Alcohol's effect on women’s health and evidence-based treatment for reducing intake

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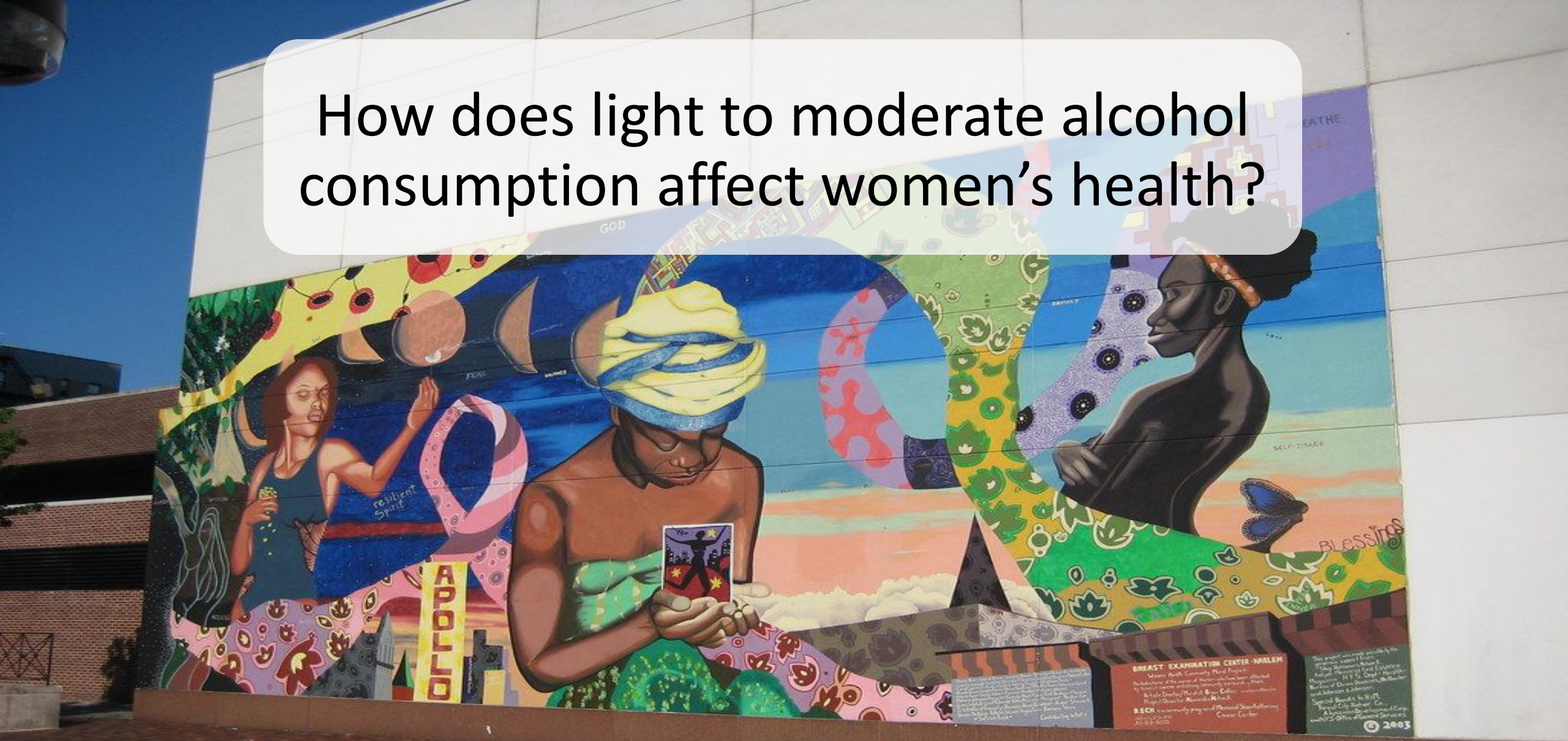
Disclosure

- Staff physician at Labrix by Doctor's Data since May 2018

How does light to moderate alcohol consumption affect women's health?



Learning Objectives

1. Weigh the benefits and risks associated with women's alcohol consumption
2. Discuss how alcohol shifts hormone balance and contributes to risk of breast cancer
3. Learn how alcohol impacts neurotransmitter balance and mood
4. Gain tools for assessing alcohol use and its influence on health, hormones and neurotransmitters
5. Learn evidence-based strategies to help patients with problematic drinking including counseling and pharmacotherapy

Changes in women's drinking habits in 2020

- Heavy drinking among women (≥ 4 drinks in an occasion) increased 41% compared to 2019, meaning that 1 in every 5 woman surveyed drank to excess one more day per month in 2020.[1]
- Women seem to be drinking to cope as they have been more likely to report rises in alcohol use during the pandemic if they experienced increased stress.
- Almost 1 in 10 women reported an increase in alcohol-related problems.[1]
- Having children in the home associated with more drinking[2]

1. Pollard MS, Tucker JS, Green HD. Changes in Adult Alcohol Use and Consequences During the COVID-19 Pandemic in the US. *JAMA Netw Open.* 2020;3(9):e2022942. doi:10.1001/jamanetworkopen.2020.22942

2. Pattani A. Women Now Drink As Much As Men – Not So Much For Pleasure, But To Cope. All things Considered, NPR. 9 June 2021. Available at https://www.npr.org/sections/health-shots/2021/06/09/1003980966/women-now-drink-as-much-as-men-and-suffer-health-effects-more-quickly Accessed 28 June 2021.

Definitions

- **Alcohol use disorder***: pattern of alcohol use involving trouble controlling alcohol consumption, continued use despite consequences, requiring more alcohol to achieve desired effects, or experiencing withdrawal with stopping.

  *AUD integrates the older terms **alcohol abuse** and **alcohol dependence**. Can be mild, moderate, or severe.

- **Alcoholism**: addiction to alcohol or the most severe type of AUD

https://www.mayoclinic.org/diseases-conditions/alcohol-use-disorder/symptoms-causes/syc-20369243. Accessed 12/4/20.

Definitions

- **Abstainers**: nondrinkers
- **Light Drinking**: ≤ 3 drinks per week
- **Moderate Drinking**:
  - ≤1 drink/day (women)
  - ≤2 drinks/day (men)*
- **Heavy Drinking**:
  - 8+ drinks/week (women)
  - 15+ drinks/week (men)
- **Binge Drinking**:
  - 4+ drinks in ~2 hours (females)
  - 5+ drinks in ~2 hours (males)

*The 2020 Dietary Guidelines Advisory Committee recommended tightening consumption limits for men to 1 drink per day on days when alcohol is consumed but this change was not adopted into the new USDA Dietary Guidelines.

https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics Accessed 9/8/2021

https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics Accessed 9/2/2021

Definitions

1 Drink: 14 grams of alcohol:

= 12 oz beer (5%ABV)

= 8 oz malt liquor (7%ABV)

= 5 oz wine (12%ABV)

= 1.5 oz liquor (80 proof)

1 Unit (UK): 10ml or 8g of pure alcohol, roughly the average amount an adult can process in an hour.

Sex Differences in Alcohol Pharmacokinetics

Females attain higher BACs (and greater intoxication) than do males if they drink the same amount of alcohol because:

1. **Body composition**: In females a greater percentage of body mass is fat compared to males
   Result – The concentration of alcohol is increased in the female bloodstream compared to the male body

2. **Stomach ADH**: Females have very little of this enzyme compared to males
   Result – Females do not metabolize alcohol before it gets out of the stomach. Therefore BAC is higher for females vs males

3. **Liver ADH**: Females have a less active form of this enzyme than do males.
   Result – Females do not metabolize alcohol as efficiently as do males, thereby increasing the BAC

Fama R, Le Berre AP, Sullivan EV. Alcohol's Unique Effects on Cognition in Women: A 2020 (Re)view to Envision Future Research and Treatment. Alcohol Res. 2020 Sep 10;40(2):03. doi: 10.35946/arcr.v40.2.03. PMID: 32923307; PMCID: PMC7473713.
https://sites.duke.edu/apep/module-1-gender-matters/explore-more/summary-of-differences-between-girls-n-guys/ Accessed 7/20/21

Sex Differences in Alcohol Consequences

- Women are more susceptible to alcohol-related **organ damage**
- Develop **liver disease** sooner than men and after less alcohol consumed[1]
- More likely to develop **hepatitis**; more susceptible to **death from cirrhosis**[1]
- Possibly more susceptible to alcohol-related impairment of cognitive performance, especially in tasks involving delayed **memory** or divided attention functions[2]

As of March 2021, **cases of alcoholic liver disease** (fatty liver, cirrhosis, alcoholic hepatitis) were **up 30%** over the last year at the University of Michigan's Health System. It seems that **younger women** may be fueling this trend.

1. https://pubs.niaaa.nih.gov/publications/aa46.htm. Accessed 4/5/2021
2. Mumenthaler MS, Taylor JL, O'Hara R, Yesavage JA. Gender differences in moderate drinking effects. Alcohol Res Health. 1999;23(1):55-64. PMID: 10890798; PMCID: PMC6761697.
3. https://pubs.niaaa.nih.gov/publications/aa46.htm. Accessed 4/5/2021
4. Noguchi Y. Sharp, 'Off the Charts' Rise In Alcoholic Liver Disease Among Young Women. NPR Morning Edition. 16 March 2021. Available at https://www.npr.org/sections/health-shots/2021/03/16/973684753/sharp-off-the-charts-rise-in-alcoholic-liver-disease-among-young-women Accessed 6/26/2021.

Can alcohol improve one's health?

Health benefits **associated with** alcohol consumption for women

- Stroke risk
- Kidney, thyroid, lung and hematologic cancer
- Heart attack and death from heart attack
- Death rate
- "Successful aging"

Pop Quiz!

Question:

How many grams of alcohol are in 1 standard drink such as a 5oz glass of wine?

A) 8 grams

B) 14 grams

C) 18 grams

Answer:

B) A standard drink contains 14 grams of alcohol.

Stroke Risk

- 1 in 5 women has a stroke in their lifetime[1]
- Light consumption (<7drinks/week) was associated with a decreased stroke risk for women by 30% vs abstainers[2]
  - Due to antithrombotic effects
  - Unrelated or slightly higher risk of hemorrhagic stroke
- Heavy consumption (>40g/day) was associated with a doubled risk for women vs abstainers[2]
  - Increased hemorrhagic stroke risk possibly partially due to increased blood pressure.
  - Can trigger A fib which increases clot-provoked stroke risk

1. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, et al. The lifetime risk of stroke: estimates from the Framingham Study. Stroke. 2006;37:345-50.
2. Zhang C, et al, Alcohol intake and risk of stroke: A dose–response meta-analysis of prospective studies, Int J Cardiol (2014), http://dx.doi.org/10.1016/j.ijcard.2014.04.225

Coronary Heart Disease and Sudden Death

- 23% lower incidence of CHD in women consuming up to 1 drink per day vs abstainers
- ~1/3 lower incidence of sudden cardiac death in women consuming up to 2 drinks per day.
- 15% higher risk of sudden cardiac death with >2 drinks per day.

