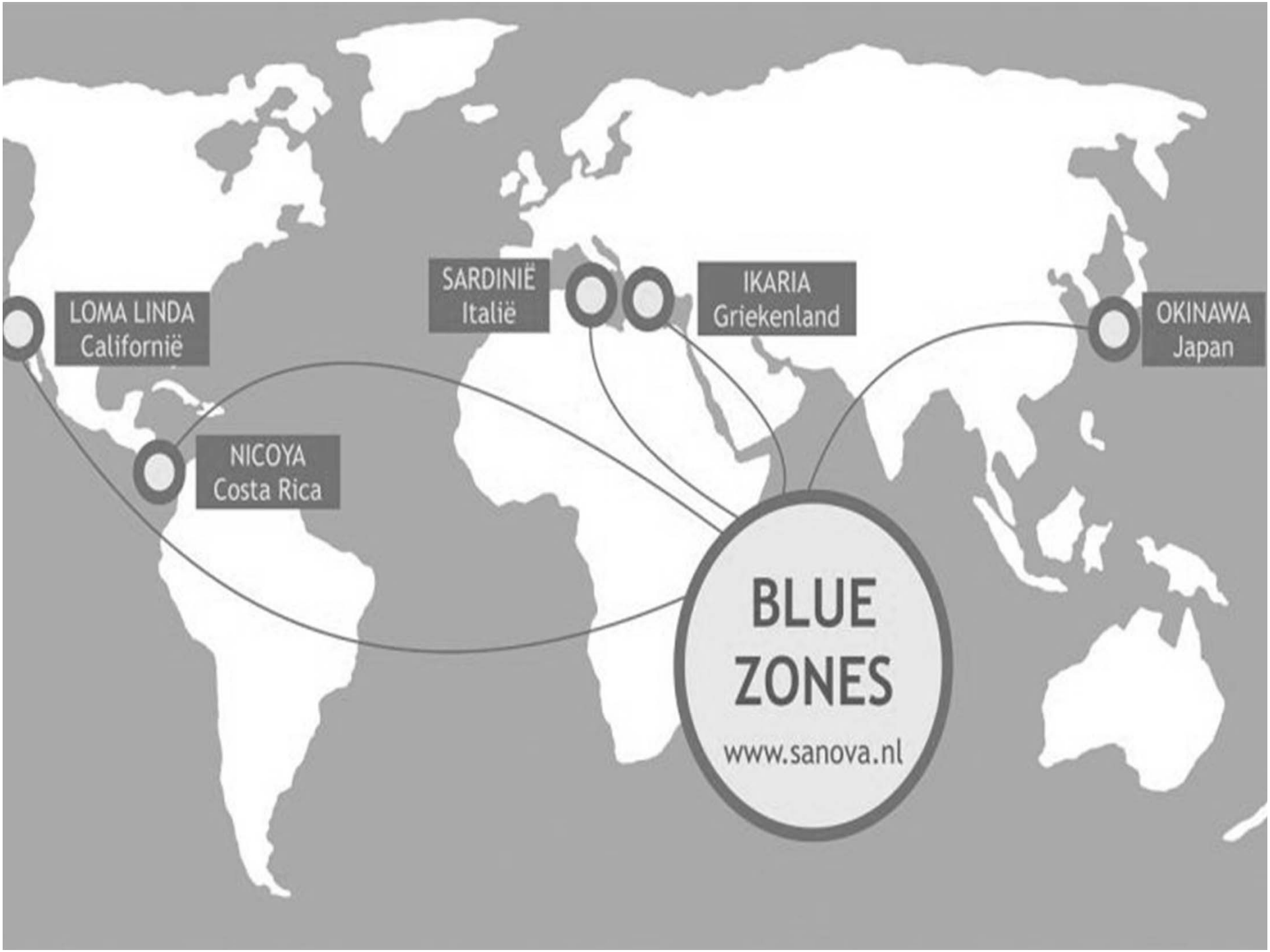
Integrative Psychiatry



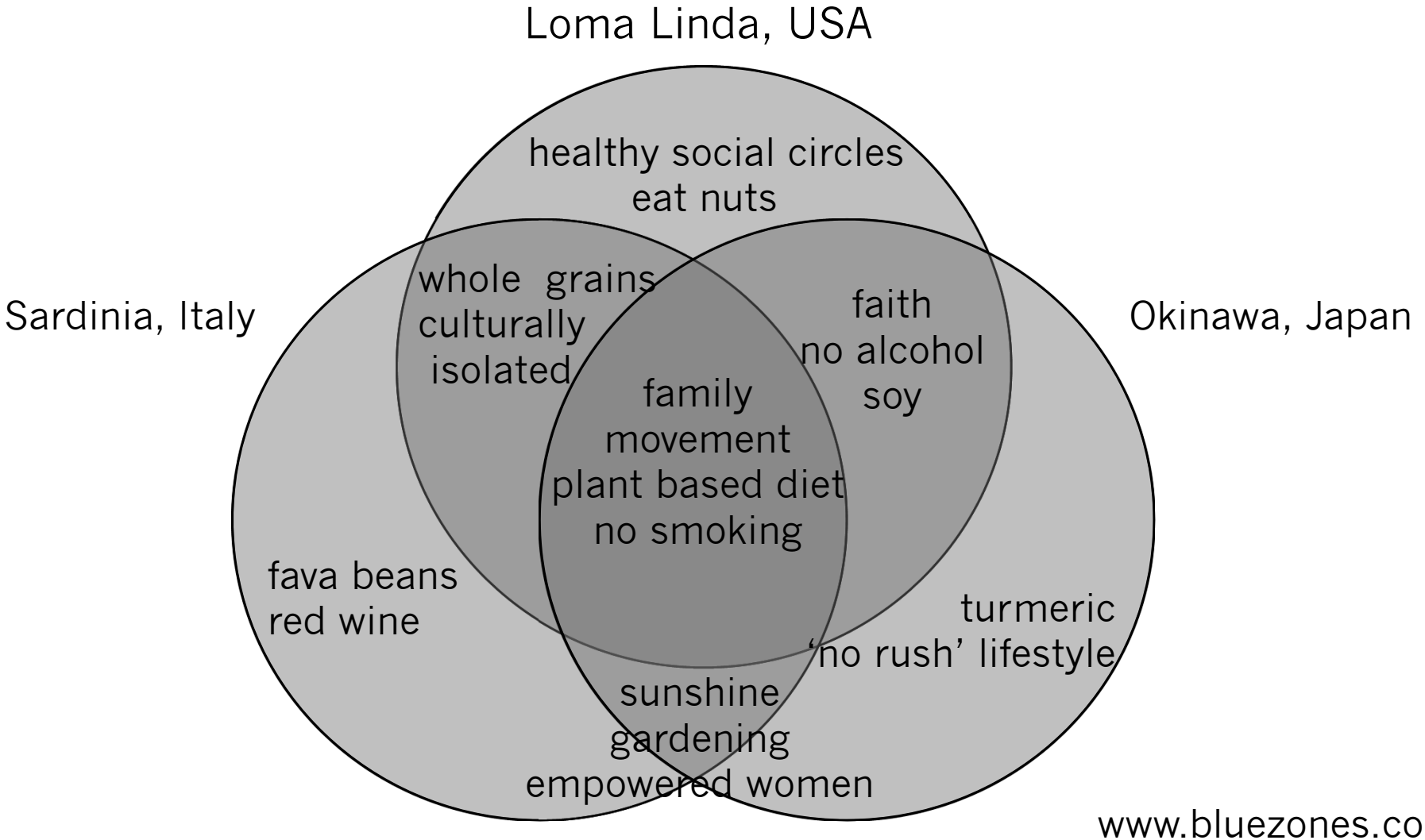
Blue Zone Project

- 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.

