Alcohol Use Disorder (AUD) and its Treatment with Medications and Nutrition

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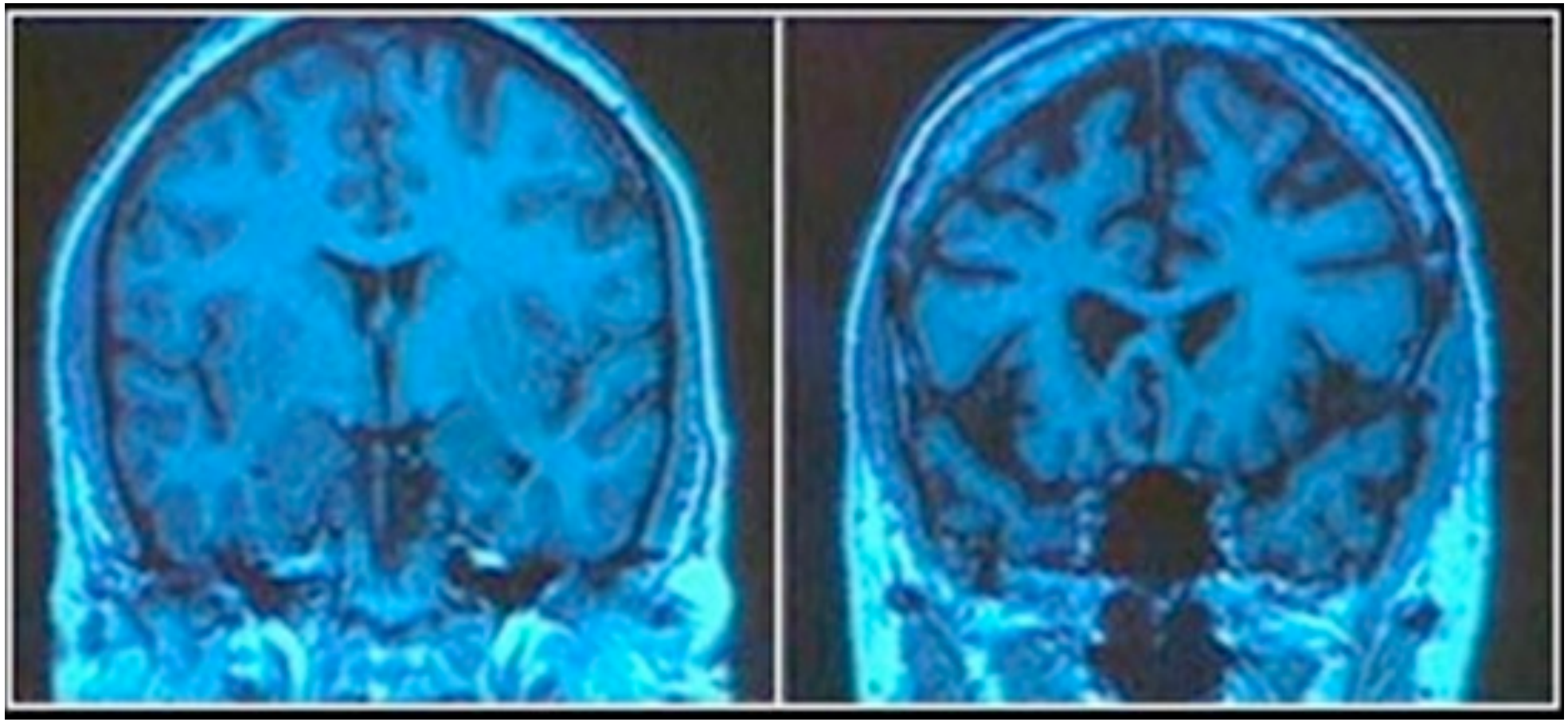
International Society of Substance Use Professionals (ISSUP)
Kenya Chapter
October 5, 2022, 6pm Nairobi

Outline:

- **Clear the Mind**
- **Cut the Craving**
- **Create a Culture**

MRI shows brain Atrophy with Alcohol Use Disorder

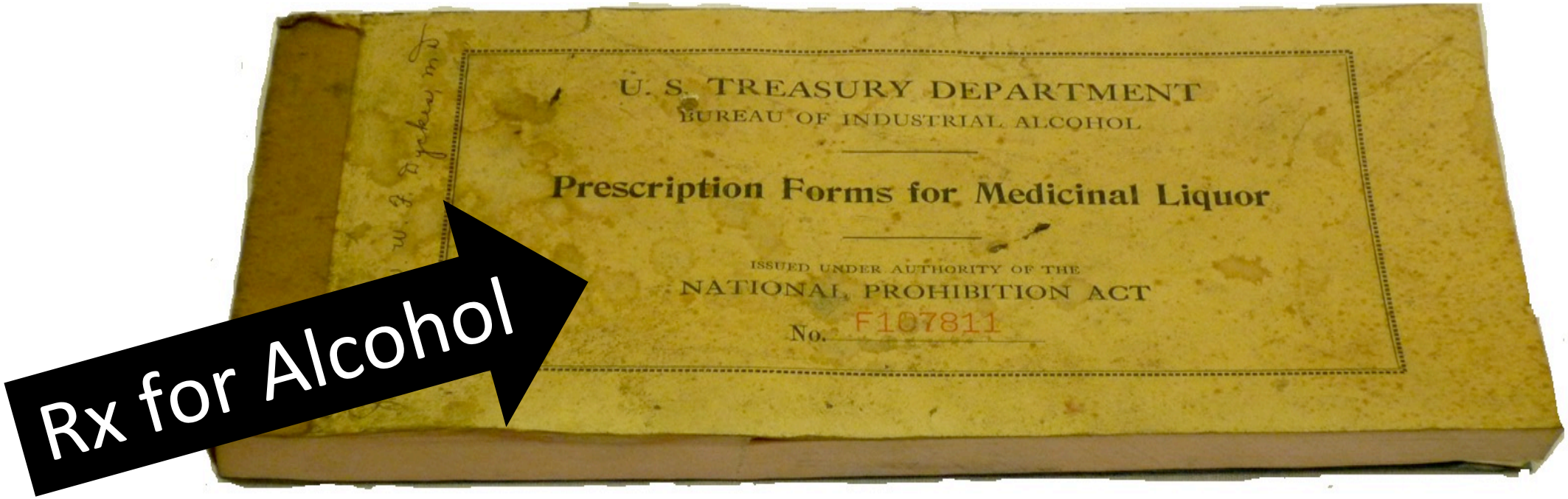


Healthy Brain vs. Impaired Brain

Jernigan TL, Ostergaard AL. When Alcoholism Affects Memory Functions: MRI of the Brain. Alcohol Health Res World. 1995;19(2):104-107.

Accessed from http://www.francoisguite.com/2007/05/les-effets-de-lalcool-sur-le-cerveau-images/

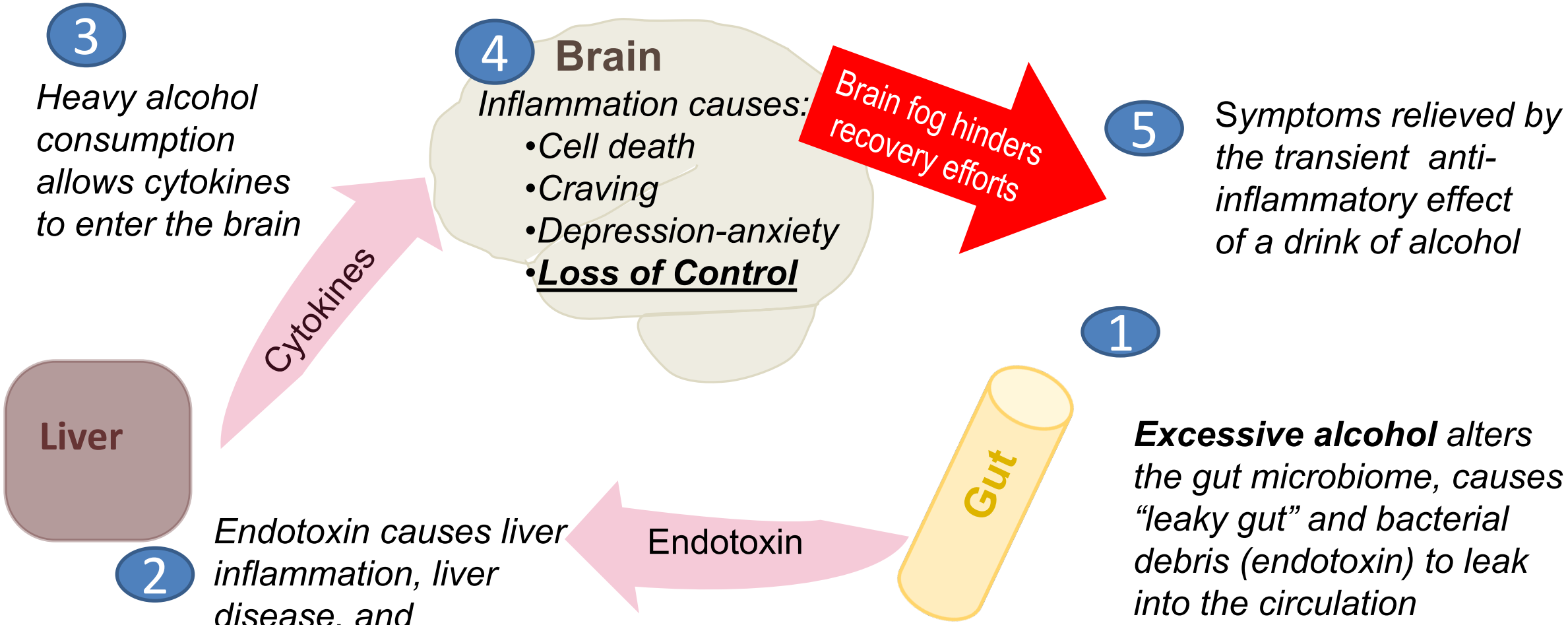
A prescription pad for alcohol –
Alcohol can be anti-inflammatory and reduce inflammatory cytokines



Inflammatory Cytokines Are Chemical Messengers of the "Sickness Response"

- Fever
- Fatigue
- Social withdrawal
- Malaise
- Appetite suppression
- Sleep disturbances
- Amplification of pain
- Irritability
- Decreased social interaction
- Reduced libido
- Increased anxiety
- Anhedonia
- Cognitive defects
- Dysphoria