Mostofsky E, Mukamal KJ, Giovannucci EL, Stampfer MJ, Rimm EB. Key Findings on Alcohol Consumption and a Variety of Health Outcomes From the Nurses' Health Study. *Am J Public Health*. 2016;106(9):1586-1591. doi:10.2105/AJPH.2016.303336

Yoon SJ, Jung JG, Lee S, et al. The protective effect of alcohol consumption on the incidence of cardiovascular diseases: is it real? A systematic review and meta-analysis of studies conducted in community settings. *BMC Public Health*. 2020;20(1):90. Published 2020 Jan 21. doi:10.1186/s12889-019-7820-z

Beer vs Wine vs Spirits?

Frequency matters but type of beverage does not

1 drink per day at least 4x per week associated with lower MI and death rates than same amount of alcohol taken in 1 or 2 days each week

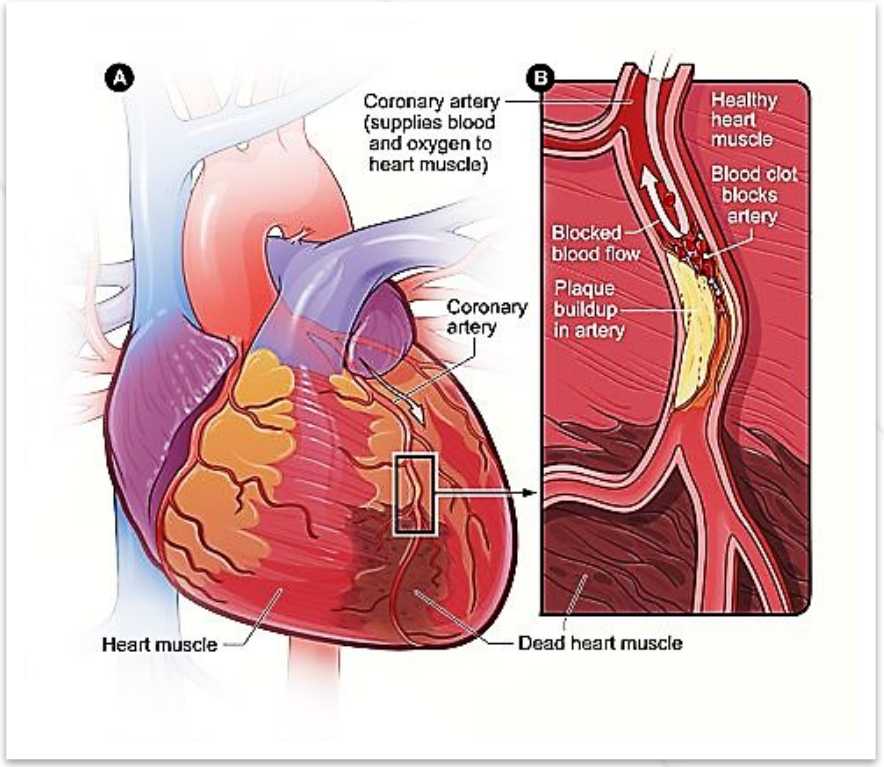
All types of alcohol were associated with:

- Decreased cardiovascular disease risk
- Increased breast cancer risk.

Mostofsky E, Mukamal KJ, Giovannucci EL, Stampfer MJ, Rimm EB. Key findings on alcohol consumption and a variety of health outcomes from the Nurses' Health Study. American journal of public health. 2016 Sep;106(9):1586-91.

Possible causal link between alcohol and reduced risk of coronary artery disease

- Low alcohol consumption does not raise triglycerides
- Moderate alcohol consumption associated w/:
  - Significantly increased HDL by ~3.5 to 4mg/dl
    - More than FDA-approved medications
  - Increased adiponectin
    - Insulin-sensitizing
    - Anti-inflammatory
    - Anti-atherogenic
  - Lowered fibrinogen
    - Involved in blood clotting
  - Increased apolipoprotein A1
    - Structurally makes up about 70% of HDL
    - Generally protective against cardiovascular disease



BMJ 2011;342:d636
Achari AE, Jain SK. Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction. *Int J Mol Sci*. 2017;18(6):1321. Published 2017 Jun 21. doi:10.3390/ijms18061321

Cancer Risk

Alcohol Intake	Increased Risk/Incidence	Decreased Risk/Incidence
Light (up to 1 drink qd)	**Female Breast Cancer[1]**	Lung Cancer[1] Thyroid Cancer[1]*
Moderate (1 – 2 drinks qd)	Male Colorectal Cancer[1] **Female Breast Cancer[1]**	Renal Cell Cancer[2]** Hematologic Malignancy[1]

*Marginally significant decrease in risk. FYI: Thyroid cancer is 2.9x more common in women.[3]
**Higher consumption confers no further benefit.

1. Choi YJ, Myung SK, Lee JH. Light Alcohol Drinking and Risk of Cancer: A Meta-Analysis of Cohort Studies. Cancer Res Treat. 2018 Apr;50(2):474-487. doi: 10.4143/crt.2017.094. Epub 2017 May 22. PMID: 28546524; PMCID: PMC5912140.
2. Song DY, Song S, Song Y, Lee JE. Alcohol intake and renal cell cancer risk: a meta-analysis. *Br J Cancer*. 2012;106(11):1881-1890. doi:10.1038/bjc.2012.136
3. Rahbari R, Zhang L, Kebebew E. Thyroid cancer gender disparity. *Future Oncol*. 2010;6(11):1771-1779. doi:10.2217/fon.10.127

Mortality in Middle Aged and Older Women

Alcohol Intake (daily average)	Change in death rate
~ 1/4-1 drink/day (1-7 drinks/week)	~ 10-15% reduction in mortality
~ 1 3/4 drinks/day (12 drinks/week)	no effect
2 drinks/day (14 drinks/week)	~ 3% increase in mortality
3 drinks/day (21 drinks/week)	~ 20% increase in mortality
>3 drinks/day (>21 drinks/week)	further significant increases

Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. Arch Intern Med. 2006;166:2437-45
Roehm E. Women & Alcohol: Special Considerations. NutritionHeart.com 2011. Accessed 11/10/2020.

Successful aging in women

Drinking regularly was associated with “successful aging”

- Defined as living to age 70+, being free of 11 major chronic diseases without cognitive or physical impairment or mental health limitations.

Sun Q, Townsend MK, Okereke OI, et al. Alcohol consumption at midlife and successful ageing in women: a prospective cohort analysis in the nurses' health study. *PLoS Med*. 2011;8(9):e1001090. doi:10.1371/journal.pmed.1001090

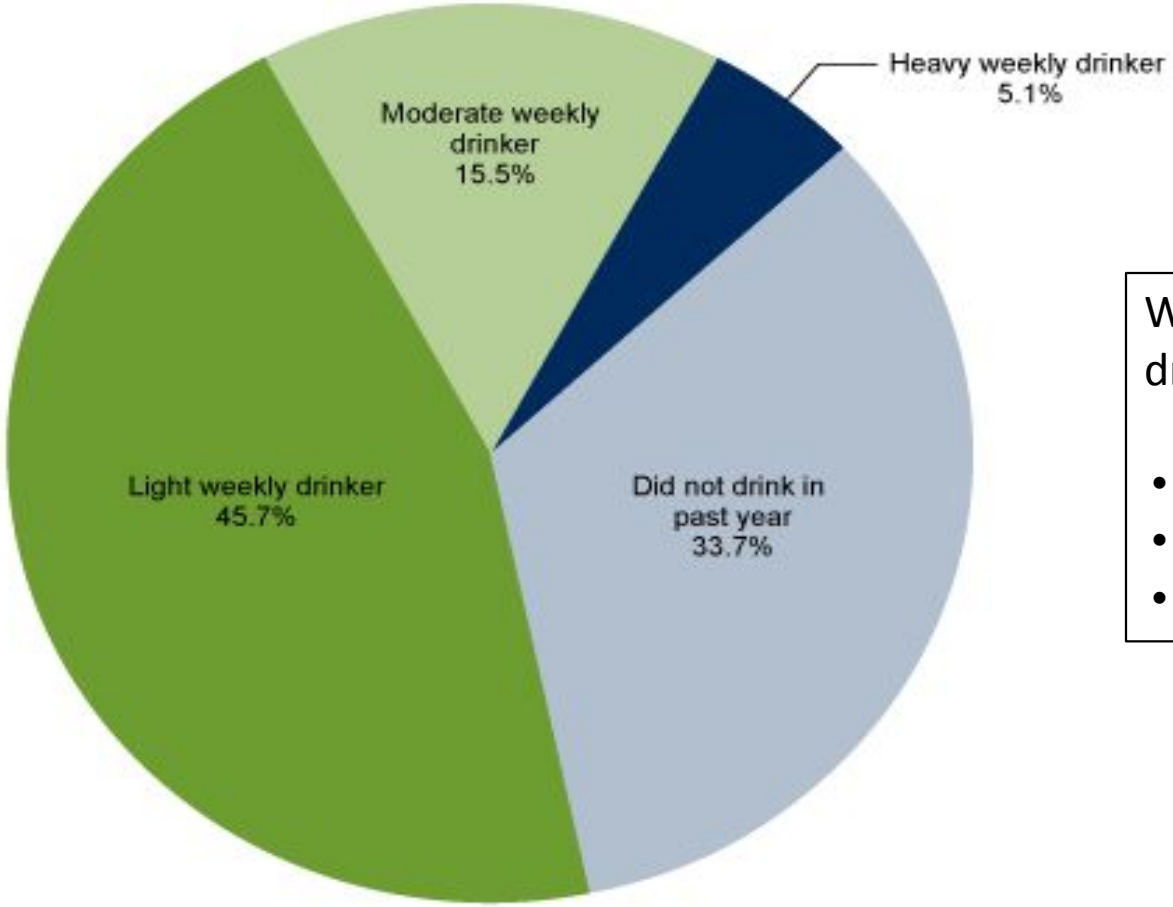
Successful Aging

"Independent of total alcohol intake, participants who drank alcohol at regular patterns throughout the week, rather than on a single occasion, had somewhat better odds of successful aging"

# Days Drinking per Week	Odds Ratio (OR) vs Nondrinkers
1 to 2	1.10
3 to 4	1.29
5 to 7	1.47

Sun Q, Townsend MK, Okereke OI, et al. Alcohol consumption at midlife and successful ageing in women: a prospective cohort analysis in the nurses' health study. *PLoS Med*. 2011;8(9):e1001090. doi:10.1371/journal.pmed.1001090

US Drinking Norms



Women's average weekly drinks over the past year

- Heavy: > 7
- Moderate: 4 to 7
- Light: ≤ 3

National Center for Health Statistics, National Health Interview Survey, 2018.