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



www.bluezones.com

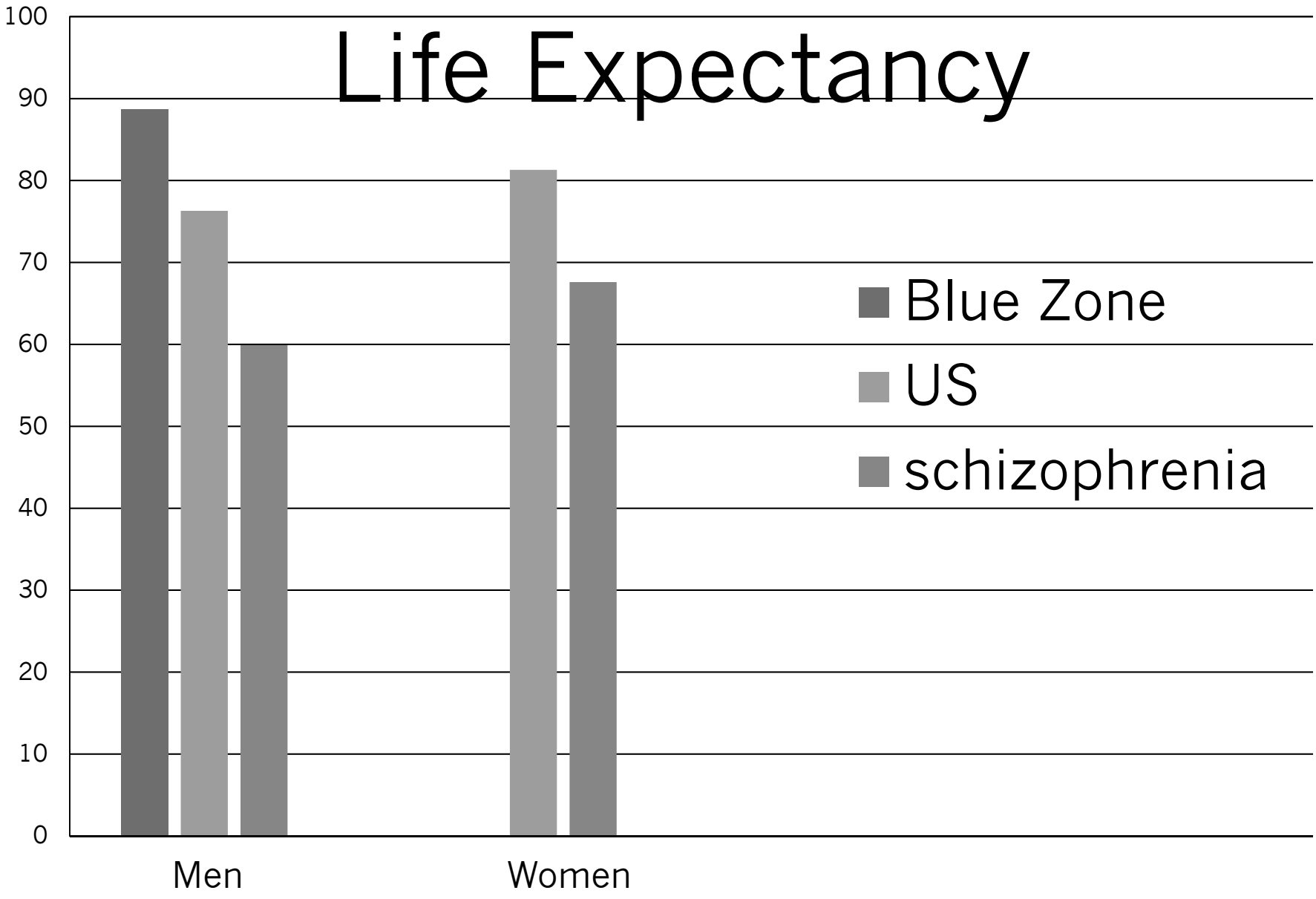
Health/ longevity predicting traits

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
100
90
80
70
60
50
40
30
20
10
0
Men
Women
Blue Zone
US
schizophrenia