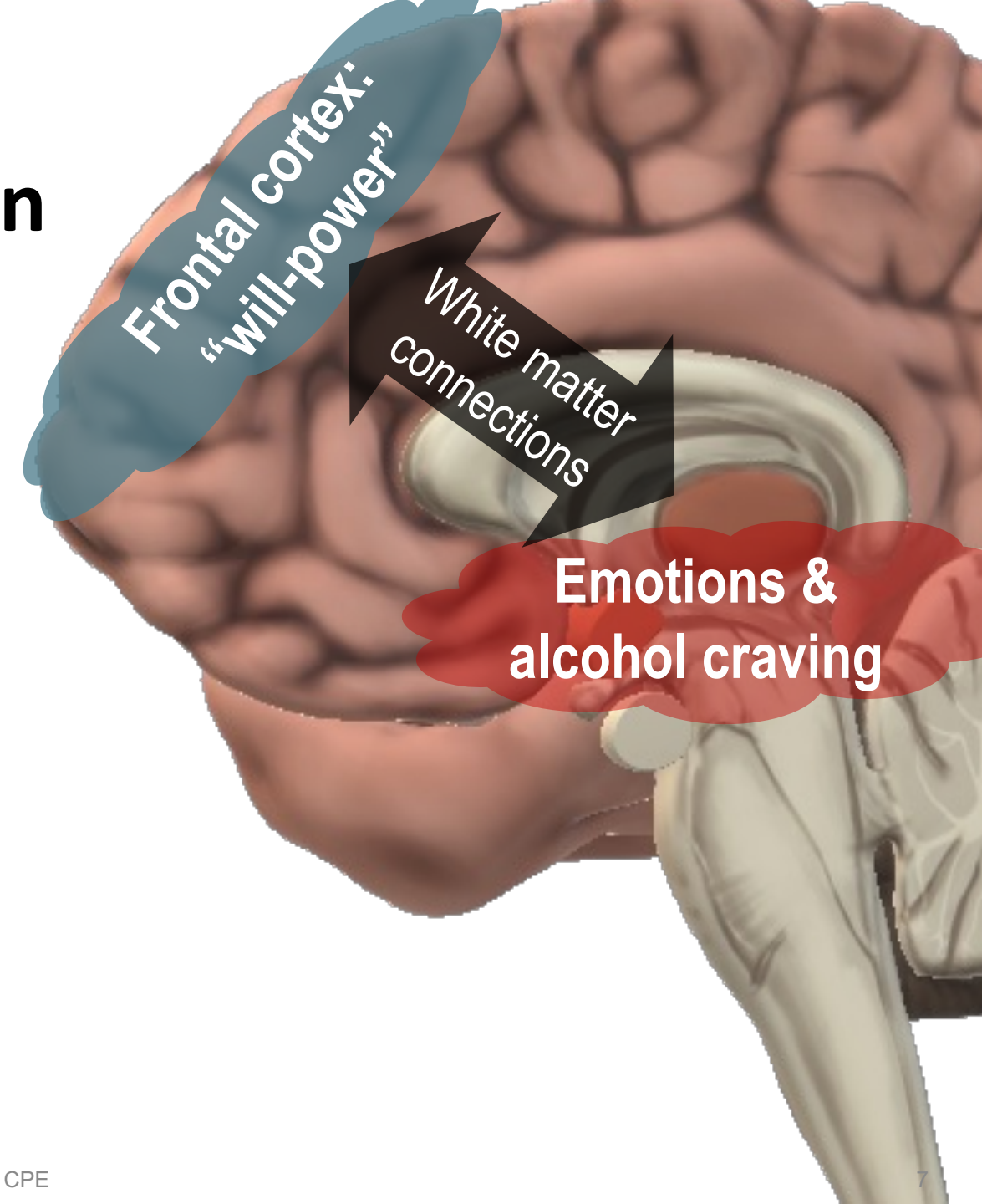
Inflammatory Cycle of Alcohol Use Disorder



Umhau, John C., et al. Alcoholism: Clinical and Experimental Research 38.5 (2014): 1301-1306.

Brain Inflammation Disrupts Brain Connections in Alcohol Use Disorder

- Frontal cortex action is degraded
- Brain areas “disconnected”
- Insight is limited
- Emotions poorly regulated
- Impulse control impaired
- Alcohol craving is unchecked



The Brain Can Recover!

- Brain volume is 2% **larger** 6 weeks after detox
- This increase in volume is white matter, nerve fibers connecting different parts of the brain
- Restored brain connections allow “will power” from the frontal cortex to overcome subconscious craving in lower brain

How can we maximize brain recovery?

Physical activity improves brain function:

Moderate physical activity* (30 minutes, 3 days /week):

- Reduces inflammation
- Reduces alcohol consumption, depression, and anxiety
- Increases healthy endorphins (brain opioids)

*Moderate physical activity = a pulse rate increase to 75% of someone's age-appropriate maximum heart rate

Georgakouli, Kalliopi, et al. "Exercise training reduces alcohol consumption but does not affect HPA-axis activity in heavy drinkers." *Physiology & behavior* 179 (2017): 276-283; Paolucci, E. M. et al. (2018).. Biological Psychology, 133, 79–84; Kandola, Aaron, et al. "Aerobic exercise as a tool to improve hippocampal plasticity and function in humans: practical implications for mental health treatment." *Frontiers in Human Neuroscience* 10 (2016): 373.

Nutrition improves brain function in AUD:

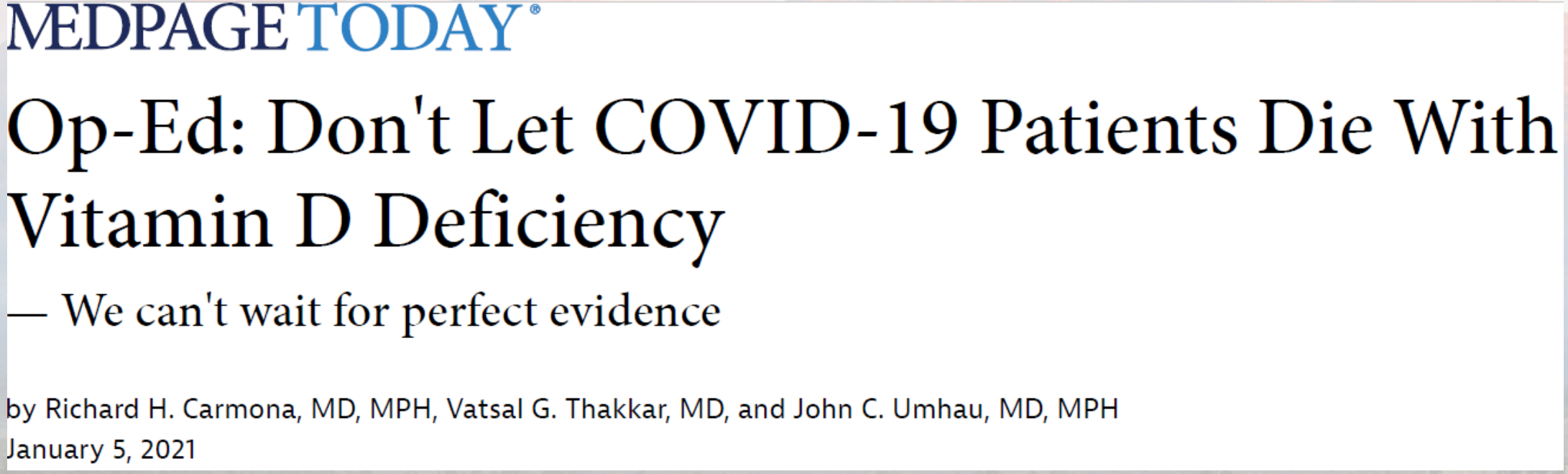
B Vitamins:

- Vitamin B1 (thiamin)
- Vitamin B2 (riboflavin)
- Vitamin B3 (niacin)
- Vitamin B5 (pantothenic acid)
- Vitamin B6 (pyridoxine)
- Vitamin B7 (biotin)
- Vitamin B9 (folate, **MTHF**)
- Vitamin B12 (cobalamin)

- **Omega-3 fats**
- Zinc
- Magnesium
- Calcium
- Probiotics (lactobacillus gg)
- Vitamin C
- Vitamin D (sunlight)

If dihydrofolate reductase (MTHFR) is deficient, MTHF may be critical!

Vitamin D deficiency damages the brain and the immune system



MEDPAGE TODAY®

Op-Ed: Don't Let COVID-19 Patients Die With Vitamin D Deficiency

— We can't wait for perfect evidence

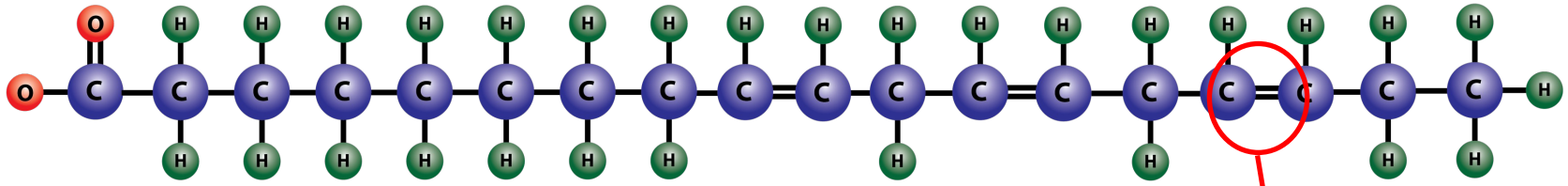
by Richard H. Carmona, MD, MPH, Vatsal G. Thakkar, MD, and John C. Umhau, MD, MPH
January 5, 2021

Kemény, Lajos V., et al. "Vitamin D deficiency exacerbates UV/endorphin and opioid addiction." Science Advances 7.24 (2021): eabe4577;Vitamindforall.org; also, Akbar, Mohammad Rizki, et al. "Low Serum 25-hydroxyvitamin D Level Is Associated With Susceptibility to COVID-19, Severity, and Mortality: A Systematic Review and Meta-Analysis." Frontiers in Nutrition 8 (2021): 131. Umhau, John C., et al. "Low vitamin D status and suicide: a case-control study of active duty military service members." PLoS One 8.1 (2013): e51543.

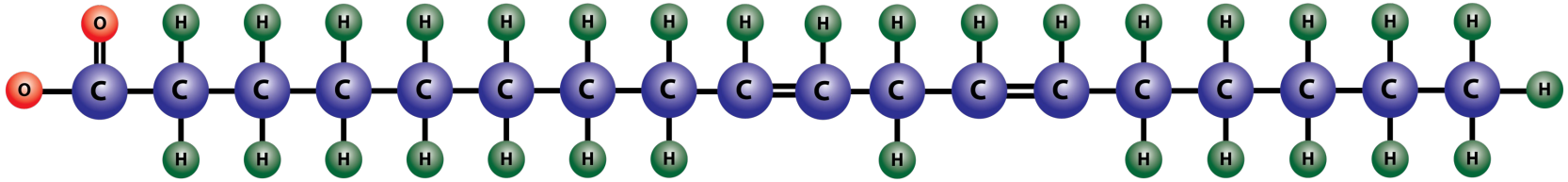
Omega-3 vs. Omega-6 Polyunsaturated Fat

- Like vitamins, these fats are essential
- Omega-6 fat cannot be converted to omega-3 fat
- Omega-3 & -6 fats have different effects on **inflammation**