The Bottom Line

For women who already consume alcohol, the standard advice is to keep intake to **7 drinks or less weekly** (American Heart Association)

Don’t advise nondrinkers to start drinking alcohol for the proposed benefits as there is a lack of randomized data and **there is the potential to develop an alcohol use disorder** regardless of apparent predisposition or family history. (The Dietary Guidelines for Americans 2015-2020)

Alternative Theories

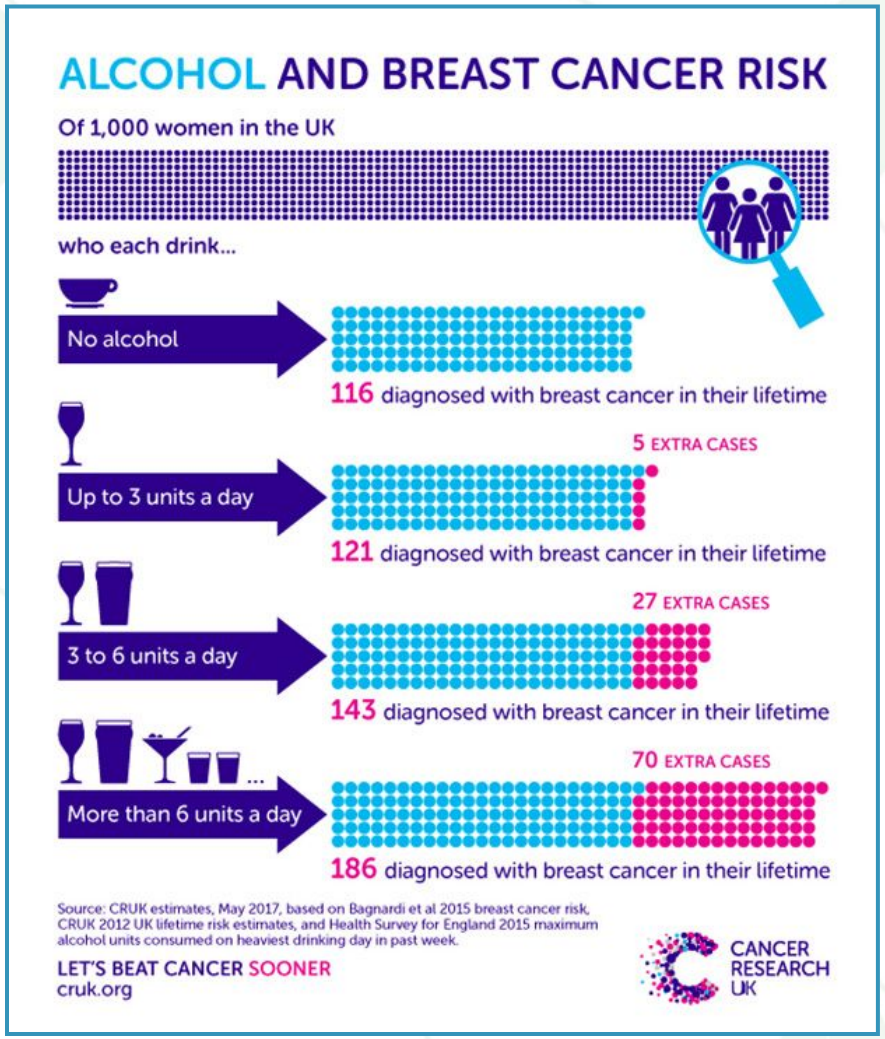
- Sick quitter and sick non-starter hypothesis
- Higher socio-economic status among regular drinkers
- Lower educational attainment in non-drinkers

Ng Fat, L; (2014) Investigating the health of non-drinkers: the sick-quitter and sick non-starter hypotheses. Doctoral thesis , UCL (University College London).

Sour Grapes (the Bad News)

- Breast Cancer
- Hormone effects
- Osteoporosis
- Neurotransmitter balance and mood

Alcohol and Breast Cancer Risk



- Consuming alcohol increases the risk of developing breast cancer
- The risk increases proportionally with the amount consumed.

Drinking Patterns and Breast Cancer Risk

Compared to abstaining from alcohol...

- 3 to 6 drinks per week associated with 15% increase in breast cancer
- 2 drinks per day increased risk 51%
- Binge drinking associated with modestly increased risk after controlling for cumulative intake
- Type of alcoholic beverage preferred did not affect risk
- Alcohol may **increase aromatase activity, decrease liver catabolism of androgens, and increase adrenal steroid production**

Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WC. Moderate Alcohol Consumption During Adult Life, Drinking Patterns, and Breast Cancer Risk. *JAMA.* 2011;306(17):1884–1890. doi:10.1001/jama.2011.1590

Postmenopausal Women's Alcohol Study

30g alcohol daily increased possible breast cancer risk factors

- Significant decrease in the antioxidant alpha-tocopherol
- Marginally significant increase in isoprostane levels, indicating oxidative stress

Hartman TJ, Baer DJ, Graham LB, Stone WL, Gunter EW, Parker CE, Albert PS, Dorgan JF, Clevidence BA, Campbell WS, Tomer KB, Judd JT, Taylor PR. Moderate alcohol consumption and levels of antioxidant vitamins and isoprostanes in postmenopausal women. Eur J Clin Nutr. 2005 Feb;59(2):161-8. doi: 10.1038/sj.ejcn.1602051. PMID: 15367922.

Alcohol and Breast Cancer Mortality

Participants: Women from the Women's Health Initiative observational study and randomized trial diagnosed with breast cancer (n = 7,835)

Conclusion: **Consumption of alcohol before or after breast cancer diagnosis did not increase risks of overall or cause-specific mortality**

Lowry SJ, Kapphahn K, Chlebowski R, Li CI. Alcohol Use and Breast Cancer Survival among Participants in the Women's Health Initiative. Cancer Epidemiol Biomarkers Prev. 2016 Aug;25(8):1268-73. doi: 10.1158/1055-9965.EPI-16-0151. Epub 2016 May 19. PMID: 27197280; PMCID: PMC4970888.

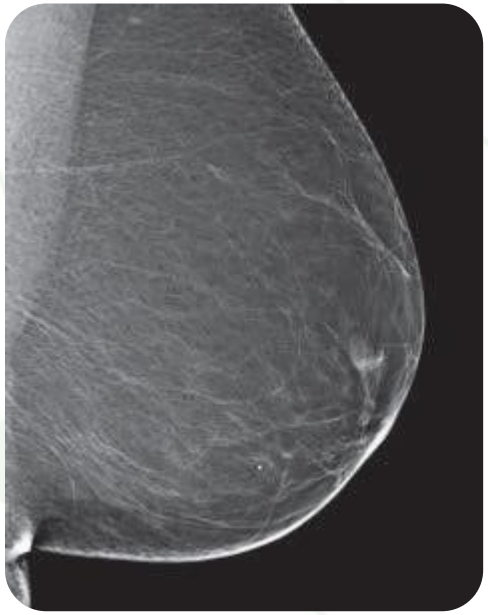
Alcohol weakens the effect of Tamoxifen

- Alcohol treatment attenuated the anti-proliferative effects tamoxifen in ER-positive breast cancer cells
- Alcohol consumption correlates with parameters that result in increased breast cancer risk
  - Increased proportion of dense tissue in the breast
  - Decreased β-carotene circulation
- “Drinking is associated with an increased risk of disease recurrence in women with early stage breast cancer”

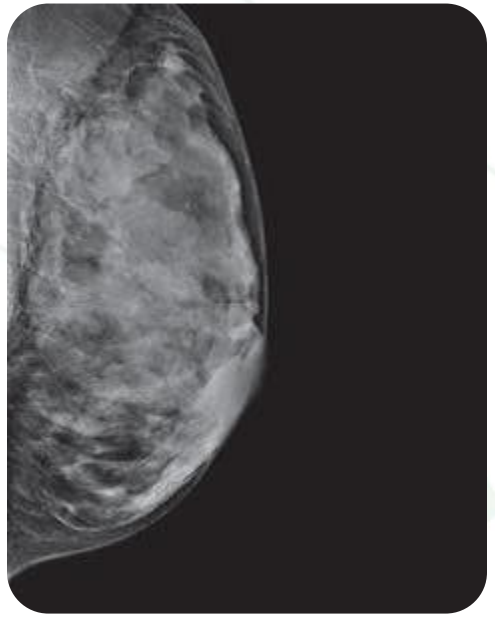
Candelaria NR, Weldon R, Muthusamy S, et al. Alcohol Regulates Genes that Are Associated with Response to Endocrine Therapy and Attenuates the Actions of Tamoxifen in Breast Cancer Cells. *PLoS One*. 2015;10(12):e0145061. Published 2015 Dec 14. doi:10.1371/journal.pone.0145061

Increased Mammographic Density

- Higher percentage of dense tissue in the breast
- More fibrous and/or glandular tissue and less fatty tissue
- Difficult to see tumors



Less dense/mostly adipose



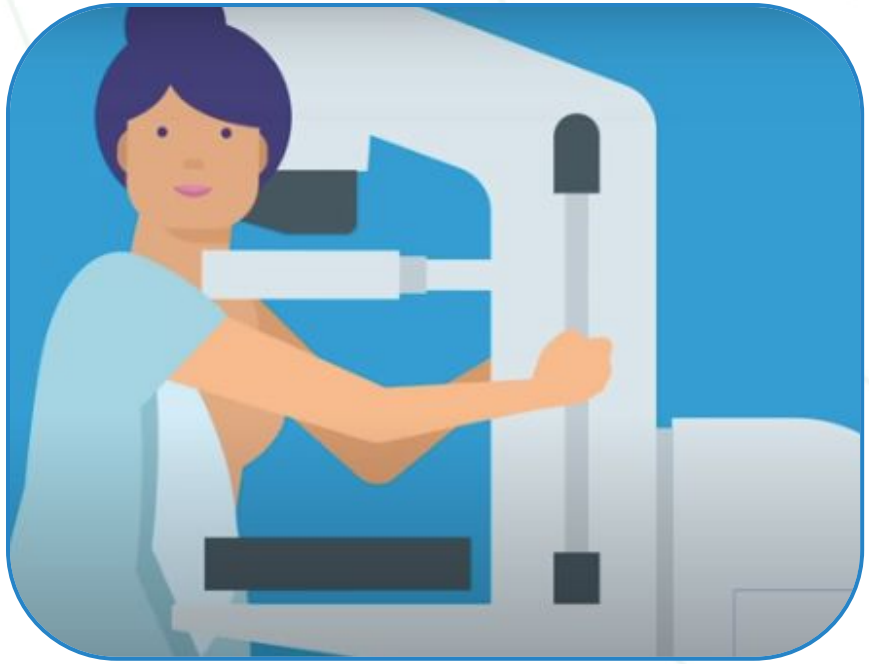
Extremely dense

https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/mammograms/breast-density-and-your-mammogram-report.html. Accessed 11/16/2020.

Mammographic Density and Alcohol

- Increased mammographic density is a strong independent risk factor for breast cancer (4 to 6x risk)[1]

- 5x higher odds of having mammographic density above median with 7+ drinks per week vs <1 drink per week[2]



1. Duffy SW, Morrish OWE, Allgood PC, et al. Mammographic density and breast cancer risk in breast screening assessment cases and women with a family history of breast cancer. *Eur J Cancer*. 2018;88:48-56. doi:10.1016/j.ejca.2017.10.022
2. Frydenberg H, Flote VG, Larsson IM, Barrett ES, Furberg AS, Ursin G, Wilsgaard T, Ellison PT, McTiernan A, Hjartåker A, Jasienska G, Thune I. Alcohol consumption, endogenous estrogen and mammographic density among premenopausal women. Breast Cancer Res. 2015 Aug 7;17(1):103. doi: 10.1186/s13058-015-0620-1. PMID: 26246001; PMCID: PMC4531831.

Strategies that may reduce/prevent breast density

- Diet: **Avoid alcohol** (<3 drinks per week), eliminate caffeine, increase plant-based foods, reduce saturated fats and red meats, avoid high glycemic load meals, decrease caloric intake
- Environmental: Reduce BPA and soft plastic exposure
- Lifestyle: Exercise 40 min per day, increase sun exposure

http://mammalivefoundation.org/decrease-breast-density-reduce-breast-cancer-risk/ Accessed 12/1/2020.