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

<u>However</u>

- 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

Trial	N	wks	dose	Outcome: significant improvements			
			g/d	PANSS positive	PANSS negative	cognition	other
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 te
- 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		
		wks		negative	anxiety	other
Kardashev 2018 RDBPC	40	8	400 mg + 50 mg pregnenolone	*	*	
Ritsner 2011 RDBPC	40	8	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

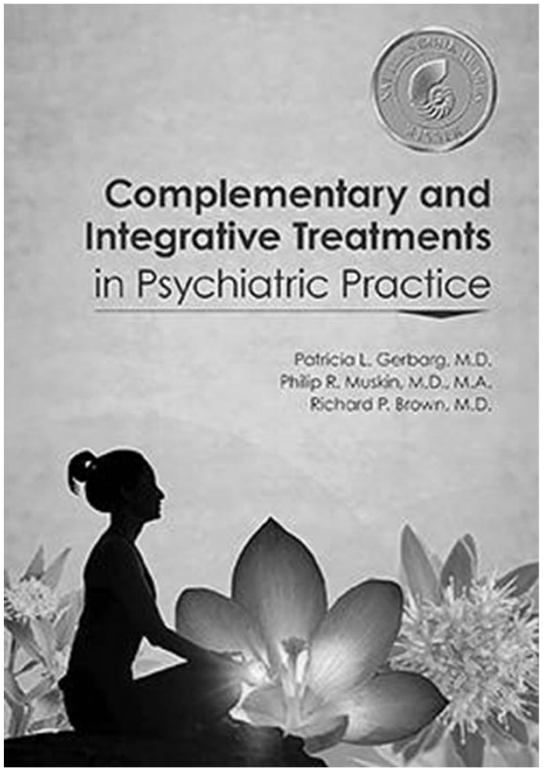
- Jenny is a 24 year old student with schizophrenia
  - has + sx well controlled with aripiprazole 15 mg daily
  - but with low mood, moderate anxiety, and insomnia
  - BMI is 29, and she eats out for many meals
  - walks to and from classes but no other physical activity
  - likes school but finds it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

References

Statistics of CAM usage in general population in the US.
http://nccih.nih.gov/research/statistics/NHIS/2012

Use of CAM among those with mental illness.
Kessler et al. The use of complementary and alternative therapies to tx anxiety and depression in the United States. Am J psychiatry 2001; 158(2):289-94.
Elkins G, et al., Complementary and alternative medicine use by psychiatric inpatients. Psychol Rep 2005;96(1):163-6.
Hazra M, Noh S, Boon H, Taylor A, Moss K, Mamo D. Complementary & alternative medicine in psychotic disorders. J Altern Complement Med 2010;7:1–15
Unutzer J et al., Mental disorders and the use of alternative medicine: results from a national survey Am J Psychiatry 2000 Nov;157(11):1851-7.

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.
Blue zone longevity data from a presentation by Poulain, Legrand, Herm and Pes, on Causes of death and exceptional longevity in Ikaria and the Sardinian Blue Zone
https://reves.site.ined.fr/fichier/s_rubrique/25685/reves.2016.6.1.fr.pdf

Anti-inflammatory Diet
www.drweil.com/diet

Exercise and Schizophrenia

Bhatia T, Mazumdar S, Wood J, et al. A randomized controlled trial of adjunctive yoga and adjunctive physical exercise training for cognitive dysfunction in schizophrenia. Acta Neuropsychiatr 2016; 1–13. Aug 12

Dauwan M, Begemann MJ, Heringa SM, et al. Exercise improves clinical symptoms, quality of life, global functioning, and depression in schizophrenia: a systematic review and meta-analysis. Schizophr Bull 2016; 42:588–599.