Omega-3



Omega-6



Double bond at third carbon

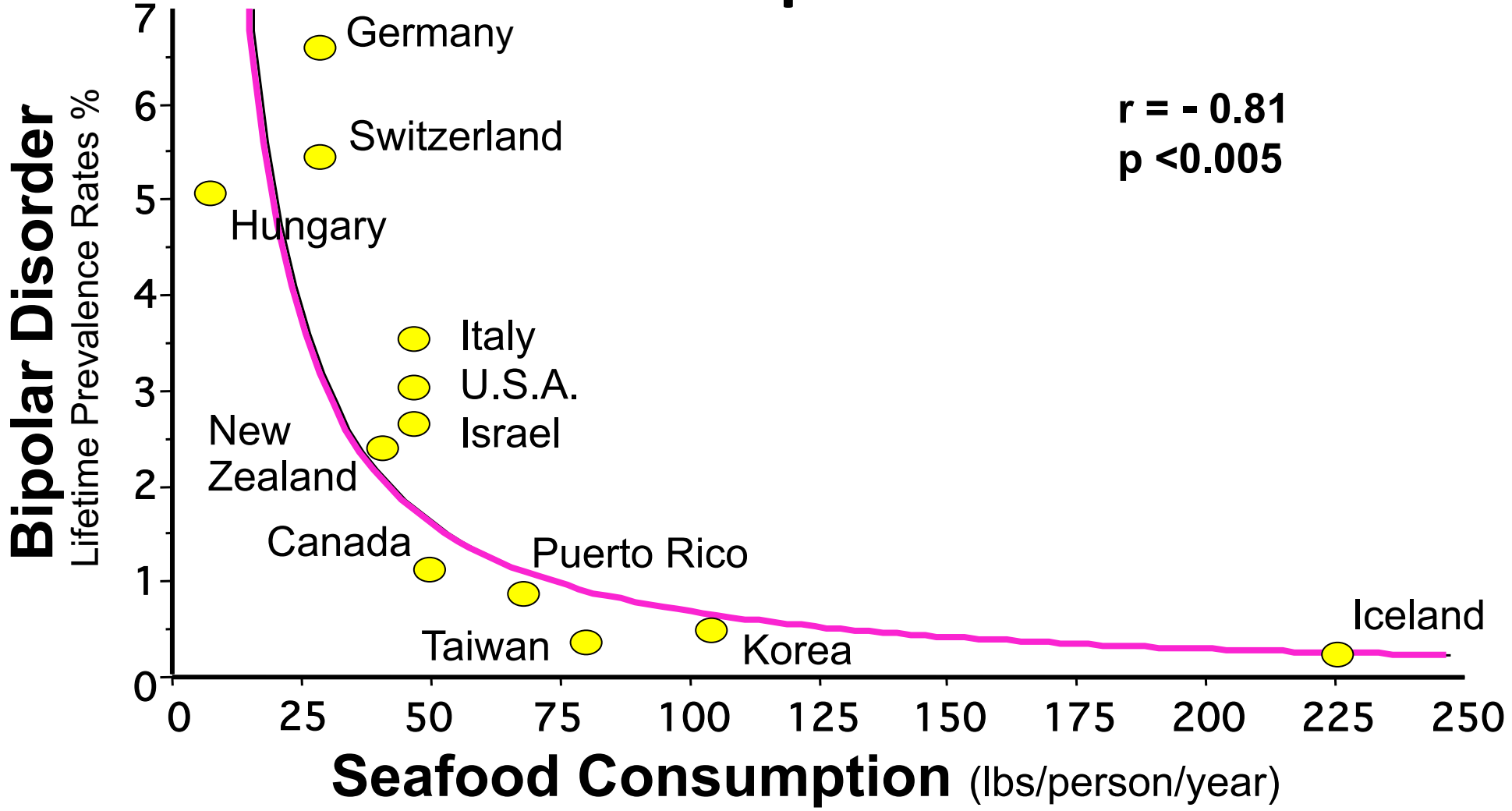
An Excessive Omega-6 Diet Overwhelms Omega-3

- **Omega-3** – "anti-inflammatory"
  (LIMITED: wild game, mother's milk, fish, leafy plants)
- **Omega-6** – "pro-inflammatory"
  (ABUNDANT: vegetable oil: soy, corn, peanut, etc.)

Saturated fat low in omega-6 is healthy
(Coconut oil, olive oil, grass fed lard & butter)

Umhau, John C., and Karl M. Dauphinais. "Omega-3 polyunsaturated fatty acids and health." *Low-Cost Approaches to Promote Physical and Mental Health*. Springer New York, 2007. 87-101.; Mori, Trevor A., and Lawrence J. Beilin. "Omega-3 fatty acids and inflammation." *Current atherosclerosis reports* 6.6 (2004): 461-467. Blasbalg, Tanya L., et al. "Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century." *The American journal of clinical nutrition* 93.5 (2011): 950-962. Ramsden, Christopher E., et al. *Bmj* 346 (2013): e8707.

Countries that eat less seafood have less omega-3 and more bipolar disorder



Noaghiul S, Hibbeln JR. Noaghiul, Simona, and Joseph R. Hibbeln. "Cross-national comparisons of seafood consumption and rates of bipolar disorders." American Journal of Psychiatry 160.12 (2003): 2222-2227.

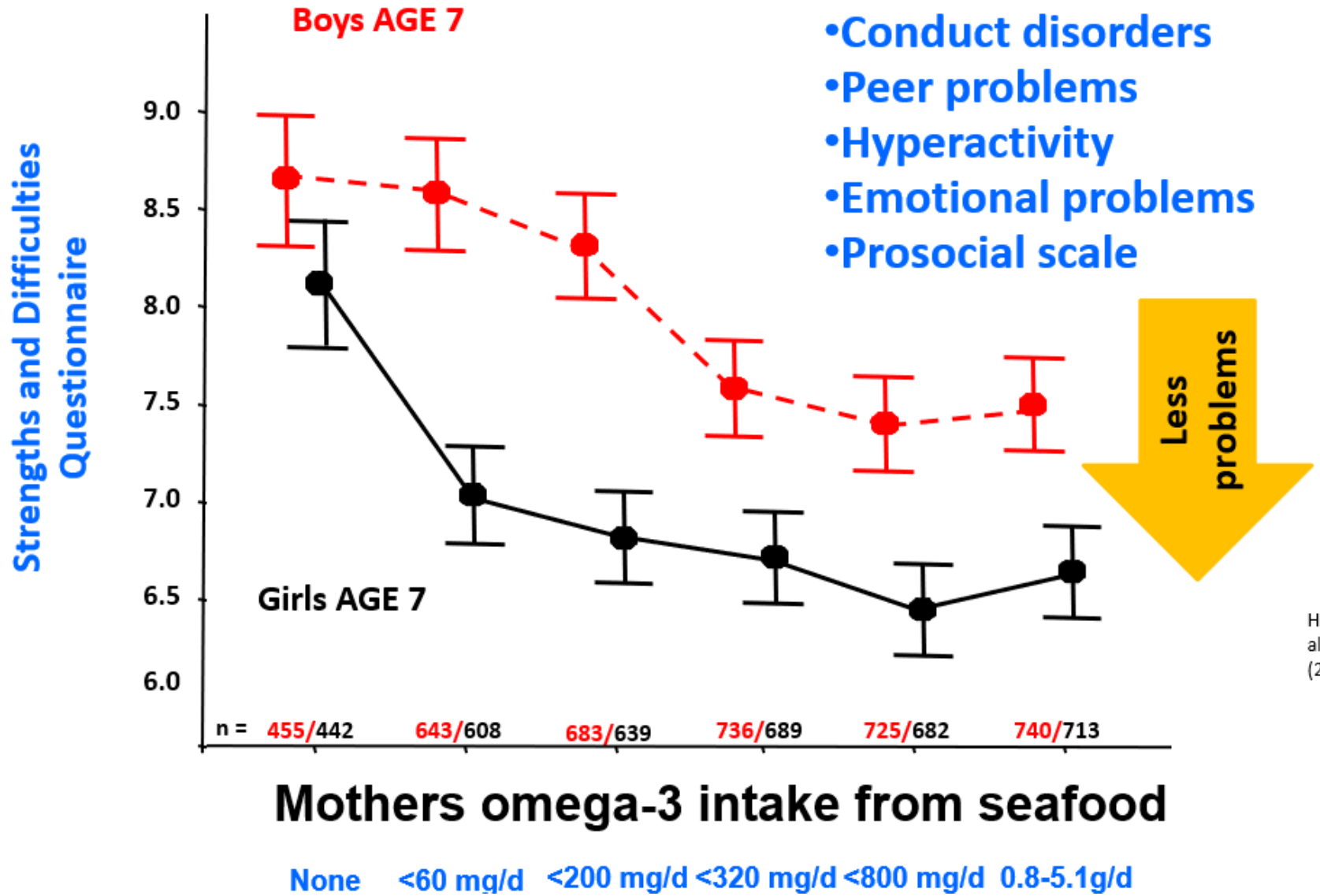
Avon Longitudinal Study of Parents and Children (ALSPAC)

- Every pregnancy for 21 months beginning in 1991 in Avon England was enrolled in the study - 14,000 births
- Women who ate no fish while pregnant had more depression and their 7 year old children had more behavioural problems
- Early deprivation of omega-3 fats could result in long lasting deficits in the brain

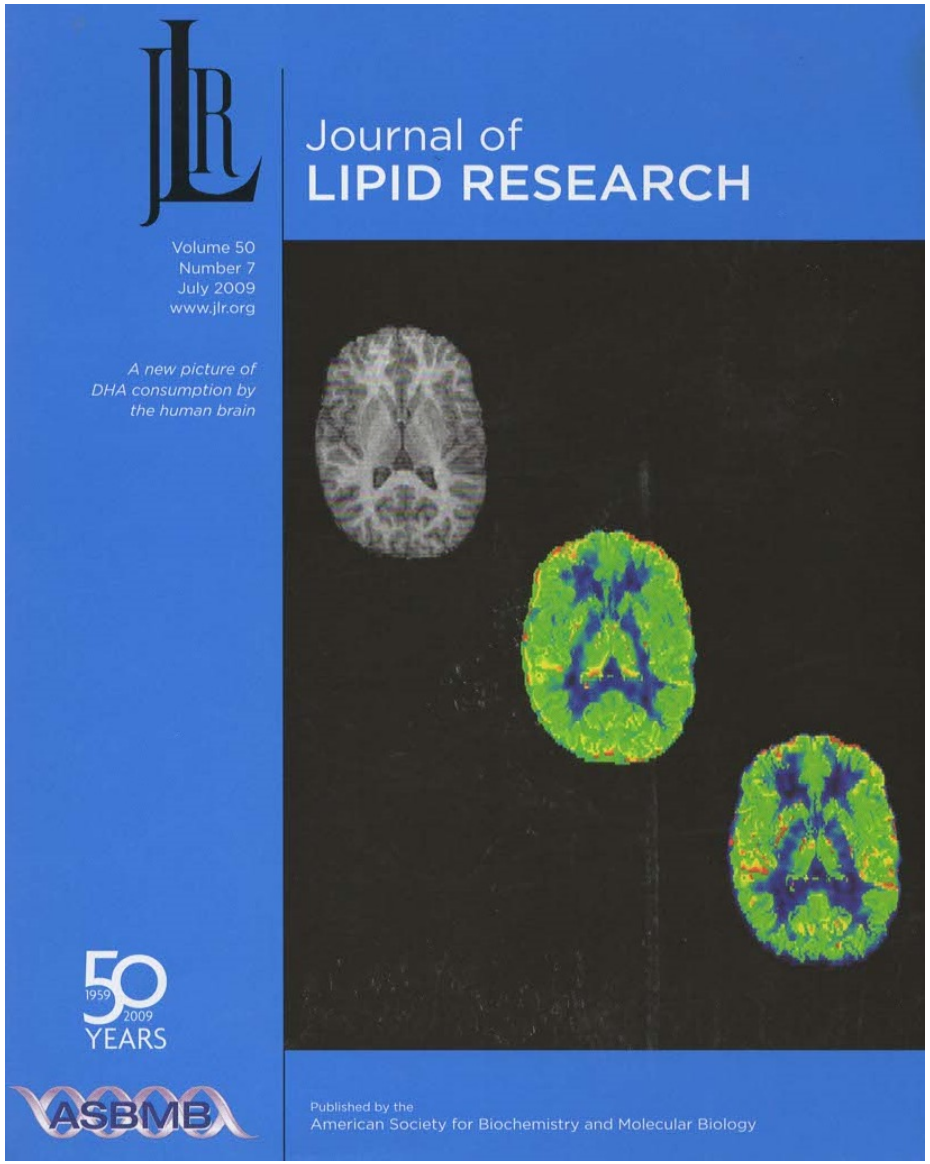
Hibbeln, Joseph R., et al. *The Lancet* 369.9561 (2007): 578-585

Children have less behavioural problems when pregnant mothers eat fish

Bad Behavior



Hibbeln, Joseph R., et al. *The Lancet* 369.9561 (2007): 578-585.