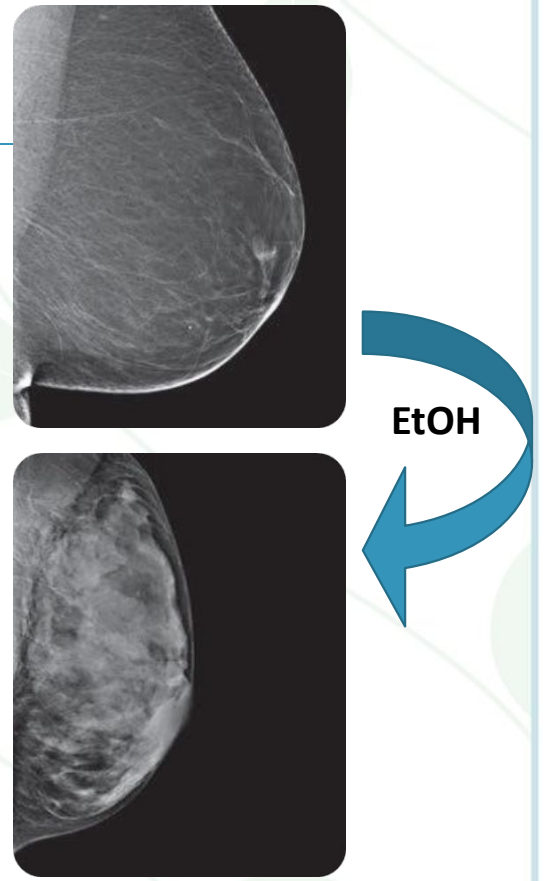
Masala G, Assedi M, Sera F, et al. Can Dietary and Physical Activity Modifications Reduce Breast Density in Postmenopausal Women? The DAMA Study, a Randomized Intervention Trial in Italy. Cancer Epidemiol Biomarkers Prev. 2019;28(1):41-50. doi:10.1158/1055-9965.EPI-18-0468

Wu SH, Ho SC, So E, et al. Sunlight exposure and breast density: a population-based study. J Breast Cancer. 2013;16(2):171-177. doi:10.4048/jbc.2013.16.2.171

Sprague BL, Trentham-Dietz A, Hedman CJ, et al. Circulating serum xenoestrogens and mammographic breast density. Breast Cancer Res. 2013;15(3):R45. Published 2013 May 27. doi:10.1186/bcr3432

Women's Drinking Patterns and Breast Cancer Risk Summary

- 3 to 6 drinks per week (vs 0) associated with 15% increase in breast cancer
- 2 drinks per day (vs 0) increased risk 51%
- Binge drinking associated with modestly increased risk after controlling for cumulative intake
- Alcohol damages cells, increases damage from tobacco, promotes hormone patterns linked to breast cancer, and breaks down into cancer-causing chemicals
- Decreases antioxidants (beta-carotene, alpha-tocopherol), increases oxidative stress (higher isoprostane levels) with 30g per day
- **Attenuated the anti-proliferative effects of tamoxifen** in ER-positive breast cancer cells
- Increases risk of disease recurrence in woman with early stage breast cancer
- 7 drinks per week quintuples the odds of higher mammographic density (vs 1 per wk), which increases breast cancer risk by 4 to 6x.



Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WC. Moderate Alcohol Consumption During Adult Life, Drinking Patterns, and Breast Cancer Risk. *JAMA.* 2011;306(17):1884–1890. doi:10.1001/jama.2011.1590
Candelaria NR, Weldon R, Muthusamy S, et al. Alcohol Regulates Genes that Are Associated with Response to Endocrine Therapy and Attenuates the Actions of Tamoxifen in Breast Cancer Cells. *PLoS One*. 2015;10(12):e0145061. Published 2015 Dec 14. doi:10.1371/journal.pone.0145061
Duffy SW, Morrish OWE, Allgood PC, et al. Mammographic density and breast cancer risk in breast screening assessment cases and women with a family history of breast cancer. *Eur J Cancer*. 2018;88:48-56. doi:10.1016/j.ejca.2017.10.022
Frydenberg H, Flote VG, Larsson IM, Barrett ES, Furberg AS, Ursin G, Wilsgaard T, Ellison PT, McTiernan A, Hjartåker A, Jasienska G, Thune I. Alcohol consumption, endogenous estrogen and mammographic density among premenopausal women. Breast Cancer Res. 2015 Aug 7;17(1):103. doi: 10.1186/s13058-015-0620-1. PMID: 26246001; PMCID: PMC4531831.
Hartman TJ, Baer DJ, Graham LB, Stone WL, Gunter EW, Parker CE, Albert PS, Dorgan JF, Clevidence BA, Campbell WS, Tomer KB, Judd JT, Taylor PR. Moderate alcohol consumption and levels of antioxidant vitamins and isoprostanes in postmenopausal women. Eur J Clin Nutr. 2005 Feb;59(2):161-8. doi: 10.1038/sj.ejcn.1602051. PMID: 15367922.

Folate and Fiber may protect vs. BC risk from EtOH

- Women with high vegetable fiber intake (>24.2 g/day) who also drank up to 1 alcoholic beverage per day did not have increased risk of breast cancer
- Women with low vegetable fiber intake (<18.5 g/day) had a 6% increase in risk of breast cancer per drink per day.
- Another study found that taking a multivitamin containing **folate attenuated the increased risk of breast cancer from alcohol** consumption.

1 cup cooked collard greens + 1 cup raspberries + 1 avocado + ½ cup beans = 24 to 25 grams fiber

Romieu I, et al. Int J Cancer. 2017;140(2):316
Maruti S. et al., Am J Clin Nutr. 2009 Feb;89(2):624-33

Pop Quiz!

Question: True or False? Alcohol consumption following a breast cancer diagnosis has been associated with an increased risk of mortality

Answer: False! Alcohol was not associated with an increased risk of breast cancer mortality.

Pop Quiz!

Question:

True or False? Alcohol should not be consumed while on **tamoxifen** because it decreases the effectiveness of this medication

Answer: True!

Alcohol and Hormone Balance

Oral Estrogen + Alcohol Estrogen Dominance

Acute effects

- Premenopausal women on OCPs experienced acute increases in E2 after 1 to 2 alcoholic beverages*, but women not taking OCPs had no change[3]
- Both groups had acute decreases in progesterone*[3]

*Compared to lingonberry juice (placebo)

Long term effects

- Premenopausal women who consumed 5+ alcoholic beverages per week had 22% higher estradiol levels (mid-luteal phase) vs abstainers[1]
- Postmenopausal women on oral E2 who consumed alcohol had higher serum E2 levels than those who did not[2]

1. Hartman TJ, Sisti JS, Hankinson SE, Xu X, Eliassen AH, Ziegler R. Alcohol Consumption and Urinary Estrogens and Estrogen Metabolites in Premenopausal Women. Horm Cancer. 2016 Feb;7(1):65-74. doi: 10.1007/s12672-015-0249-7. Epub 2016 Jan 4. PMID: 26728472; PMCID: PMC4729640.
2. Sriprasert I, Kono N, Karim R, Hodis HN, Stanczyk FZ, Shoupe D, Mack WJ. Factors Associated With Serum Estradiol Levels Among Postmenopausal Women Using Hormone Therapy. Obstet Gynecol. 2020 Oct;136(4):675-684. doi: 10.1097/AOG.0000000000004006. PMID: 32925623; PMCID: PMC7529896.
3. Sarkola T, Mäkisalo H, Fukunaga T, Eriksson CJ. Acute effect of alcohol on estradiol, estrone, progesterone, prolactin, cortisol, and luteinizing hormone in premenopausal women. Alcohol Clin Exp Res. 1999 Jun;23(6):976-82. PMID: 10397281.

Considerations to address E2 dominance

- DIM (100-200mg qd), I3C (200-400mg qd)
- Liver support (milk thistle, burdock, dandelion root), dietary fiber to reduce excess hormone levels
- **Reduce alcohol intake** to less than 5 drinks per week and avoid binge drinking. (Stopping alcohol would be even better.)
- Support ovulation to increase natural progesterone production
  - Seed cycling – 1 or 2 TB of freshly ground seeds per day plus optional oils
  - 1 to 2 grams per day of myo-inositol
  - Alternating botanical tinctures:

    Formula I (Used on days 1-14) - 1 tsp BID

    (4) Cimicifuga racemosa (Black cohosh

    (4) Vitex agnus-castus (Chaste berry)

    (4) Angelica sinensis (Dong quai)

    (4) Medicago sativa (Alfalfa)

    Formula II (Used on days 15-28) - 1 tsp BID

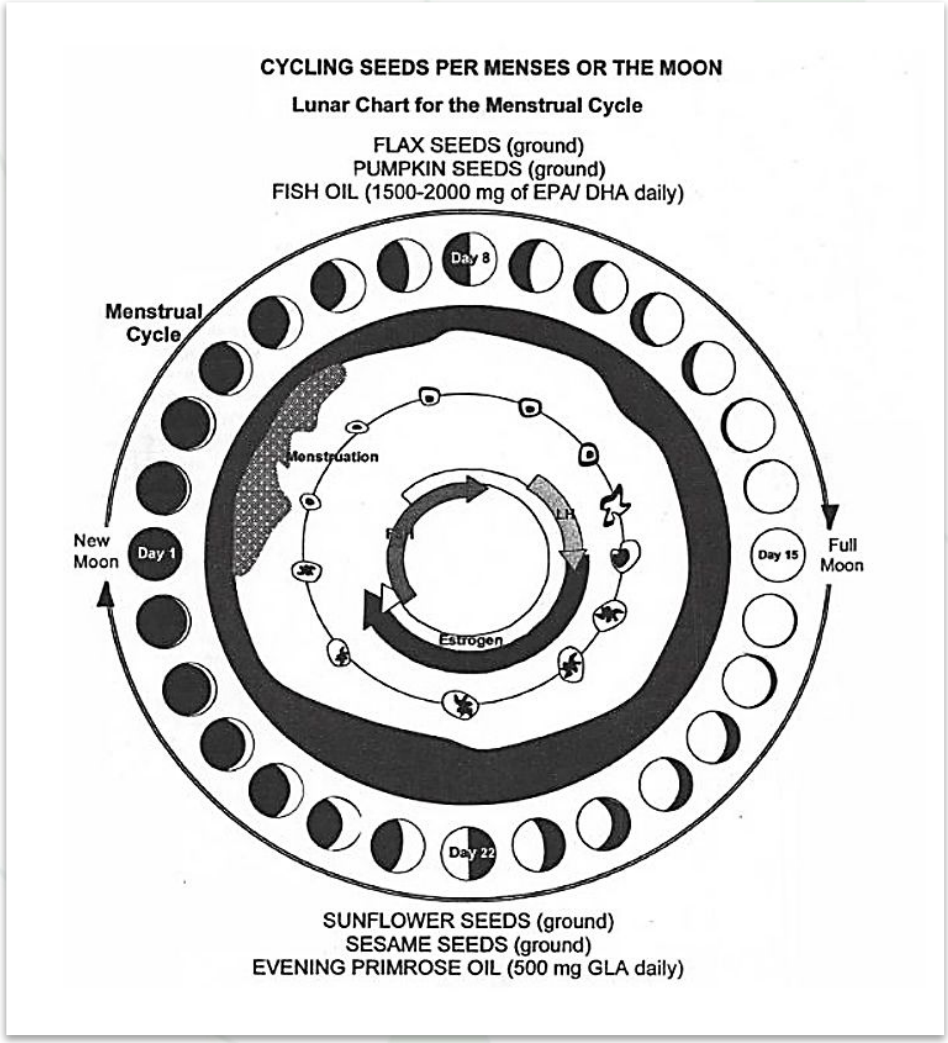
    (2) Vitex agnus-castus (Chaste berry)

    (4) Mitchella Repens (Partridge berry)

    (4) Smilax regelii (Jamacian sarsaparilla)

    (2) Pulsatilla (Pasque flower)

    (4) Diascorea mexicana (Mexican yam)
- Balance with progesterone supplementation
  - 20 to 30mg topical per day during luteal phase or continuous if postmenopausal; double the dosage if weight is above 150lb



Androgen and Estrone Excess

Postmenopausal women consuming 1 or 2 alcoholic beverages per day saw significant increases in **serum estrone sulfate and DHEAs**[1].