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

Ho RT, Fong TC, Wan AH, et al. A randomized controlled trial on the psychophysiological effects of physical exercise and Tai-chi in patients with chronic schizophrenia. Schizophr Res 2016; 171:42–49.

Kimhy D, Lauriola V, Bartels MN, et al. Aerobic exercise for cognitive deficits in schizophrenia: the impact of frequency, duration, and fidelity with target training intensity. Schizophr Res 2016; 172:213–215

Lin J, Chan SK, Lee EH, et al. Aerobic exercise and yoga improve neurocognitive function in women with early psychosis. NPJ Schizophr 2015; 1:15047.

Vancampfor D, Vansteelandt K, Scheewe T et al. Yoga in schizophrenia: a systematic review of randomized controlled trials. Acta Psychiatr Scand 2012;126:12–20.

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

Amminger GP, Schafer MR, Schlogelhofer M, et al., Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study, Nat. Commun. 6 (2015) 7934.

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, and Landro NI, Neurocognitive effects of an omega-3 fatty acid and vitamins E+C in schizophrenia: A randomized controlled trial. Prostaglandins, leukotrienes, and essential fatty acids, Oct 2017.

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.

Bozzatello P, Brignolo E, De Grandi E et al., Supplementation with Omega-3 fatty acids in psychiatric disorders: a review of literature data. J Clin Med. 2016 Aug; 5(8): 67.

Chen AT, et al., META-ANALYSIS OF OMEGA-3 AUGMENTATION IN SCHIZOPHRENIA 2015 Annals of Clinical Psychiatry: 27 (4) 289-296.
Includes; Fenton et al., Am J psychiatry 2001, 158:2071-2074 & Emsley et al., Am J psychiatry 2002 159:1596

Emsley R, Chiliza B, Asmal L, et al. A RCT of o mega-3 fatty acids plus an antioxidant for relapse prevention after antipsychotic discontinuation in first-episode schizophrenia. Schizophr Res. 2014 Sep;158(1-3):230-5

Jamilian H, Solhi H, Jamilian M. RPC clinical trial of omega-3 as supplemental treatment in schizophrenia. Glob J Health Sci. 2014 Sep 18;6(7 Spec No):103-8.

McGorry PD, Nelson B, Markulev C et al., Effect of w-3 Polyunsaturated Fatty acids in young people at ultrahigh risk for psychotic disorders. JAMA Psychiatry. 2017 Jan 1;74(1):19-27.

Mischoulon D, Freeman MP. Omega-3 fatty acids in psychiatry. Psychiatr Clin North Am. 2013 Mar;36(1):15-23.

Pawełczyk T, Grancow M, Kotlicka-Antczak M, et al. Omega-3 fatty acids in first-episode schizophrenia – a RC study of efficacy and relapse prevention (OFFER): rationale, design, and methods. BMC Psychiatry. 2015 May 2;15:97.

Pawełczyk, T., Grancow-Grabka, M., Kotlicka-Antczak, M., et al. A randomized controlled study of the efficacy of six-month supplementation
with concentrated fish oil rich in omega-3 polyunsaturated fatty acids in first episode schizophrenia. J. Psychiatr. Res. 2016:73:34–44.

Rosenblat JD, Kakar R, Berk M, et al., Anti-inflammatory agents in the treatment of bipolar depression: a systematic review and meta-analysis. Bipolar Disord. 2016 Mar;18(2):89-101.

Vitamin D

Bjelakovic G, Gluud LL, Nikolova D, et al., Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev. 2014 Jan 10;(1):CD007470.

Bjelakovic G, Gluud LL, Nikolova D, et al., Vitamin D supplementation for prevention of cancer in adults. Cochrane Database Syst Rev. 2014 Jun 23;(6):CD007469.