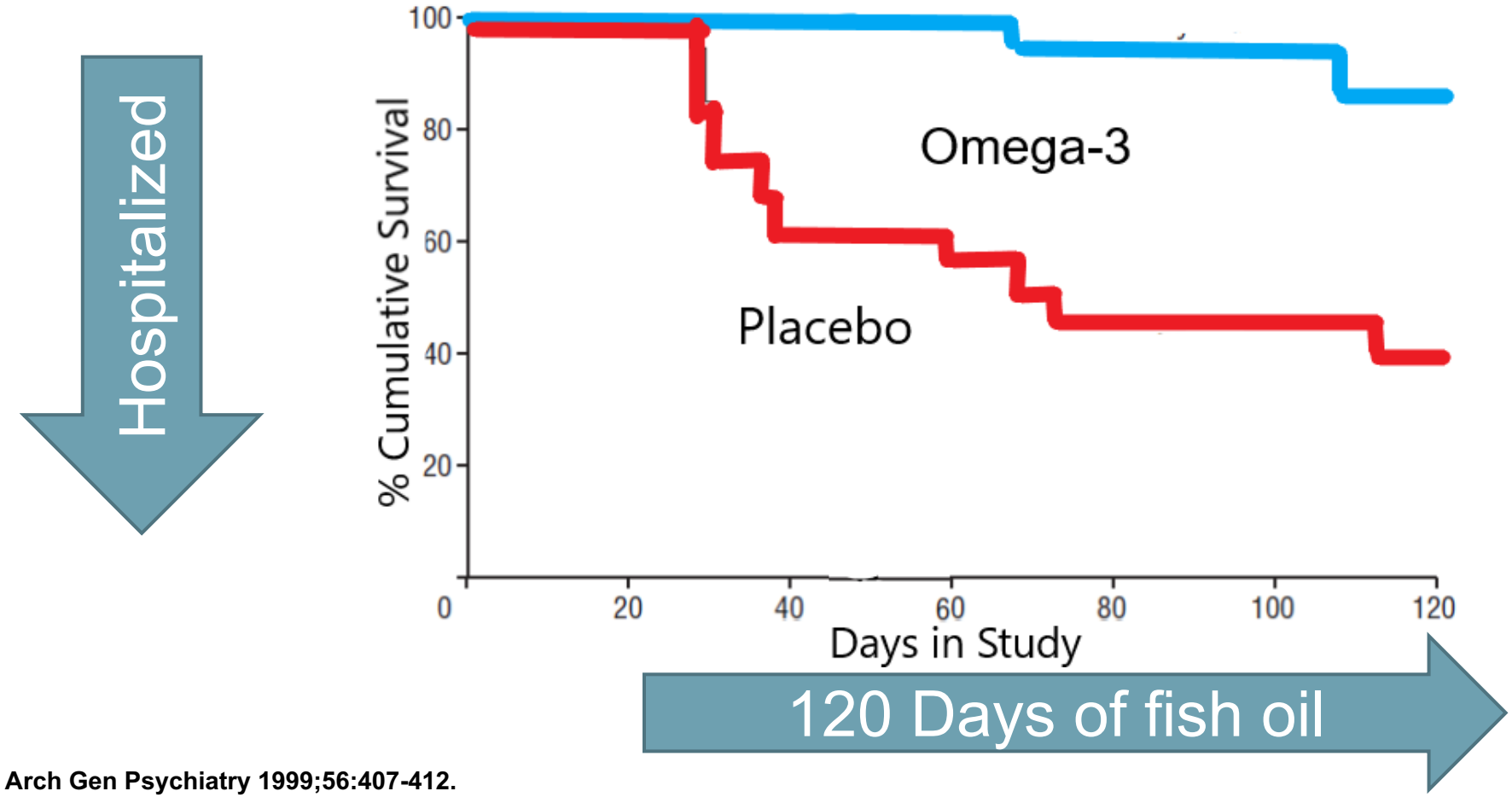


Alcohol Damaged Brain Connections Require Omega-3 (DHA) to heal

- The half-life of omega-3 stored in the brain is ~2.5 years
- Therefore, a high dose supplement may be very helpful

Umhau, John C., et al. "Brain docosahexaenoic acid [DHA] incorporation and blood flow are increased in chronic alcoholics: a positron emission tomography study corrected for cerebral atrophy." PloS one 8.10 (2013): e75333.

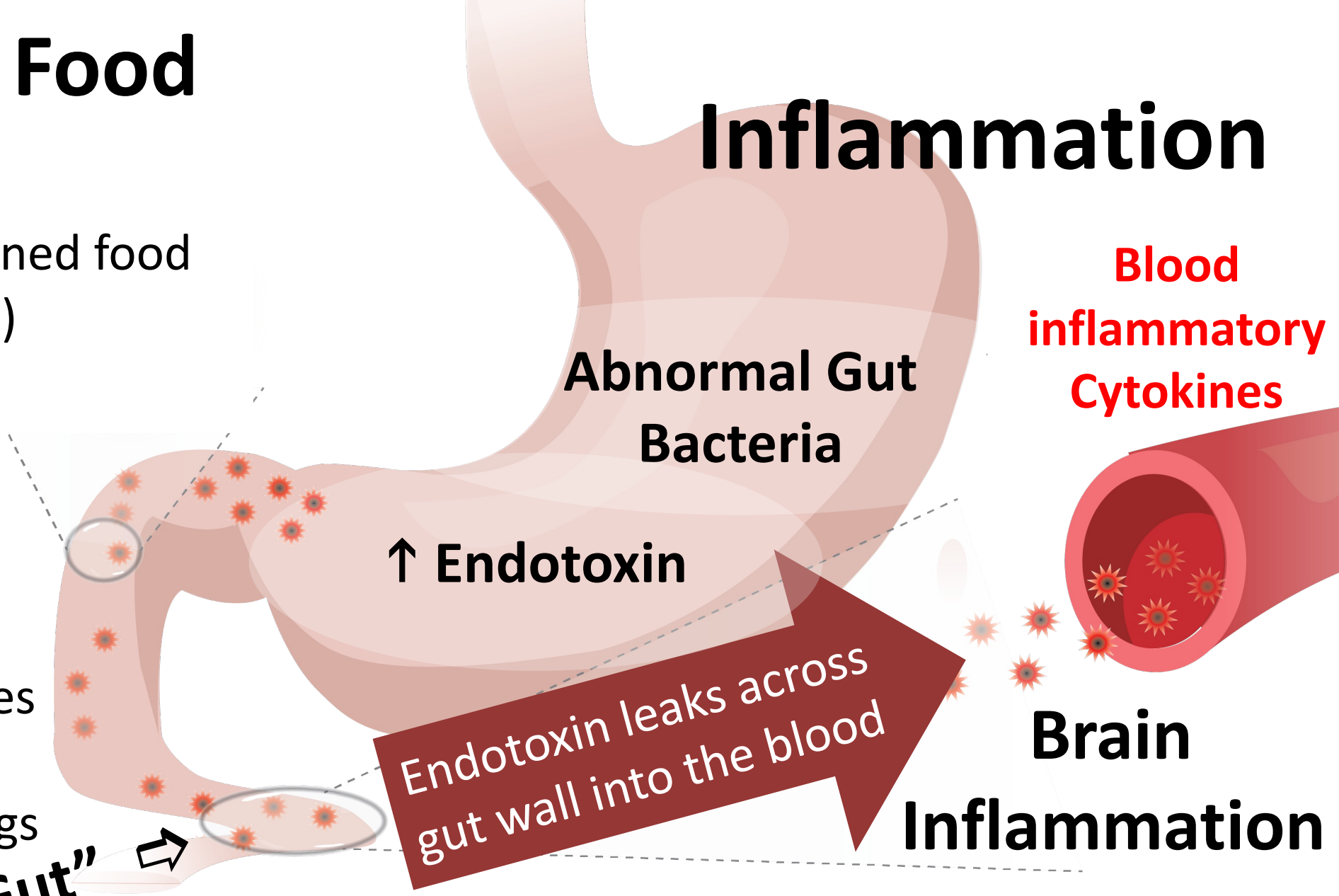
Omega-3 fat (14 capsules) 6.2g EPA + 3.4g DHA/day keeps bipolar patients from hospitalization



Stoll, A. L. et al. Arch Gen Psychiatry 1999;56:407-412.

Unhealthy Food

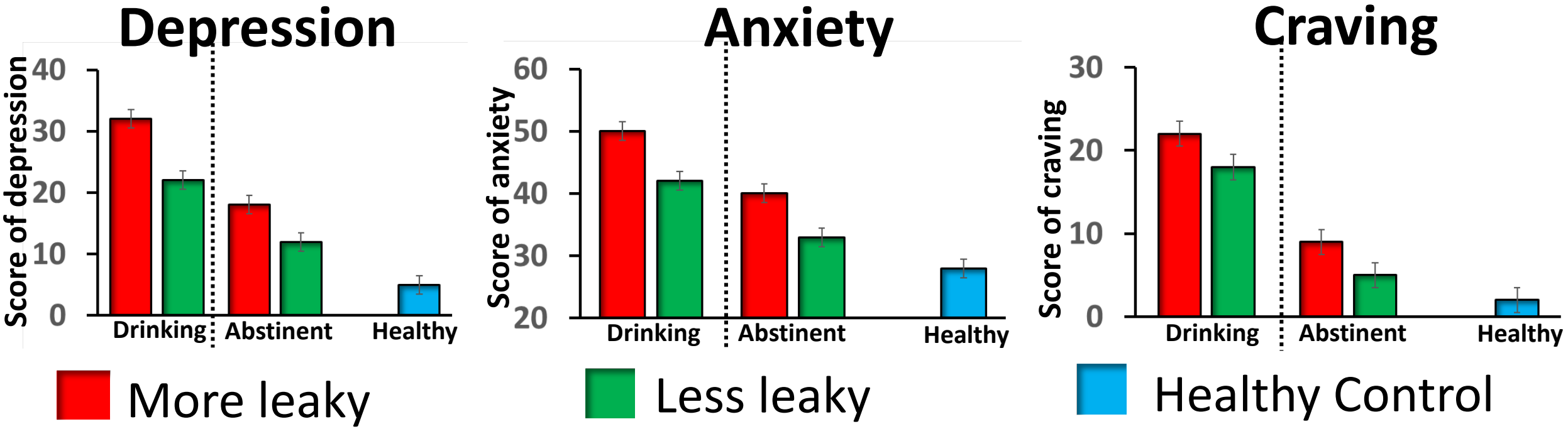
- ↑Alcohol
- ↑Processed /refined food
- ↑Fructose (HFCS)
- ↑Omega-6 fat
- ↓Omega-3 fat
- ↓Vitamins
- ↓Zinc
- Food additives
- Toxins / pesticides
- Glyphosate
- Antibiotics / drugs