Premenopausal women had significant increases in **total testosterone** following alcohol consumption and this was exacerbated by **oral contraceptive use**[2].

1. Dorgan JF, Baer DJ, Albert PS, Judd JT, Brown ED, Corle DK, Campbell WS, Hartman TJ, Tejpar AA, Clevidence BA, Giffen CA, Chandler DW, Stanczyk FZ, Taylor PR. Serum hormones and the alcohol-breast cancer association in postmenopausal women. J Natl Cancer Inst. 2001 May 2;93(9):710-5. doi: 10.1093/jnci/93.9.710. PMID: 11333294.
2. Sarkola T, Fukunaga T, Mäkisalo H, Peter Eriksson CJ. Acute effect of alcohol on androgens in premenopausal women. *Alcohol Alcohol*. 2000;35(1):84-90. doi:10.1093/alcalc/35.1.84

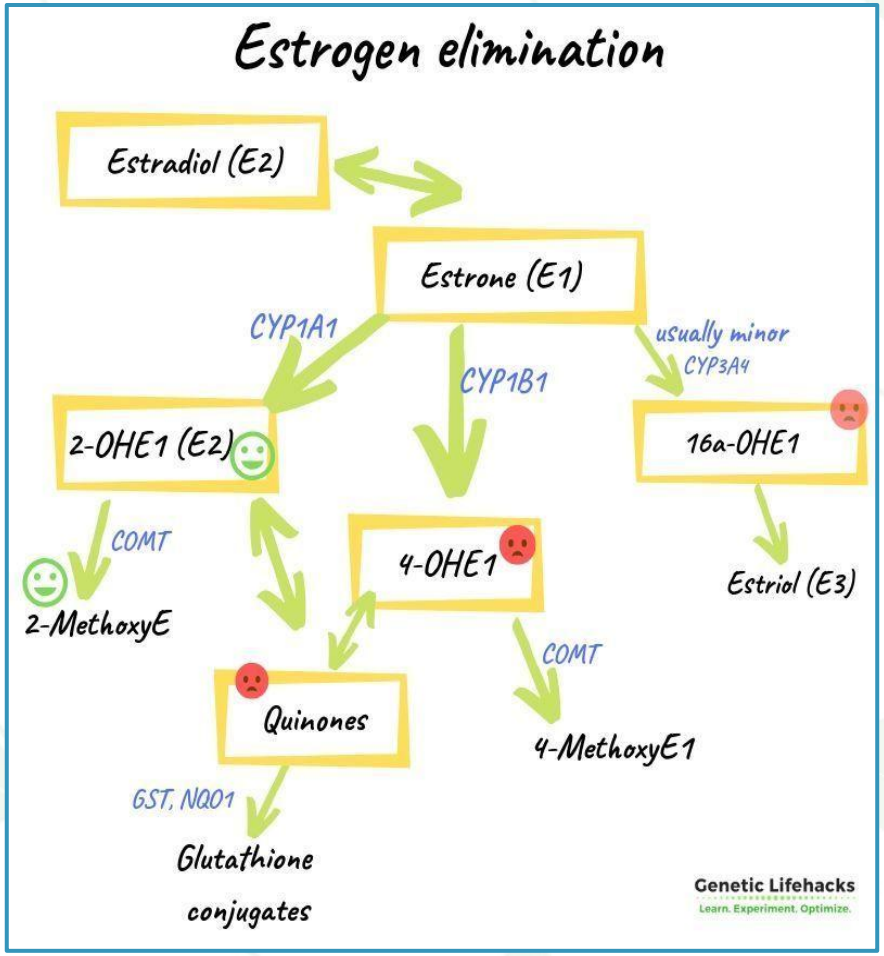
Considerations for androgen excess

- Aromatize to estradiol with CYP19
  - Forskolin, quercetin[5], genistein[5] (isoflavone/phytoestrogen), rutin[6] (bioflavonoid)
- Herbs:
  - 2 cups of tea per day (green, spearmint[4], or marjoram[2])
  - 1:1 ratio of white peony and licorice root[1]
- **Reduce alcohol intake**
- Balance blood sugar
  - 150min exercise per week or more
  - Low glycemic index diet
- Calm stress (may acutely elevate DHEA[3])

1. Armanini D, Mattarello MJ, Fiore C, Bonanni G, Scaroni C, Sartorato P, Palermo M. Licorice reduces serum testosterone in healthy women. Steroids. 2004 Oct-Nov;69(11-12):763-6. doi: 10.1016/j.steroids.2004.09.005. PMID: 15579328.
2. Haj-Husein I, Tukan S, Alkazaleh F. The effect of marjoram (Origanum majorana) tea on the hormonal profile of women with polycystic ovary syndrome: a randomised controlled pilot study. J Hum Nutr Diet. 2016 Feb;29(1):105-11. doi: 10.1111/jhn.12290. Epub 2015 Feb 9. PMID: 25662759.
3. Maninger N, Capitanio JP, Mason WA, Ruys JD, Mendoza SP. Acute and chronic stress increase DHEAS concentrations in rhesus monkeys. *Psychoneuroendocrinology*. 2010;35(7):1055-1062. doi:10.1016/j.psyneuen.2010.01.006
4. Grant P. Spearmint herbal tea has significant anti-androgen effects in polycystic ovarian syndrome. A randomized controlled trial. *Phytother Res*. 2010;24(2):186-188. doi:10.1002/ptr.2900
5. Sanderson JT, Hordijk J, Denison MS, et al. Induction and Inhibition of Aromatase (CYP19) Activity by Natural and Synthetic Flavonoid Compounds in H295R Human Adrenocortical Carcinoma Cells, *Toxicological Sciences*, Volume 82, Issue 1, November 2004, Pages 70–79, https://doi.org/10.1093/toxsci/kfh257
6. Jahan, S., Munir, F., Razak, S. *et al.* Ameliorative effects of rutin against metabolic, biochemical and hormonal disturbances in polycystic ovary syndrome in rats. *J Ovarian Res* **9,** 86 (2016). https://doi.org/10.1186/s13048-016-0295-y

Considerations for elevated Estrone

- Promote conversion to 2OH-E1 (CYP1A1) and then to 2-MeOE1 (COMT)
- Balance with estriol (E3) if indicated
  - 0.5 to 1mg topical or vaginally qd x 2 weeks, then 2 to 3x per week
- Promote CYP1A1
  - **Decrease/eliminate** refined sugar and **alcohol consumption**
  - Brassica vegetables, DIM (100 – 200mg qd), I3C (200 – 400mg qd), rosemary, flax
  - Optimize thyroid function if needed
    - B12, selenium, zinc
    - Ashwaganda for subclinical hypothyroid
- Support COMT
  - SAMe (100 – 500mg), Mag, B6, B12, methylfolate, betaine



Significant Changes to Hormones in Women Who Consume Alcohol vs Abstainers (Estrogen dominance and Androgen excess)

Menopausal Status, Oral E2 use?	Estradiol	Estrone Sulfate	Progesterone	Testosterone	DHEAs
Premenopausal, None	↑ 22%* with ≥5 drinks q wk; No acute change		Acute ↓ after 1 to 2 drinks	Acute ↑**	
Premenopausal, OCP	Acute ↑ after 1 to 2 drinks		Acute ↓ after 1 to 2 drinks	Acute ↑ ↑ (exacerbated by OCPs)**	
Postmenopausal, None		↑ with 1 to 2 drinks qd**			↑ with 1 to 2 drinks qd**
Postmenopausal, Oral E2	↑** in consumers of alcohol				

Note: A blank cell does not imply no effect, only that research investigating this connection was not found.
*Urinary, mid-luteal; **Serum

Hartman TJ, Sisti JS, Hankinson SE, Xu X, Eliassen AH, Ziegler R. Alcohol Consumption and Urinary Estrogens and Estrogen Metabolites in Premenopausal Women. Horm Cancer. 2016 Feb;7(1):65-74. doi: 10.1007/s12672-015-0249-7. Epub 2016 Jan 4. PMID: 26728472; PMCID: PMC4729640.

Sriprasert I, Kono N, Karim R, Hodis HN, Stanczyk FZ, Shoupe D, Mack WJ. Factors Associated With Serum Estradiol Levels Among Postmenopausal Women Using Hormone Therapy. Obstet Gynecol. 2020 Oct;136(4):675-684. doi: 10.1097/AOG.0000000000004006. PMID: 32925623; PMCID: PMC7529896.

Sarkola T, Mäkisalo H, Fukunaga T, Eriksson CJ. Acute effect of alcohol on estradiol, estrone, progesterone, prolactin, cortisol, and luteinizing hormone in premenopausal women. Alcohol Clin Exp Res. 1999 Jun;23(6):976-82. PMID: 10397281.

Dorgan JF, Baer DJ, Albert PS, Judd JT, Brown ED, Corle DK, Campbell WS, Hartman TJ, Tejpar AA, Clevidence BA, Giffen CA, Chandler DW, Stanczyk FZ, Taylor PR. Serum hormones and the alcohol-breast cancer association in postmenopausal women. J Natl Cancer Inst. 2001 May 2;93(9):710-5. doi: 10.1093/jnci/93.9.710. PMID: 11333294.

Sarkola T, Fukunaga T, Mäkisalo H, Peter Eriksson CJ. Acute effect of alcohol on androgens in premenopausal women. *Alcohol Alcohol*. 2000;35(1):84-90. doi:10.1093/alcalc/35.1.84

Kate, 52yo postmenopausal female who consumes 7 – 10 drinks weekly

Analyte	Result	Unit	L	WRI	H	Reference Interval	Supplementation Range**
Estrone (E1)*	12.5	pg/mL		◆		< 35	
Estradiol (E2)	0.80	pg/mL		◆		0.5 – 3.2	1.0 – 6.0
Estriol (E3)*	6.1	pg/mL	↓			7.5 – 66	45 – 680
EQ (E3 / (E1 + E2)) Ratio	0.46		↓			≥ 1.0	
Progesterone (Pg)	30	pg/mL		◆		18 – 130	400 – 4000
Pg/E2 Ratio†	37.5						≥ 200
Testosterone	27	pg/mL		◆		6 – 49	25 – 60
DHEA*	74	pg/mL	↓			106 – 300	

Findings: low E3, borderline low E2, normal progesterone, and low DHEA

Considerations: topical or vaginal E3, oral DHEA, reduce alcohol consumption prior to initiating E2 if needed.