Boerman R, Cohen D, Schulte PF et al., Prevalence of Vitamin D Deficiency in Adult Outpatients With Bipolar Disorder or Schizophrenia. J Clin Psychopharmacol 2016 Dec:36(6):588-592

Brown HE, Roffman JL. Vitamin supplementation in the treatment of schizophrenia. CNS Drugs 2014 Jul;28(7):611-22.

Dealberto MJ. Clinical symptoms of psychotic episodes and 25-hydroxy vitamin D serum levels in black first-generation immigrants. Acta psychiatrica Scandinavica. 2013;128(6):475–87.

Krivoy A, Onn R, Vilner Y, et al., Vitamin D supplementation in chronic schizophrenia patients treated with Clozapine: A RDBPC clinical trial. EBioMedicine. 2017 Dec;26:138-145

Vitamin B6

Adelufosi AO, Abayomi O, Ojo TM. Pyridoxal 5 phosphate for neuroleptic tardive dyskinesia. Cochrane Database Syst Rev. 2015 Apr 13;(4):CD010501

NAC

Berk M, Copolov D, Dean O, et al., N-acetyl cysteine as a glutathione precursor for schizophrenia – a DBRPC trial. Biol Psychiatry. 2008 Sep 1;64(5):361-8.

Conus P, Seidman LJ, Fournier M, et al., N-acetylcysteine in a DBRPC trial: toward biomarker-guided treatment in early psychosis. Schizophr Bull. 2018 Feb 15;44(2):317-327

Farokhnia M, Azarkolah A, Adinehfar F, et al., N-acetylcysteine as an adjunct to risperidone for treatment of negative symptoms in patients with schronic schizophrenia: a RDBPC study. Clin Neuropharmacol. 2013 Nov-Dec;36(6):185-92.

Rapado-Castro M, Dodd S, Bush AI, et al., Cognitive effects of adjunctive N-acetyl cysteine in psychosis. Psychol Med. 2017 Apr;47(5):866-876.

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.

Rossell SL, Francis PS, Galletly C, et al., N-aceylcysteine (NAC) in schizophrenia resistant to clozapine: a DBRPC trial targeting negative symptoms. BMC Psychiatry. 2016 Sep 15;16(1):320.

L-theanine

Kardashev A, Ratner Y, Ritsner MS. Add-on pregnenolone with L-theanine to antipsychotic therapy relieves negative and anxiety symptoms of schiozophrenia.
Clin Schizophr Relat Psychoses. Spring 2018;12(1):31-41.

Ota M, Wakabayashi C, Sato N, et al., Effect of L-theanine on glutamatergic function in patients with schizophrenia. Acta Neuropsychiatr. 2015 Oct;27(5):291-6.

Ritsner MS, Miodownik C, Ratner Y, et al., L-theanine relieves positive, activation and anxiety symptoms in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry. 2011 Jan;72(1):34-42.

CBD

Boggs DL, Surti T, Gupta A et al., The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. Psychopharmacology 2018 Jul;235(7):1923-1932.

Leweke FM, Piomelli D, Pahlisch F, et al., Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry. 2012 Mar 20;2:e94.

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

McGuire P, Robson P, Cubala WJ, et al., Cannabidiol (CBD) as an adjunctive therapy inn Schizophrenia: a multicenter randomized Controlled Trial. Am J Psychiatry. 2018 Mar

Mind Body Medicine and Schizophrenia

Aust J, Bradshaw T. Mindfulness interventions for psychosis: a systematic review of the literature. J Psychiatr Mental Health Nurs. 2017 Feb;24(1):69-83.

Helgason C, Sarris J. Mind-body medicine for schizophrenia and psychotic disorders: a review of the evidence. Clin Schizophr Relat Psychosis. 2013 Oct;7(3):138-48

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

Chengappa KNR, Brar JS, Gannon JM et al., Adjunctive Use of a Standardized Extract of Withania somnifera (Ashwagandha) to Treat Symptom Exacerbation in Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Study. J Clin Psychiatry 2018 Jul 10;79(5). pii: 17m11826.