“Leaky Gut” Drives Inflammation & Symptoms

Improves with 19 days of alcohol abstinence

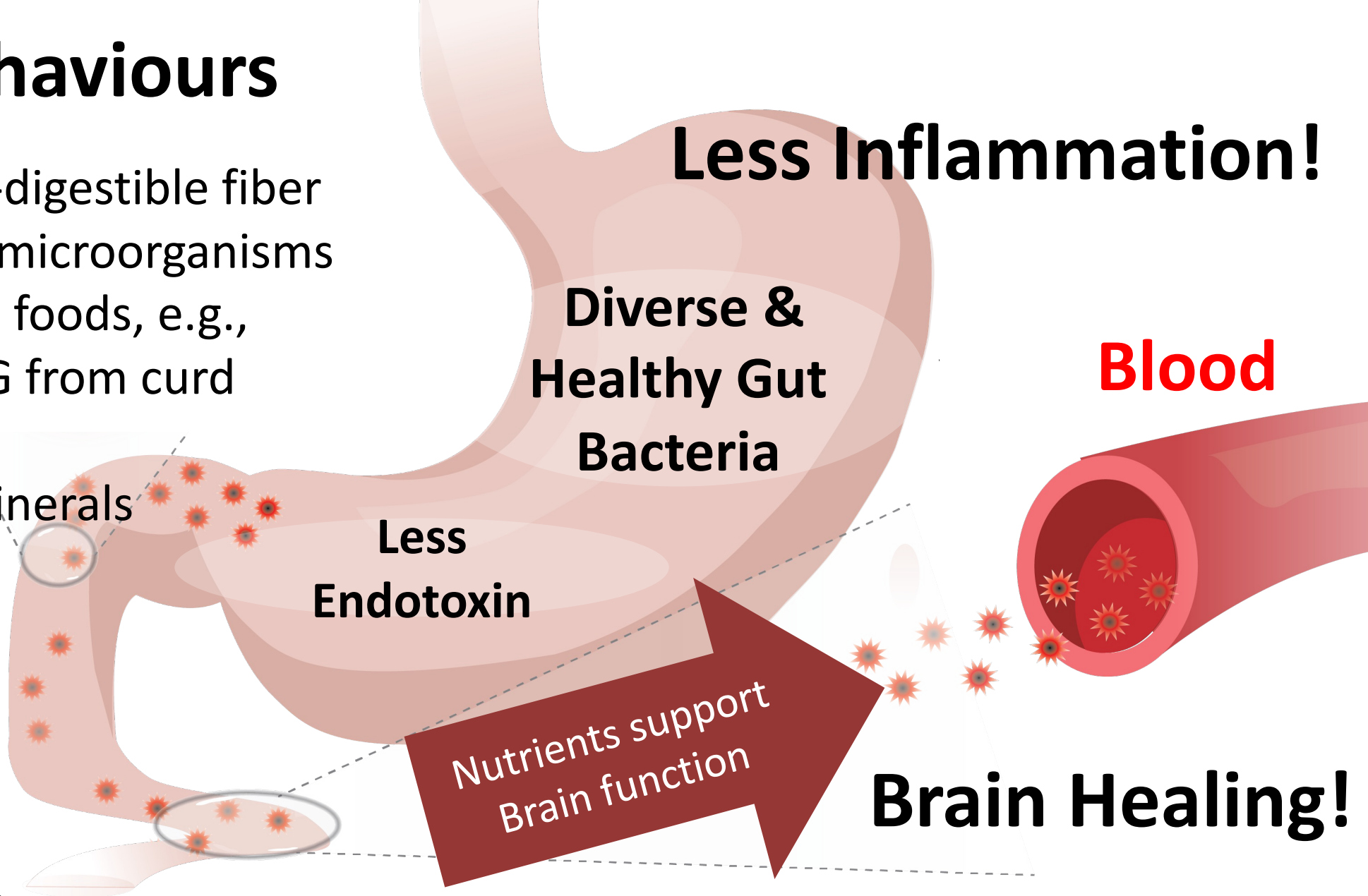
Diet Induced Leaky Gut → Endotoxin → Inflammation → Craving, etc.



Leclercq, Sophie, et al. Proceedings of the National Academy of Sciences 111.42 (2014): E4485-E4493.

Healthy Behaviours

- Prebiotics: Non-digestible fiber
- Probiotics: Live microorganisms from fermented foods, e.g., Lactobacillus GG from curd
- Physical activity
- ↑ Vitamins & minerals
- ↑ Omega-3 fat
- ↑ Minerals
- Zinc
- **Coffee!**



No Leaky Gut

Outline:

- Clear the Mind
- **Cut the Craving**
- Create a Culture

Medicines For AUD Are Underused

Approved by FDA

- Disulfiram
- Acamprosate
- Oral Naltrexone
- Injectable Naltrexone

Used “off-label”:

- Ondansetron
- Topiramate
- Baclofen
- Prazosin
- Gabapentin, etc.

A patient wrote:

“I have been on Naltrexone for about 2 weeks and what a difference!!!

The cravings have reduced, and my intake has dropped, my outlook is higher and I finally feel I can beat this.

I feel as if I have been released from prison.”

Naltrexone

- Naltrexone blocks the euphoric effects - the “buzz” - from alcohol caused by endorphins (natural brain opiates)
- It is NOT an opioid and does not cause addiction
- Blocks opioid pain medications and can cause withdrawal symptoms in people with habitual use
- Side effects: headache, nausea, anxiety, dizziness, depression, liver enzyme elevations and the “*blahs*”
- Typical dose is 50 mg with 25 mg to start
- Sometimes heavy daily drinkers start with smaller split doses

Injectable Naltrexone

- Long-acting intramuscular injection naltrexone is given every 4 weeks – Expensive!
- Very helpful if compliance is an issue
- Some people need a higher dose than others

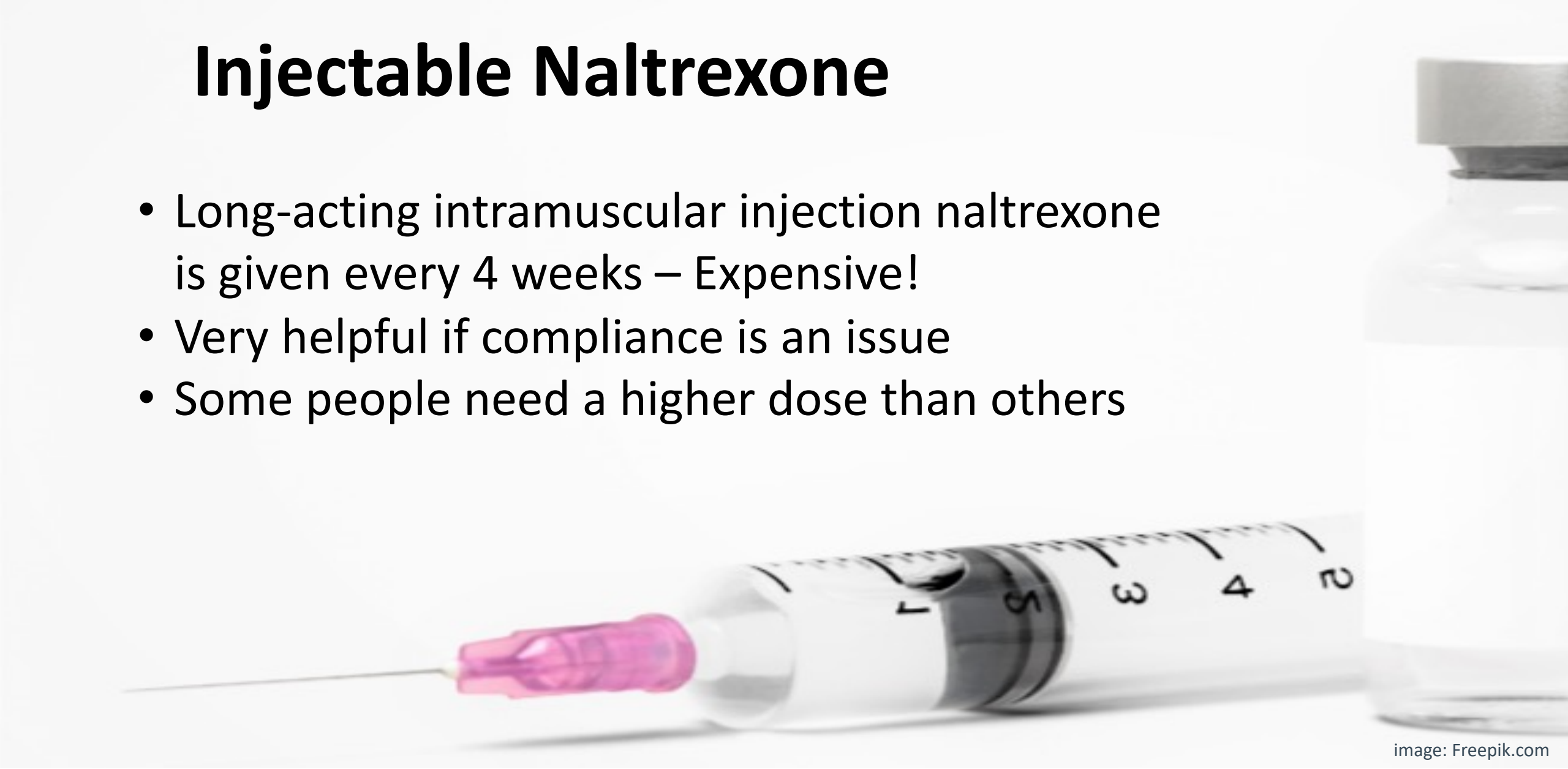


image: Freepik.com

David Sinclair, PhD studied rats trained to drink alcohol

- The longer alcohol-drinking animals were alcohol deprived, the more they pressed a lever to get it
- Repeated periods of sudden abstinence from alcohol increase the reinforcement of alcohol cravings in the brain
- Sinclair reasoned this “alcohol deprivation effect” explained the experience of increased craving the longer some people abstain from drinking alcohol

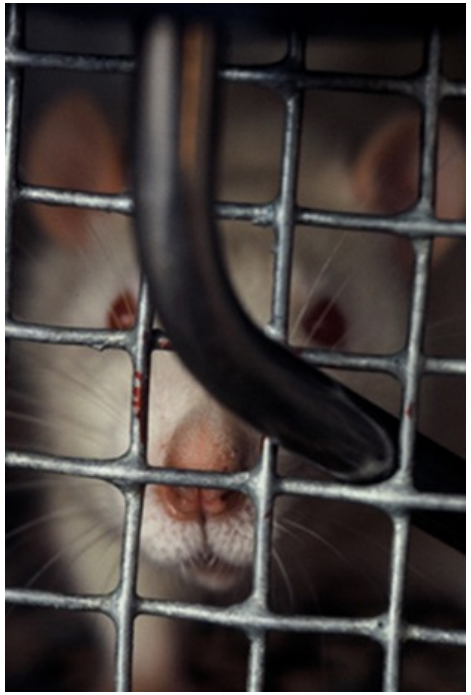


Photo courtesy of Dr. Bruce Alexander

Rodd, Z.A. et al. *Neuropsychopharmacology* (2003) **28,** 1614–1621, advance online publication, 11 June 2003; doi:10.1038/sj.npp.1300214

The Sinclair Method (TSM) targets naltrexone use before alcohol consumption

- When naltrexone blocked rat opiate receptors, alcohol's effect to reinforce behavior was blocked
- Sinclair found that rats trained to drink alcohol would unlearn or "extinguish" their drinking behavior if alcohol was ***always*** preceded by naltrexone
- Sinclair postulated that using naltrexone only before drinking would "rewire" the brain and eliminate alcoholism