Osteoporosis

"Women start losing bone at an earlier age and at a faster rate than men. Women ≥ 50 years of age have a 4x higher rate of osteoporosis and a 2x higher rate of osteopenia, and they tend to have fractures 5 - 10 years earlier compared with men."[1]

8 or more drinks per week for women:

- May increase the risk of developing osteoporosis and of suffering hip fractures.[2]
- Interferes with balance of calcium and vitamin D production along with cortisol levels – potentially weakening bone structure[2]

1. Alswat KA. Gender Disparities in Osteoporosis. J Clin Med Res. 2017;9(5):382-387. doi:10.14740/jocmr2970w
2. Davis K. Ten health risks of chronic heavy drinking. MedicalNewsToday. 2/19/2018. Accessed at https://www.medicalnewstoday.com/articles/297734 on 11/30/2020.

Pop Quiz!

Question:

Fill in the blank. Premenopausal women taking _____ experienced acute increases in estradiol following alcohol consumption whereas those not taking this medication did not. (*Sarkola et al*)

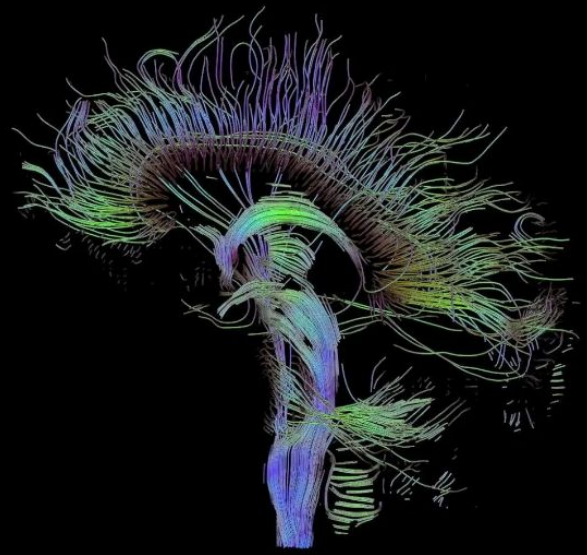
Answer:

Oral contraceptive pills (OCPs)

Brain shrinkage

Females may be more susceptible to white matter losses in frontal and temporal lobes with a history of prolonged heavy drinking, a finding that may well be influenced by blood alcohol level differences in males and females

DTI image showing white matter tracts.
Image credit: Thomas Schultz



Sharrett-Field L, Butler TR, Reynolds AR, Berry JN, Prendergast MA. Sex differences in neuroadaptation to alcohol and withdrawal neurotoxicity. *Pflugers Arch*. 2013;465(5):643-654. doi:10.1007/s00424-013-1266-4

Brain Functions affected by shrinkage

Frontal lobes: thinking, planning, reasoning

Temporal lobes: processing auditory info, encoding memory

White matter: transmits messages between brain regions, processes information

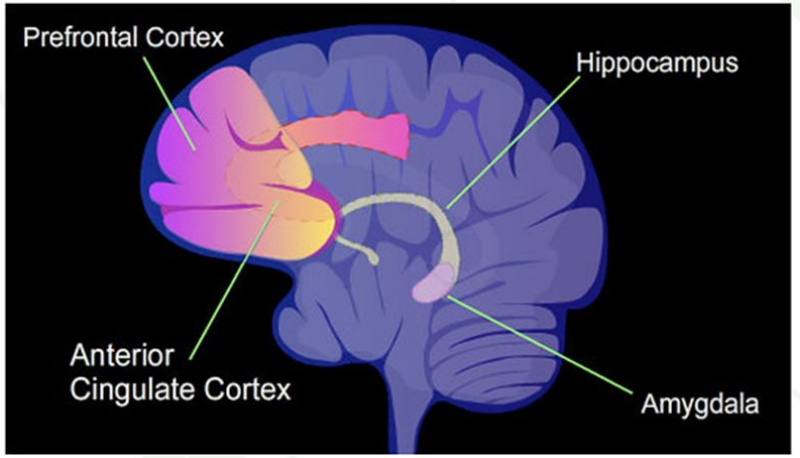
*Good news!: white matter volume was found to recover more quickly with abstinence in females, than in males

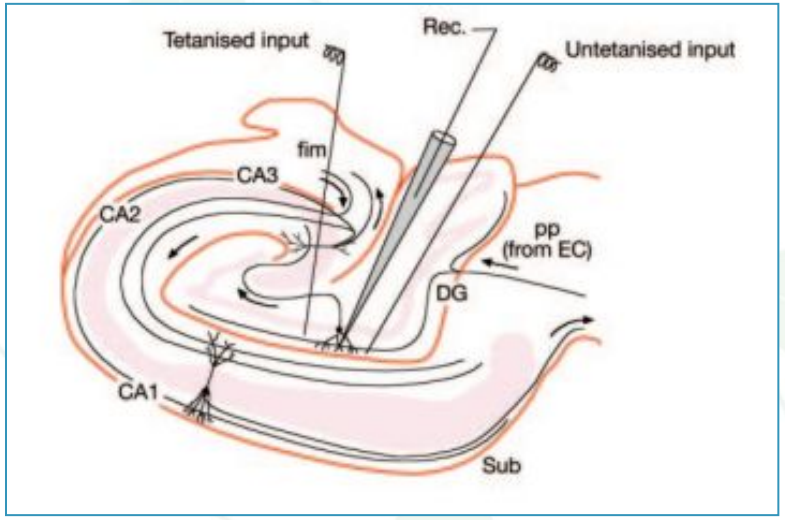
Sharrett-Field L, Butler TR, Reynolds AR, Berry JN, Prendergast MA. Sex differences in neuroadaptation to alcohol and withdrawal neurotoxicity. *Pflugers Arch*. 2013;465(5):643-654. doi:10.1007/s00424-013-1266-4

Short term effects on Memory

A sudden but lasting increase in excitatory neurotransmission (called Long Term Potentiation) in the hippocampus (requiring activation of glutamate receptors and inhibition of $GABA_A$ receptors) is necessary for memory formation.

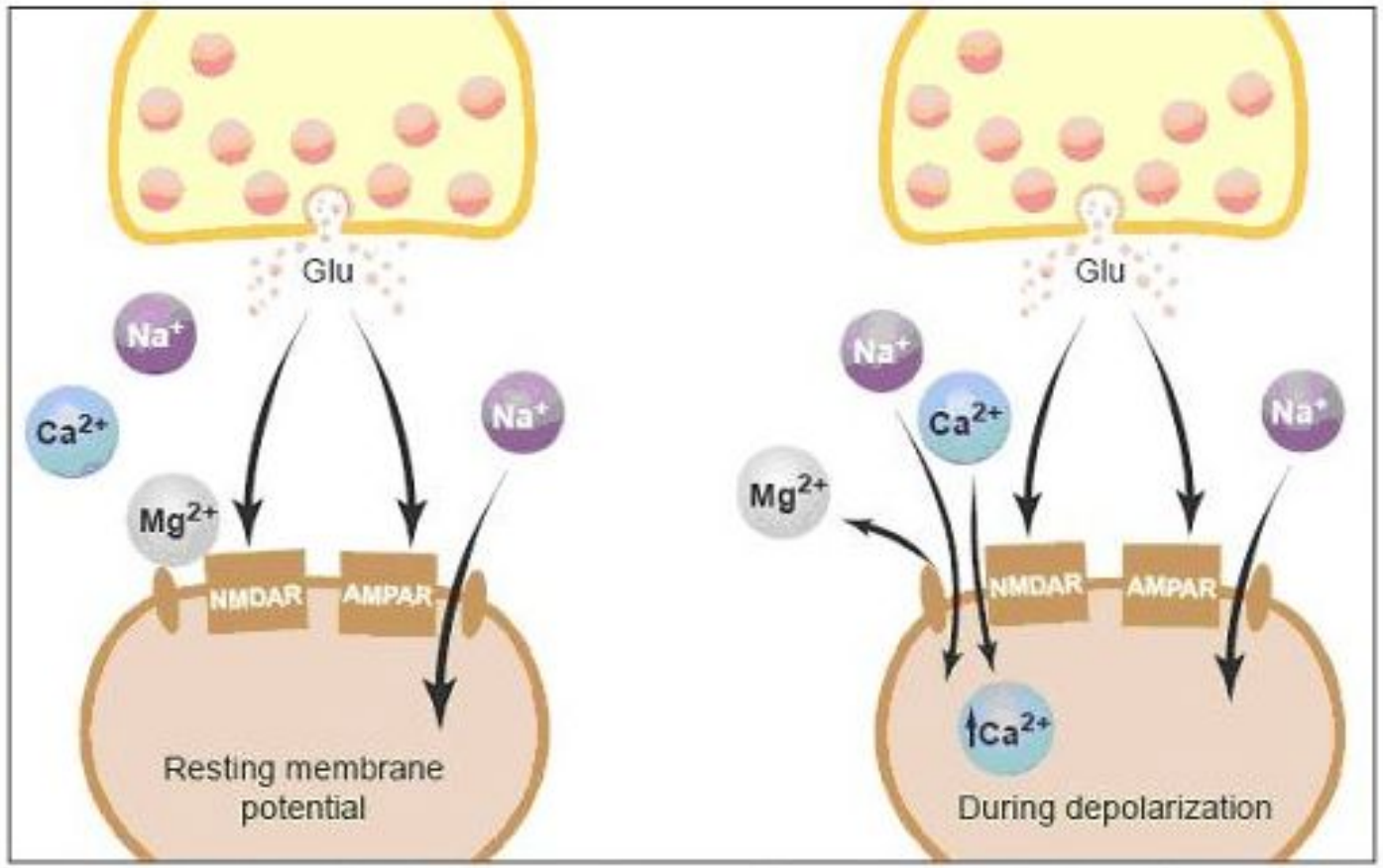
Short term alcohol decreases hippocampal LTP because it inhibits glutamate receptor function and stimulates $GABA_A$ receptor function.