Sinclair studied targeted naltrexone for AUD

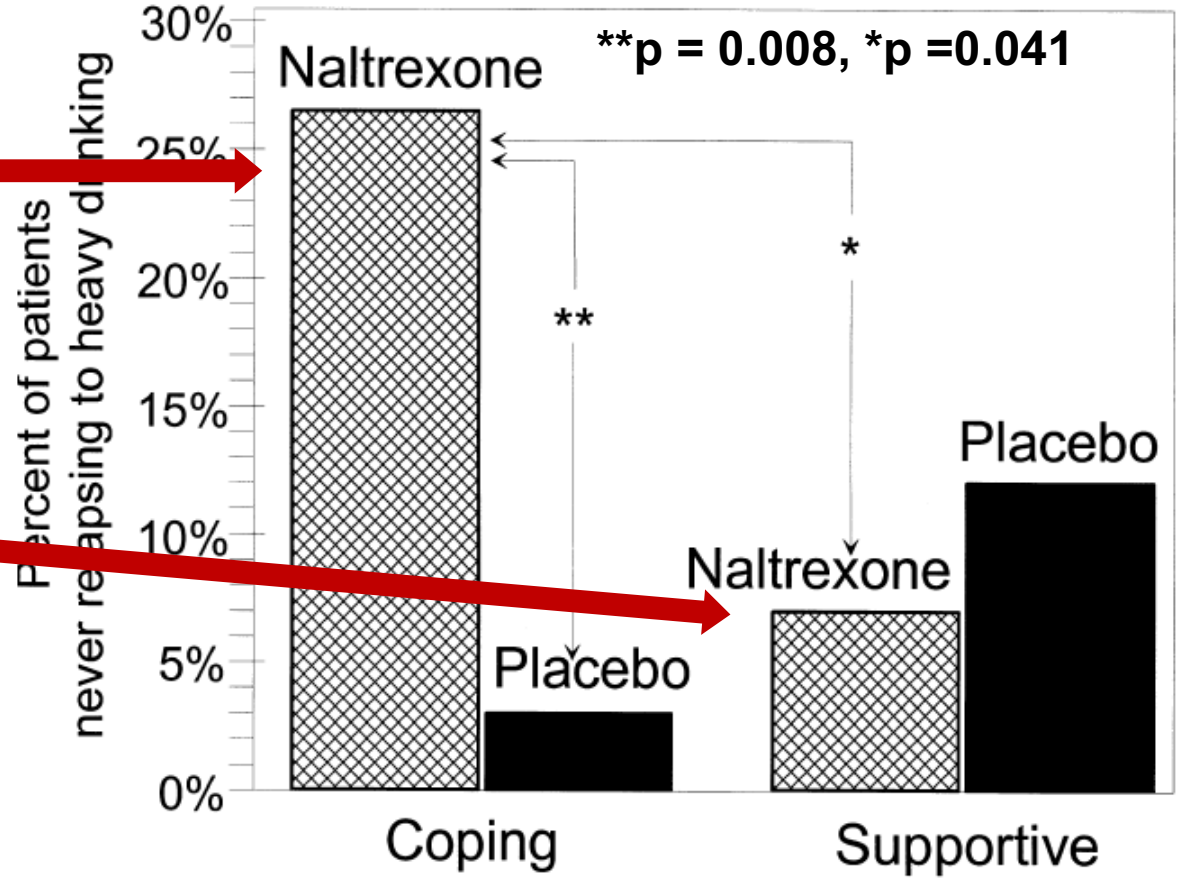
- Sinclair's research found that when people always took naltrexone an hour before drinking, after 3-12+ months ~78% would "extinguish" or lose the desire for alcohol
- Sinclair encouraged no naltrexone on non-drinking days -
  - Since opiate receptors are sensitized on non-naltrexone days, healthy endorphin producing behaviors could be reinforced
- Sinclair called the process of replacing drinking behavior with healthy behavior using naltrexone "pharmacological extinction"

David Sinclair. "Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism." Alcohol and Alcoholism 36.1 (2001): 2-10.

How Should Patients Use Naltrexone?

Patients taught how to ***"cope" with drinking*** relapsed less

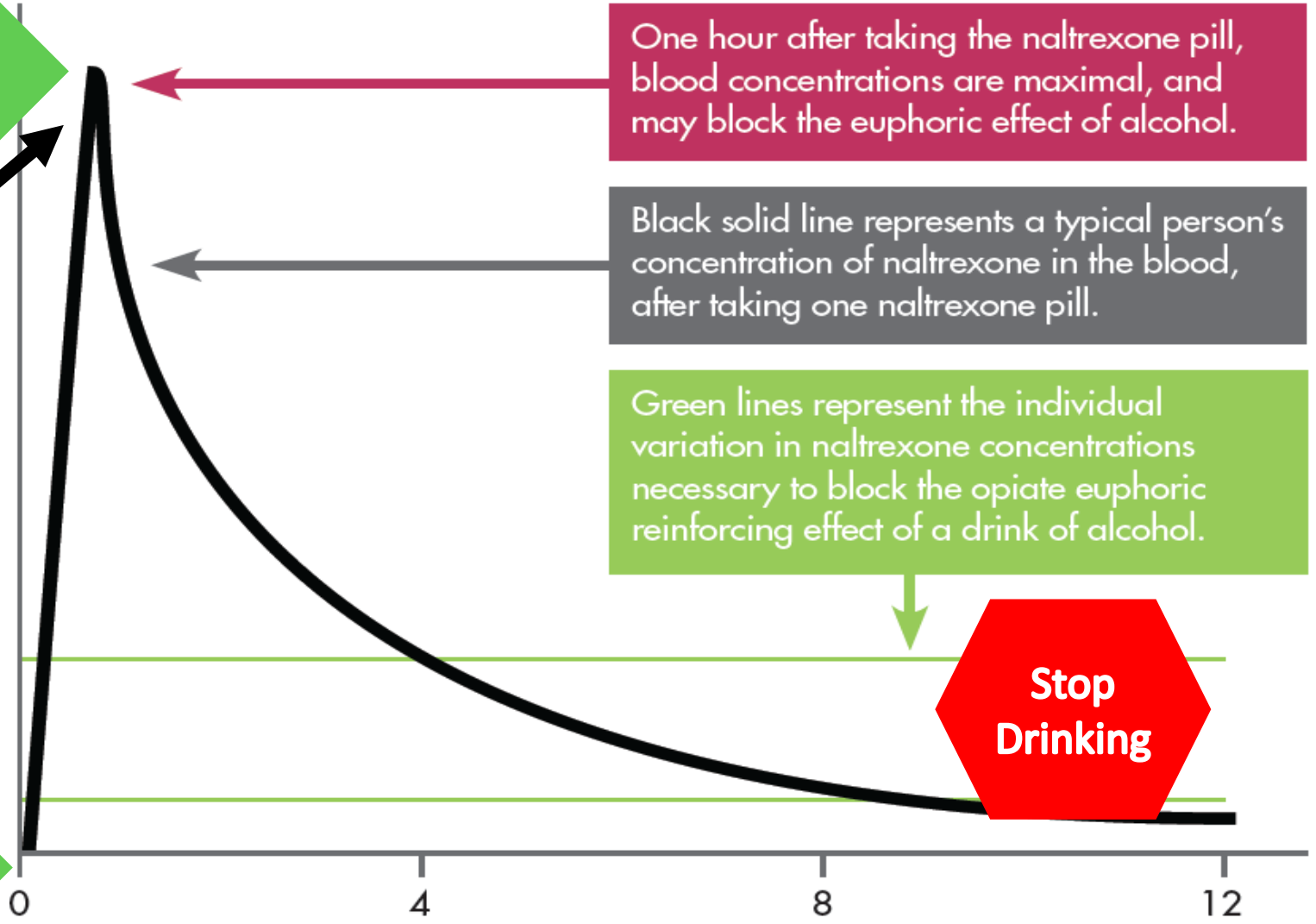
Patients told they ***must stop drinking*** - "support" relapsed **more!**



Heinälä, Pekka, et al. "Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial." Journal of clinical psychopharmacology 21.3 (2001): 287-292.

First drink occurs

Sufficient naltrexone blood level to block any alcohol reinforcement



Naltrexone blood level

Take naltrexone

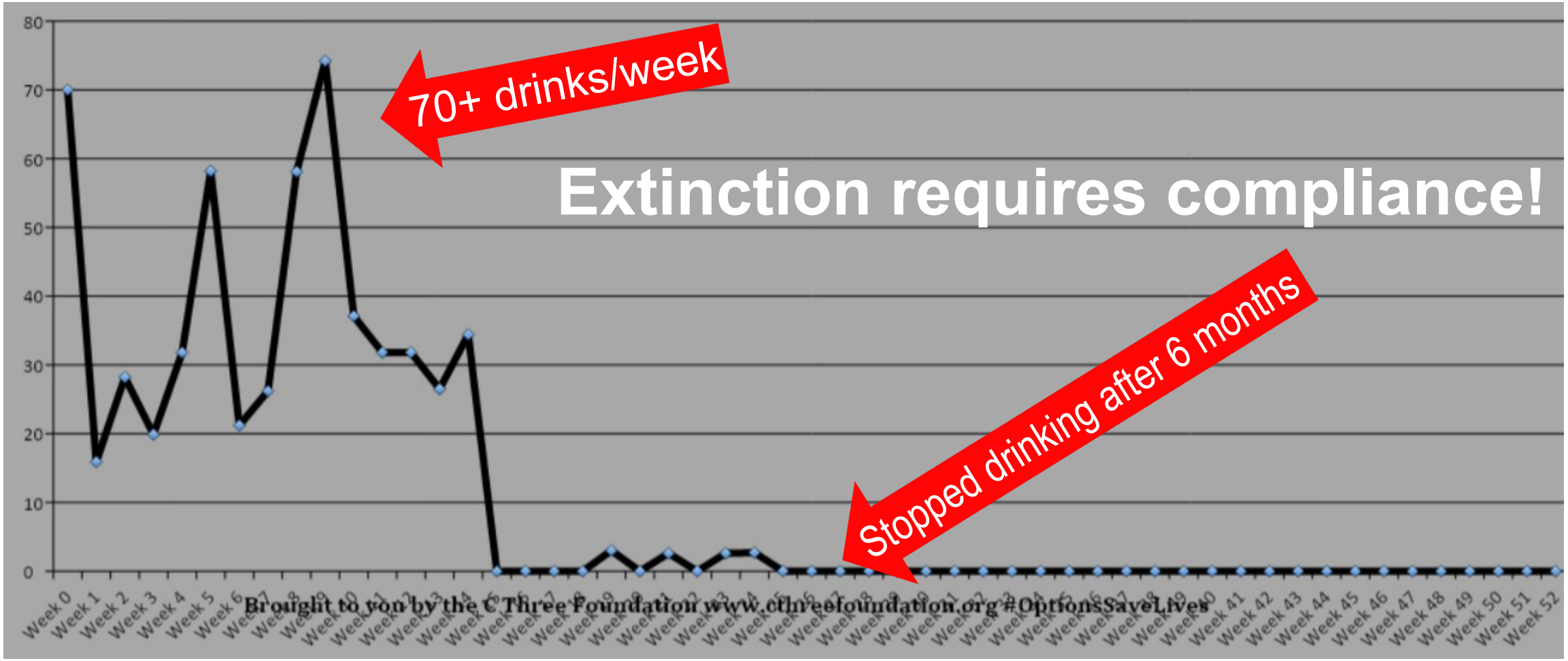
Umhau, John C. "Therapeutic Drug Monitoring and the Clinical Significance of Naltrexone Blood Levels at the Time of a First Drink: Relevance to the Sinclair Method." Alcohol and Alcoholism 54.2 (2019): 192-192.

Why does The Sinclair Method fail?

- Lack of support for the program
- Prolonged or rapid drinking overcomes “naltrexone wall”
- Forgetting or running out of naltrexone
- Naltrexone not tolerated
- If someone is poorly compliant, super-sensitized endorphins may increase consumption
- Social pressure / nostalgia for drinking / emotional suffering
- Not integrated with 12-step or other recovery programs

Umhau, John C. "Conquering the Craving: Treatment to Curb Alcohol Use Disorder." Journal of Christian Nursing 36.3 (2019): 148-156.

C-3 Weekly Drink Log Shows 52 Weeks of Naltrexone effect



https://cthreefoundation.org/resources/drink-log

Possible benefits of The Sinclair Method

- Alcohol craving may be permanently eliminated
- Patient-centered treatment
- Those who reject abstinence can be engaged in treatment
- Gradual reduction of drinking reduces the risk of DT’s
- Fewer adverse effects than with daily use
- Inpatient detox and treatment may be avoided
- Lower cost than inpatient treatment

Possible harms of The Sinclair Method

- Medication only treatment may reduce the potential for personal growth and long-term recovery following 12-step principles
- Naltrexone use may give false confidence that drinking is safe
- Patients may keep drinking even if they could choose to abstain because drinking is sanctioned by their health care provider
- Inconsistent, non-compliant use might increase consumption
- Naltrexone may further impair coordination if driving intoxicated

Acamprosate

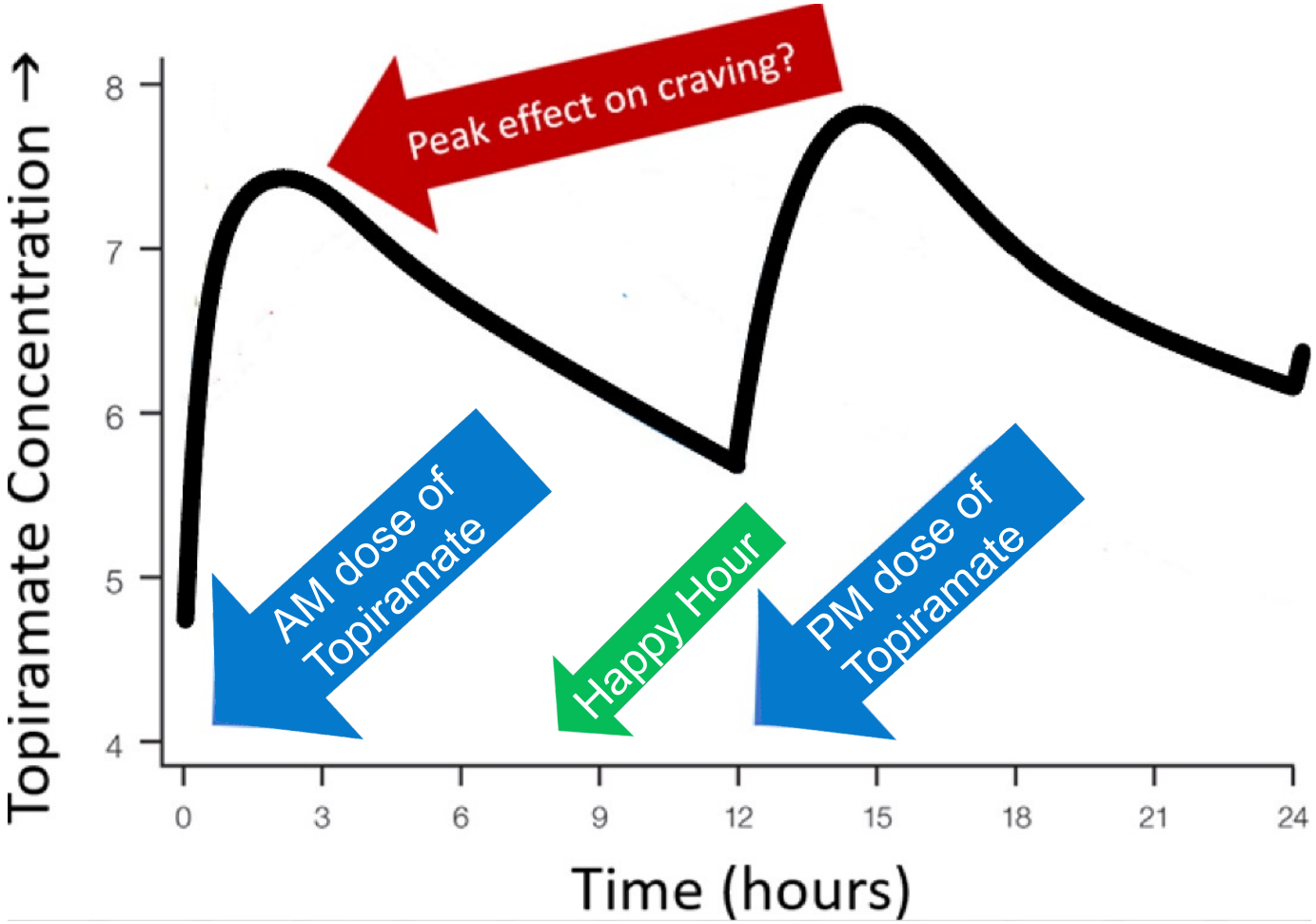
- FDA approved to promote abstinence
- Acamprosate taken three times daily reduces persistent symptoms which accompany abstinence such as insomnia, anxiety, restlessness
- Side effects: diarrhea, nausea, gout, edema
- Safe to use in people with liver inflammation
- Dose is 333mg to 666mg TID, lower if kidney issues

Off-Label: Topiramate

- FDA approved for epilepsy and migraines
- Dose is gradually increased over many weeks.
- Side effects: difficulty concentrating, tingling, taste perversions, infections, diarrhea, anorexia, nausea, memory problems, glaucoma (eye pain) … and sometimes intoxication is ***exaggerated.***
- Topiramate should be discontinued *slowly*
- Dose is less than 300mg daily

Roila, Fausto, and Albano Del Favero. Clinical pharmacokinetics 29.2 (1995): 95-109. Johnson, Bankole A., et al. "Oral topiramate for treatment of alcohol dependence: a randomised controlled trial." The Lancet 361.9370 (2003): 1677-1685.

Timing the Topiramate Dose may be Critical



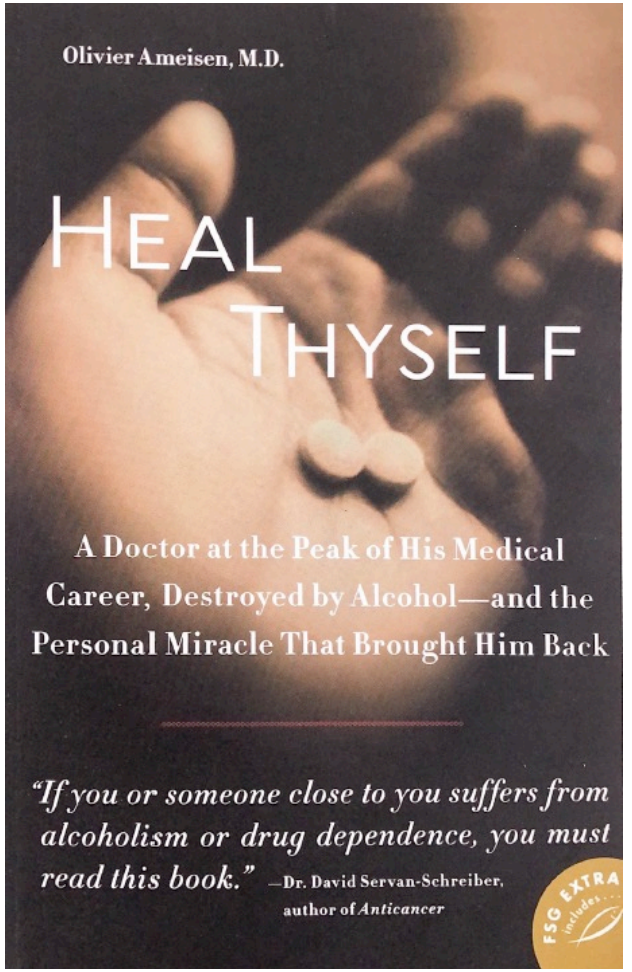
Topiramate peaks ~1.5 hours after taking a dose; Should it be targeted?

~ 5 days of daily dosing required to reach a stable level

Gidal, Barry E., et al. Epilepsy research 129 (2017): 26-32.

Off-label: Baclofen

- FDA approved as a muscle relaxant
- Dr. Olivier Ameisen was a brilliant cardiologist who developed severe AUD which failed all known treatment
- Ameisen thought suppression of symptoms (craving) should suppress his disease
- He experimented on himself using increasing doses of baclofen until he was free of craving & “indifferent” to alcohol
- Side effects common at increasing doses



AUD Baclofen Dosage is Not Established

- Daily dose increased slowly 5mg TID - paused for side effects
- Reduces alcohol withdrawal symptoms
- Works well in anxious patients (Can it be targeted?)
- Side effects are common: sedation, headache, vertigo, confusion, perspiration, muscle stiffness and/or abnormal movements, slurred speech, numbness
- Safe for patients with liver damage
- *Baclofen must be tapered off slowly to avoid seizures*

Off-Label: Ondansetron

- FDA approved at 4-8 mg for nausea
- Works only in people with certain genetics for early onset alcoholism
- The small dose required is only available as a solution or specially compounded
- Side effects: rare - headache, interacts with SSRI antidepressants

Roila, Fausto, and Albano Del Favero. Clinical pharmacokinetics 29.2 (1995): 95-109.

Ondansetron – Only a small dose is effective!

- Only ~0.4 mcg/kg is used for AUD, less than for nausea
- Give a starting dose of ~ 5 drops BID for 7 days, then give more to determine the best response (More **is not** necessarily better!)
- Ondansetron reaches the peak concentration in ~2 hours
- Should it be targeted?

Off-Label: Prazosin

- FDA approved for treatment of hypertension; used “off label” for PTSD hyper-arousal
- May work best on people with:
  - Hypertension
  - Withdrawal symptoms, e.g., shakes, craving, anxiety, and difficulty sleeping
- Start with 0.1 mg at night and increase over 2 weeks
- Side effects: low blood pressure, fainting when standing suddenly

Sinha, Rajita, et al. "Moderation of prazosin’s efficacy by alcohol withdrawal symptoms." American Journal of Psychiatry 178.5 (2021): 447-458.

Off-Label: Gabapentin

- FDA approved for epilepsy and neuropathic pain
- Frequently used “off label” for alcoholism and other drugs of abuse
- Can be addictive so may be more difficult to use without long term complications
- Side effects: dizziness, drowsiness, edema, mood changes, loss of memory, sexual dysfunction, ataxia, depression, liver problems, slurred speech

Anton, Raymond F., et al. The American journal of psychiatry 168.7 (2011): 709.

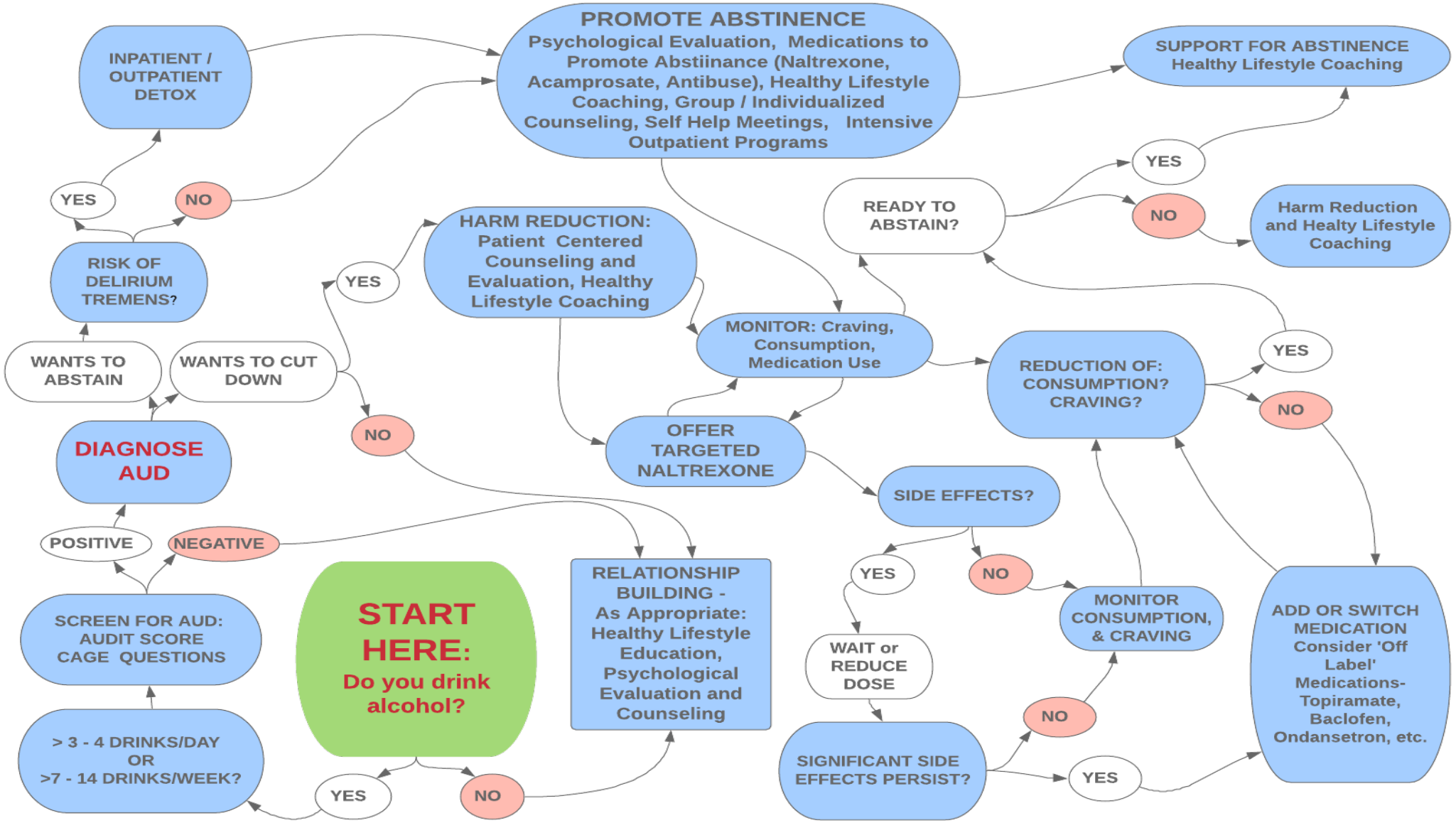
Which medication for which patient?