Valenzuela CF. Alcohol and neurotransmitter interactions. Alcohol Health & Research World. 1997;21:144–148

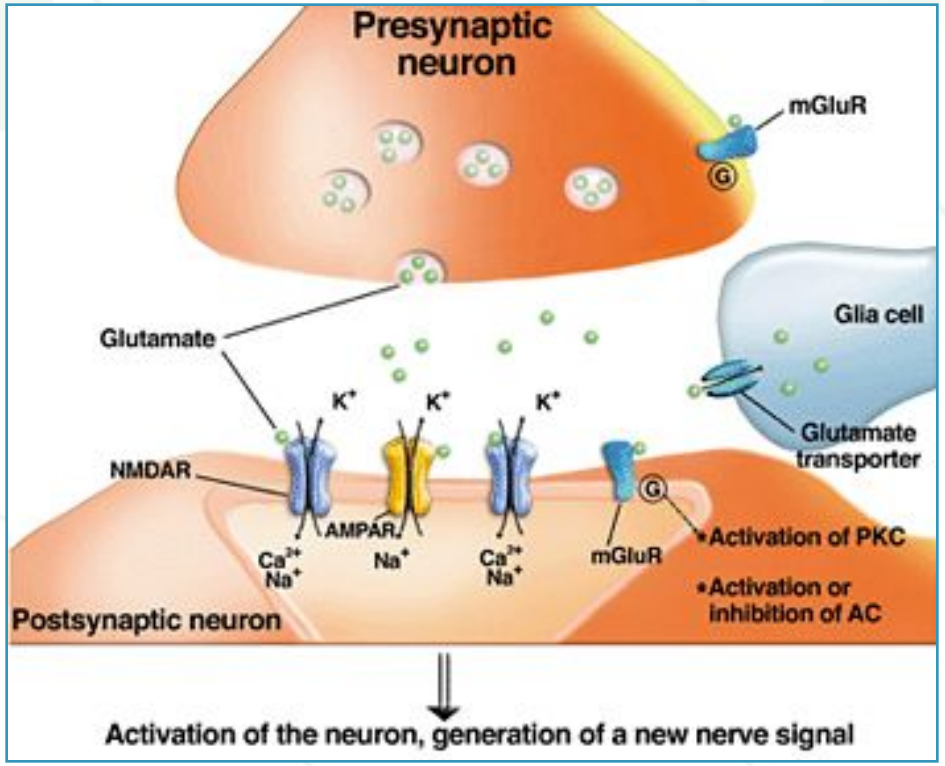
Long Term Potentiation

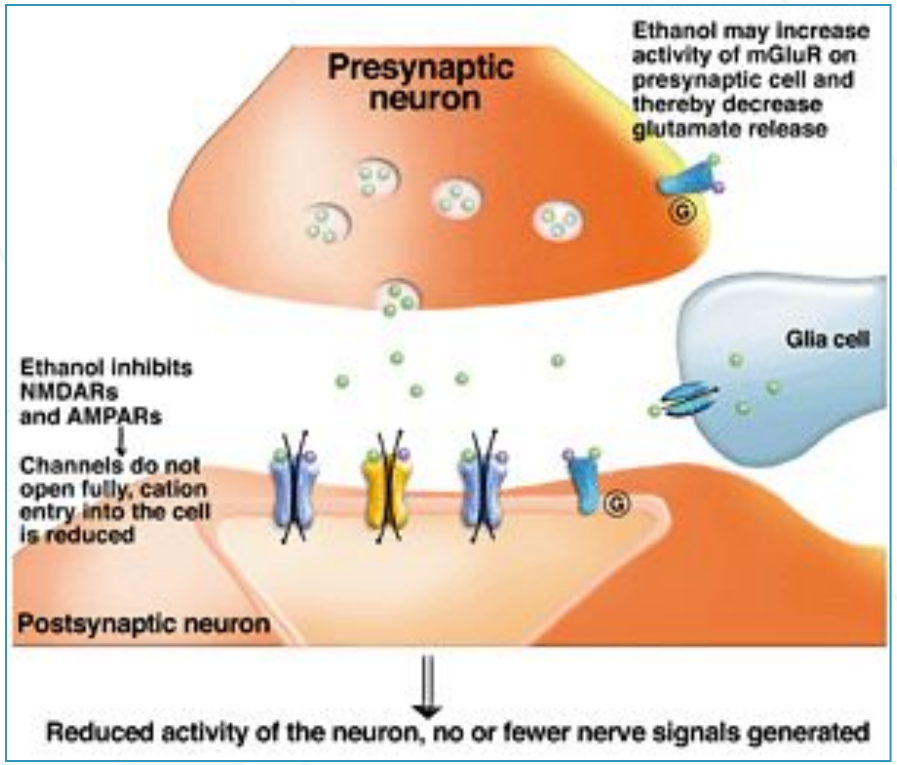


Model for the induction of LTP. During normal synaptic transmission, glutamate (Glu) is released from the presynaptic bouton and acts on both AMPA receptors (AMPARs) and NMDA receptors (NMDARs). However, Na^+ flows only through the AMPA receptor, but not the NMDA receptor, because Mg^{2+} blocks the channel of the NMDA receptor. Depolarization of the postsynaptic cell relieves the Mg^{2+} block of the NMDA receptor channel, allowing Na^+ and Ca^{2+} to flow into the dendritic spine by means of the NMDA receptor. The resultant rise in Ca^{2+} within the dendritic spine is the critical trigger for LTP.

R. C. Malenka and a. R. A. Nicoll. "Long-Term Potentiation--A Decade of Progress?" Science, September 17, 1999; 285(5435): 1870 - 1874.

The Brain's Glutamate System





Clapp P, Bhave SV, Hoffman PL. **How Adaptation of the Brain to Alcohol Leads to Dependence**: a Pharmacological Perspective. National Institute on Alcohol Abuse and Alcoholism. https://pubs.niaaa.nih.gov/publications/arh314/310-339.htm. Accessed 12/2/2020.

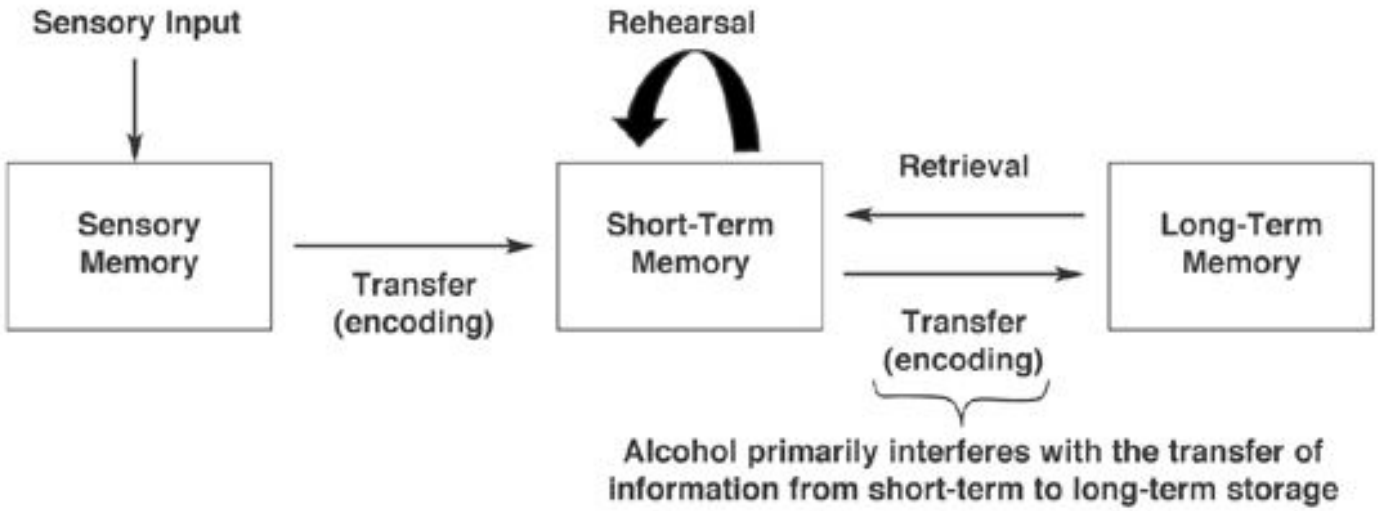
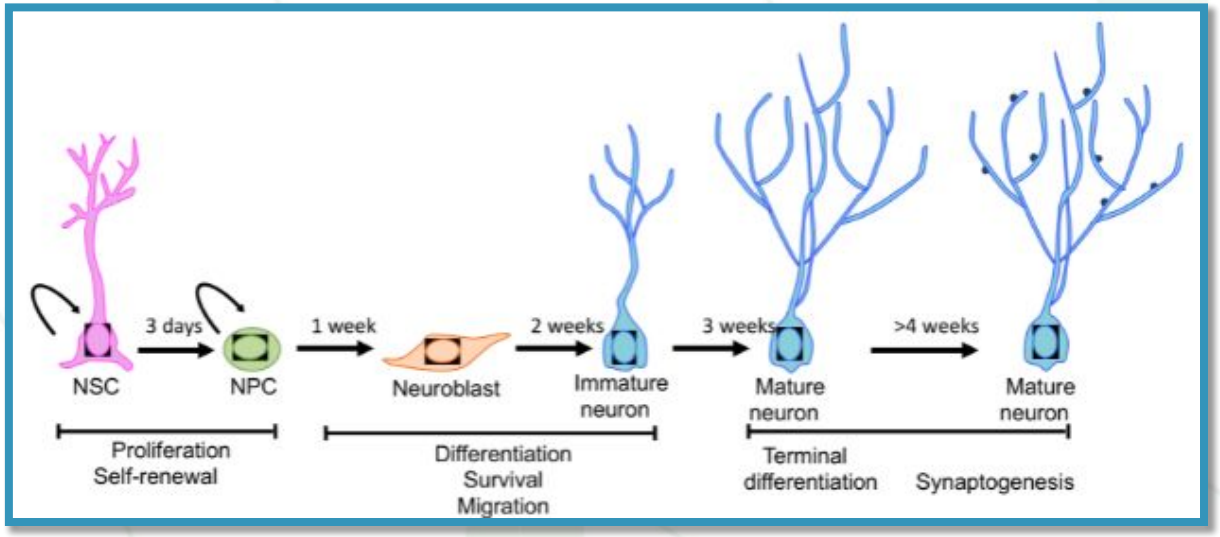


Figure 1 A general model of memory formation, storage, and retrieval based on the *modal model of memory* originally proposed by Atkinson and Shiffrin (1968). Alcohol seems to influence most stages of the process to some degree, but its primary effect appears to be on the transfer of information from short–term to long–term storage. Intoxicated subjects are typically able to recall information immediately after it is presented and even keep it active in short–term memory for 1 minute or more if they are not distracted. Subjects also are normally able to recall long–term memories formed before they became intoxicated; however, beginning with just one or two drinks, subjects begin to show impairments in the ability to transfer information into long–term storage. Under some circumstances, alcohol can impact this process so severely that, once sober again, subjects are unable to recall critical elements of events, or even entire events, that occurred while they were intoxicated. These impairments are known as blackouts.

White AM. What Happened? Alcohol, Memory Blackouts, and the Brain. Alcohol Research & Health. 2003;27(2): 186-96.

Can Alcoholic Brain Damage Be Reversed?

- Quitting alcohol can allow some of the alcohol-related cognitive impairment and memory loss to reverse
- MRI brain scans of people recovering from alcohol revealed that abstinence lead to frontal lobe and cerebellum volume increases involving both gray and white matter



- Most of the changes occurred between 7 and 30 days of abstinence; white matter volume increased at a consistent pace for the duration of the 7 ½ month study.
- Research involving alcohol-dependent rats revealed that **neurogenesis (new cell growth) took place in the brain's hippocampus with as little as four to five weeks of alcohol abstinence**, including a "twofold burst" in brain cell growth on the seventh day of being alcohol-free.
- Animal research also suggests that **exercise can promote neurogenesis**.