- Wants to stay abstinent – acamprosate, disulfiram
- Not willing to quit – targeted naltrexone
- Heavy daily drinker– naltrexone, ondansetron, topiramate
- Genetics for early onset alcoholism - ondansetron
- Liver damage – baclofen, acamprosate (not naltrexone)
- Hypertensive or withdrawal symptoms – prazosin
- Non-compliant - naltrexone injection
- Addiction unlikely to develop - gabapentin

Mason, Barbara J., and Charles J. Heyser. "Alcohol Use Disorder: The Role of Medication in Recovery." Alcohol 41.1 (2021).

Medication and typical dose	Kenyan Pricing/USA $ (Kenyan Sh 120 =$1 US)
Naltrexone: 50 mg; (Titrate from low dose); 25-100mg/day or targeted as need	K Sh 250; X 30 days: K Sh 7,500 = $ 62.50
Ondansetron 4 mg/5 mL; 0.24-0.5ml BID (~4mcg/kg)	30ml bottle for K Sh. 515/$4.30
Topiramate 25 mg; Titrate slowly as needed; 25 to 300mg / day BID	Sh 30/$.25/tablet
Baclofen 5 mg – Titrate as tolerated to: 30mg+/day, BID-TID and as needed	Sh 15/$.125/tablet
Prazosin 1mg – Titrate as tolerated to: 4mg in morning and afternoon, 8mg at night	KSh 35/$.30 for 1 mg
Gabapentin 300 mgs – Titrate PRN to: 1800mg max daily	Sh 35/$.30/tablet
Acamprosate 333mg; 666mg TID	KSh. 61/$.50
Nalmefene 18mg 1-2 hours before drinking	Not available in Kenya?

Patient Centered Approach to Alcohol Use Disorder



 AlcoholRecoveryMedicine.com Email:Info@tengoodrules.com

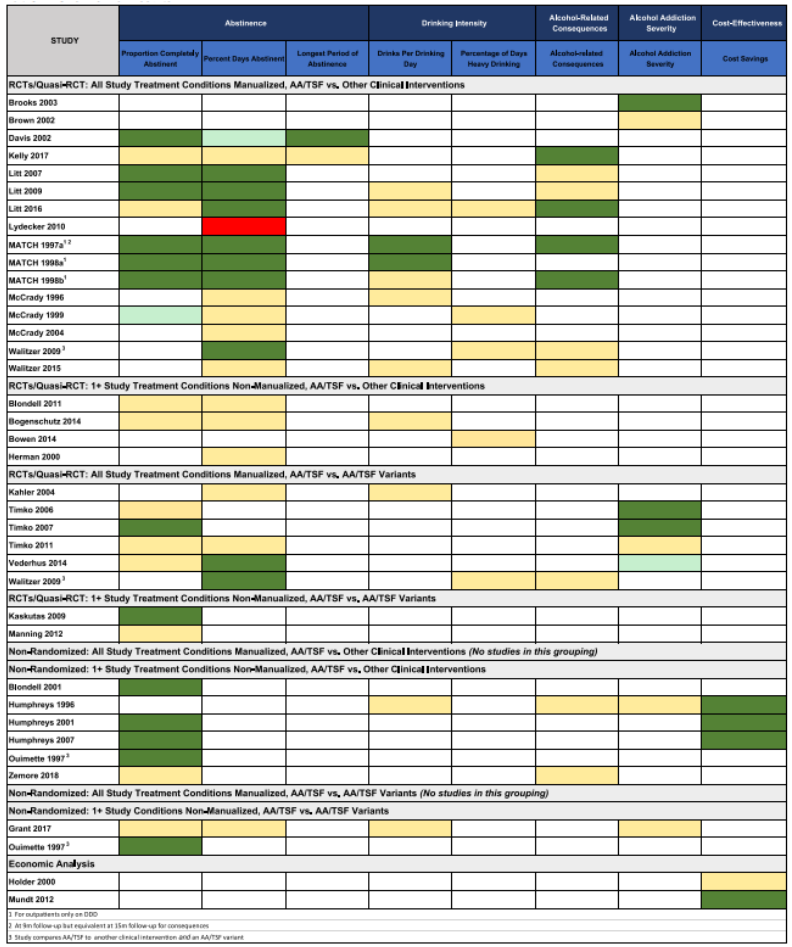
Outline:

- Clear the Mind
- Cut the Craving
- **Create a Culture**

Medications can augment 12-Step Recovery

12-Step Facilitation promotes abstinence better than other psychosocial treatments –
(Meta-analysis of 27 studies)

12-Step group participation may give healthy endorphins



STUDY	Abstinence			Drinking Intensity		Alcohol-Related Consequences	Alcohol Addiction Severity	Cost-Effectiveness
	Proportion Completely Abstinent	Percent Days Abstinent	Longest Period of Abstinence	Drinks Per Drinking Day	Percentage of Days Heavy Drinking	Alcohol-related Consequences	Alcohol Addiction Severity	Cost Savings
RCTs/Quasi-RCT: All Study Treatment Conditions Manualized, AA/TSF vs. Other Clinical Interventions								
Brooks 2003								
Brown 2002								
Davis 2002								
Kelly 2017								
Litt 2007								
Litt 2009								
Litt 2016								
Lydecker 2010								
MATCH 1997a[1,2]								
MATCH 1998a[1]								
MATCH 1998b[1]								
McCrady 1996								
McCrady 1999								
McCrady 2004								
Walitzer 2009[3]								
Walitzer 2015								
RCTs/Quasi-RCT: 1+ Study Treatment Conditions Non-Manualized, AA/TSF vs. Other Clinical Interventions								
Blondell 2011								
Bogenschutz 2014								
Bowen 2014								
Herman 2000								
RCTs/Quasi-RCT: All Study Treatment Conditions Manualized, AA/TSF vs. AA/TSF Variants								
Kahler 2004								
Timko 2006								
Timko 2007								
Timko 2011								
Vederhus 2014								
Walitzer 2009[3]								
RCTs/Quasi-RCT: 1+ Study Treatment Conditions Non-Manualized, AA/TSF vs. AA/TSF Variants								
Kaskutas 2009								
Manning 2012								
Non-Randomized: All Study Treatment Conditions Manualized, AA/TSF vs. Other Clinical Interventions *(No studies in this grouping)*								
Non-Randomized: 1+ Study Treatment Conditions Non-Manualized, AA/TSF vs. Other Clinical Interventions								
Blondell 2001								
Humphreys 1996								
Humphreys 2001								
Humphreys 2007								
Ouimette 1997[3]								
Zemore 2018								
Non-Randomized: All Study Treatment Conditions Manualized, AA/TSF vs. AA/TSF Variants *(No studies in this grouping)*								
Non-Randomized: 1+ Study Conditions Non-Manualized, AA/TSF vs. AA/TSF Variants								
Grant 2017								
Ouimette 1997[3]								
Economic Analysis								
Holder 2000								
Mundt 2012								

1. For outpatients only on DDD
2. At 9m follow-up but equivalent at 15m follow-up for consequences
3. Study compares AA/TSF to another clinical intervention and an AA/TSF variant

Dark Green = AA superior;
Red = non-AA treatment superior

Kelly, John F., et al. Alcohol and alcoholism 55.6 (2020): 641-651.

Since endorphins motivate behavior, recovery must replace endorphins from alcohol with endorphins from healthy behaviors

- Drinking alcohol, or *just thinking* about alcohol, can release endorphins and result in craving
- Optimal recovery counseling will encourage healthy activities that release endorphins to motivate new behaviors and help "rewire" the brain away from AUD

Coordinated human activity increases endorphins:

- Altruistic actions
- Group exercise
- Social laughter
- Synchronized dancing
- Group singing /music making
- Spicy/sweet food
- Christian religious ritual
- Sexual intercourse
- Sunlight
- Playing with dogs

Umhau, John C. "Conquering the Craving: Treatment to Curb Alcohol Use Disorder." Journal of Christian Nursing 36.3 (2019): 148-156. Tarr, Bronwyn, et al. "Naltrexone blocks endorphins released when dancing in synchrony." Adaptive Human Behavior and Physiology 3.3 (2017): 241-254. Lang, Martin, et al. "Sync to link: Endorphin-mediated synchrony effects on cooperation." Biological Psychology 127 (2017): 191-197. Weinstein, Daniel, et al. Evolution and human behavior: official journal of the Human Behavior and Evolution Society 37.2 (2016): 152.; Charles, Sarah, et al. "Religious rituals increase social bonding and pain threshold." (2020). Bodnar, Richard J. 2017." *Peptides* 124 (2020): 170223; Lang, Martin, et al. "Sync to link: Endorphin-mediated synchrony effects on cooperation." *Biological Psychology* 127 (2017): 191-197. Manninen, Sandra, et al. *Journal of Neuroscience* 37.25 (2017): 6125-6131; Nummenmaa, Lauri, et al. *bioRxiv* (2021); Odendaal, Johannes SJ. "Animal-assisted therapy—magic or medicine?." *Journal of psychosomatic research* 49.4 (2000): 275-280.; Wang, Yilu, et al. "Altruistic behaviors relieve physical pain." Proceedings of the National Academy of Sciences 117.2 (2020): 950-958.

***Rat Park* experiment:**

Isolation promotes opiate use

Social interaction (endorphin) replaces opiate addiction

These rats are addicted

These rats are free of addiction

Photos courtesy of Dr. Bruce Alexander

- **Clear the Mind**

  Nutrition & exercise
- **Cut the Craving**

  Inexpensive medication
- **Create a Culture**

  A partnership that builds an active, coordinated and altruistic community

Questions: Info@TenGoodRules.com


Be part of the solution - Join your colleagues for an online Zoom meeting
First Monday of each month, 11am EST
Send an email to Info@TenGoodRules.com
with ISSUP in the subject line
Special Thanks to Karen Dion of ThriveAlcoholRecovery.com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