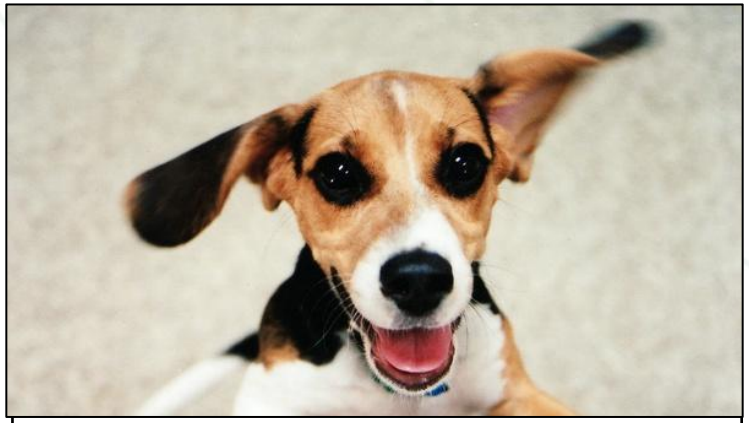
Buddy T. Quit Drinking to Revers Alcoholic Brain Damage. Verywellmind. April 7, 2021. Available at https://www.verywellmind.com/brain-cells-rebound-with-alcohol-abstinence-66614. Accessed 7/1/2021.
Int. J. Mol. Sci. 2020, *21*(14), 4869; https://doi.org/10.3390/ijms21144869

Neurotransmitter Changes

Alcohol disrupts the balance between excitatory and inhibitory NTs

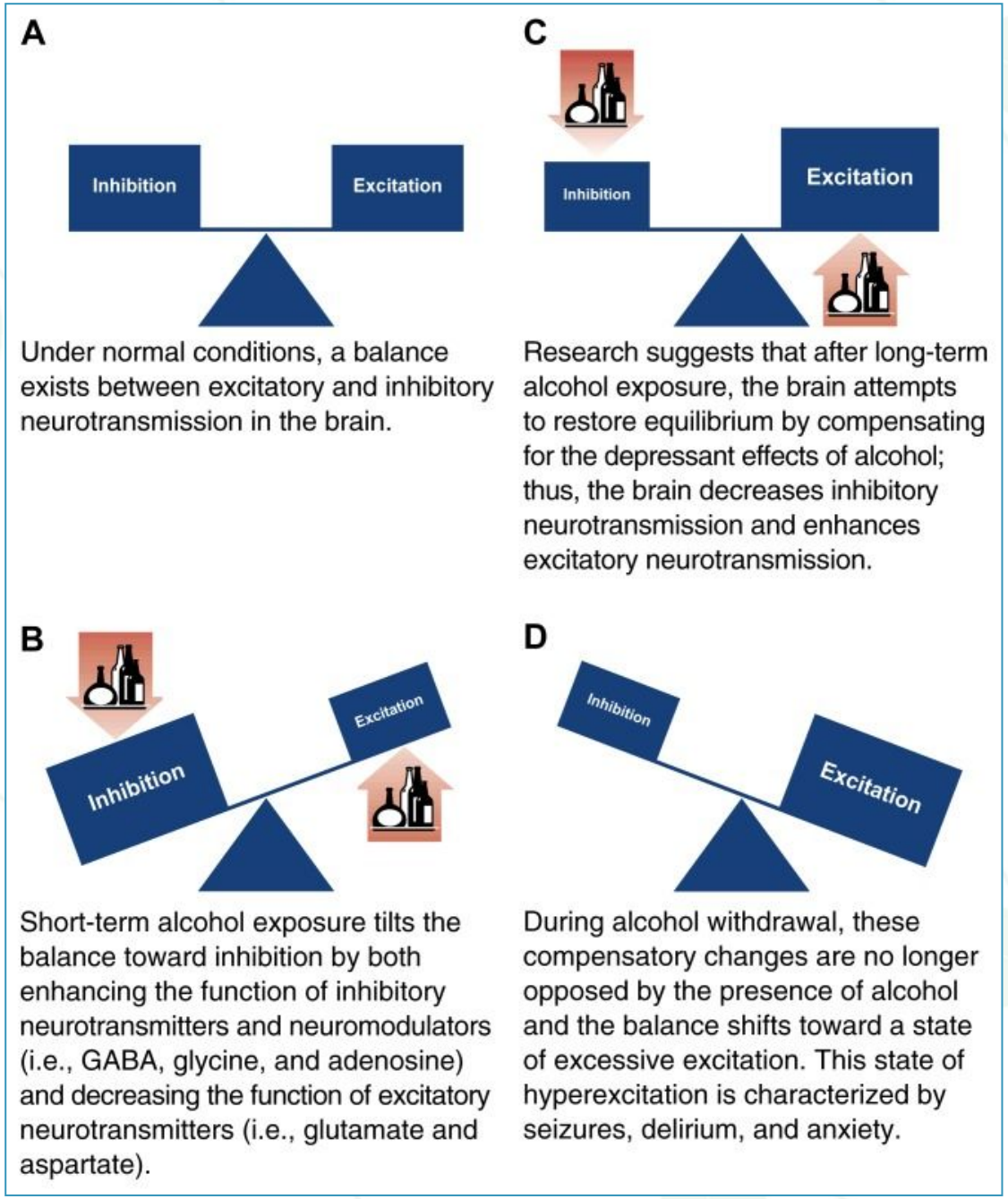
- Short term: enhanced inhibitory, attenuates excitatory
- Long-term: decreased inhibitory, increased excitatory

Inhibitory
GABA Serotonin Glycine



Excitatory
Acetylcholine Epinephrine Norepinephrine Histamine Glutamate Dopamine

Valenzuela CF. Alcohol and neurotransmitter interactions. Alcohol Health & Research World. 1997;21:144–148



Valenzuela CF. Alcohol and neurotransmitter interactions. Alcohol Health & Research World. 1997;21:144–148

Glutamate

- Glutamate is an excitatory NT involved in cognition, memory and learning.
- Excess glutamate can be **excitotoxic** – damages cells by overstimulation

- Acute alcohol intake reduces glutamate's excitatory effect (NMDA receptor downregulation)
- Chronic alcohol use **increases glutamatergic activity** (increased glutamate and upregulation of NMDA receptors) within neuronal circuits in brain structures mediating **reward, reinforcement, learning and memory**

Rao PSS, Bell RL, Engleman EA, Sari Y. **Targeting glutamate uptake to treat alcohol use disorders**. Front. Neurosci., 23 April 2015.
Sharrett-Field L, Butler TR, Reynolds AR, Berry JN, Prendergast MA. Sex differences in neuroadaptation to alcohol and withdrawal neurotoxicity. *Pflugers Arch*. 2013;465(5):643-654. doi:10.1007/s00424-013-1266-4.

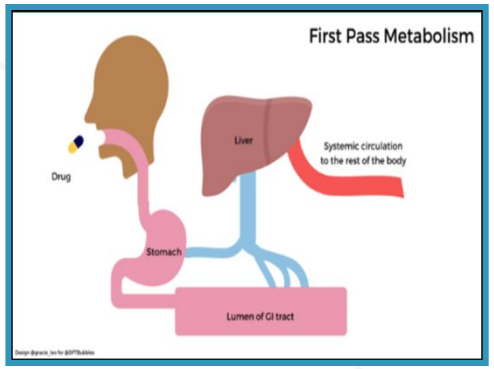
Glycine

- Glycine is a building block for proteins and an inhibitory neurotransmitter in the brainstem and spinal cord that has sleep-promoting, hypothermic qualities
- Allosteric excitatory modulator of NMDA receptors

- Acute alcohol use potentiates activation of the α1 glycine receptor
  - Involved in pain perception and motor control
  - Binding the receptor **decreases sensitivity to pain**

- Increased glycine levels have been measured in the CSF of alcohol-dependent patients at 9 and 33 days after quitting.

Cummings KA, Popescu GK. Glycine-dependent activation of NMDA receptors. *J Gen Physiol*. 2015;145(6):513-527. doi:10.1085/jgp.201411302
Tsai GE, Ragan P, Chang R, Chen S, Linnoila VM, Coyle JT. Increased glutamatergic neurotransmission and oxidative stress after alcohol withdrawal. Am J Psychiatry. 1998 Jun;155(6):726-32. doi: 10.1176/ajp.155.6.726. PMID: 9619143.



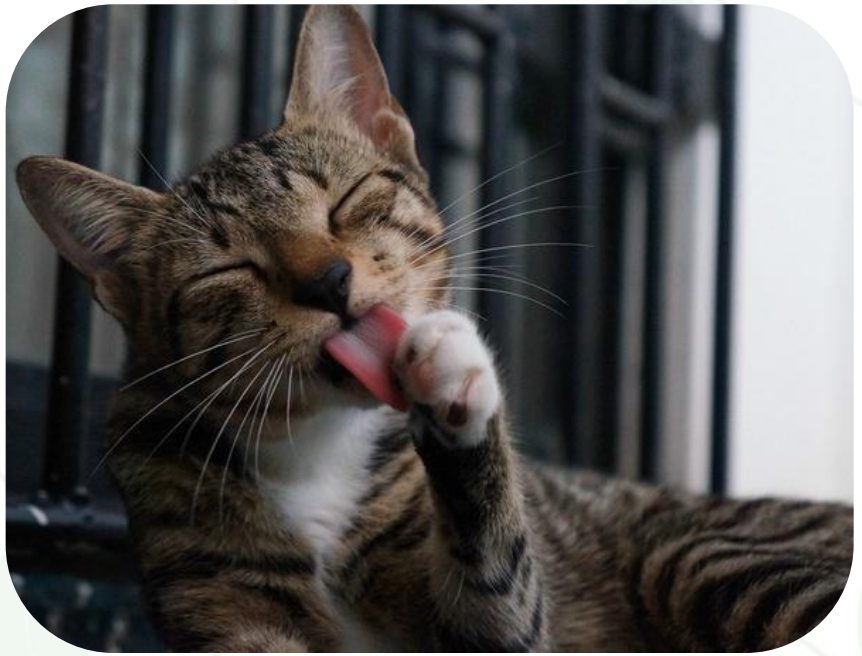
Giving Glycine to rats with AUD

- Resulted in a drop in daily alcohol consumption
  - Normalized the activity of alcohol-metabolizing enzymes
  - Modified the metabolism of dopamine and norepinephrine (increased levels in the brain)
- Minimizes alcohol-induced liver injury by preventing ethanol from reaching the liver by activating first-pass metabolism in the stomach
- Attenuated anxiety- and depression-like behaviors in rats experiencing withdrawal

Kharchenko, N.K. Effects of Glycine on the Catecholamine Levels and Activities of Alcohol-Metabolizing Enzymes in Rats with Alcohol Intoxication and Addiction. *Neurophysiology* **32,** 312–320 (2000). https://doi.org/10.1023/A:1010319305794
Iimuro Y, Bradford BU, Forman DT, Thurman RG. Glycine prevents alcohol-induced liver injury by decreasing alcohol in the rat stomach. Gastroenterology. 1996;110(5):1536-1542. doi:10.1053/gast.1996.v110.pm8613061

GABA

- GABA is the major inhibitory NT in the CNS, has a calming effect
- Acute alcohol exposure increases GABA's binding capacity and potentiates its inhibitory action
- Chronic use leads to a decrease in GABA receptor function either via fewer receptors or protein changes in the receptor
- Decreased GABA levels seen during withdrawal
  - Contribute to anxiety, dysregulated adrenal stress response, impulsivity, and possibly seizures



Valenzuela CF. Alcohol and neurotransmitter interactions. Alcohol Health & Research World. 1997;21:144–148

Dopamine

- Dopamine has excitatory and inhibitory functions and regulates pleasure/reward pathway, memory and motor control
- Excess dopamine may lead to mood swings, hyperactivity, anxiety, attention problems, memory issues
- Low dopamine is associated with depression and addictive behaviors

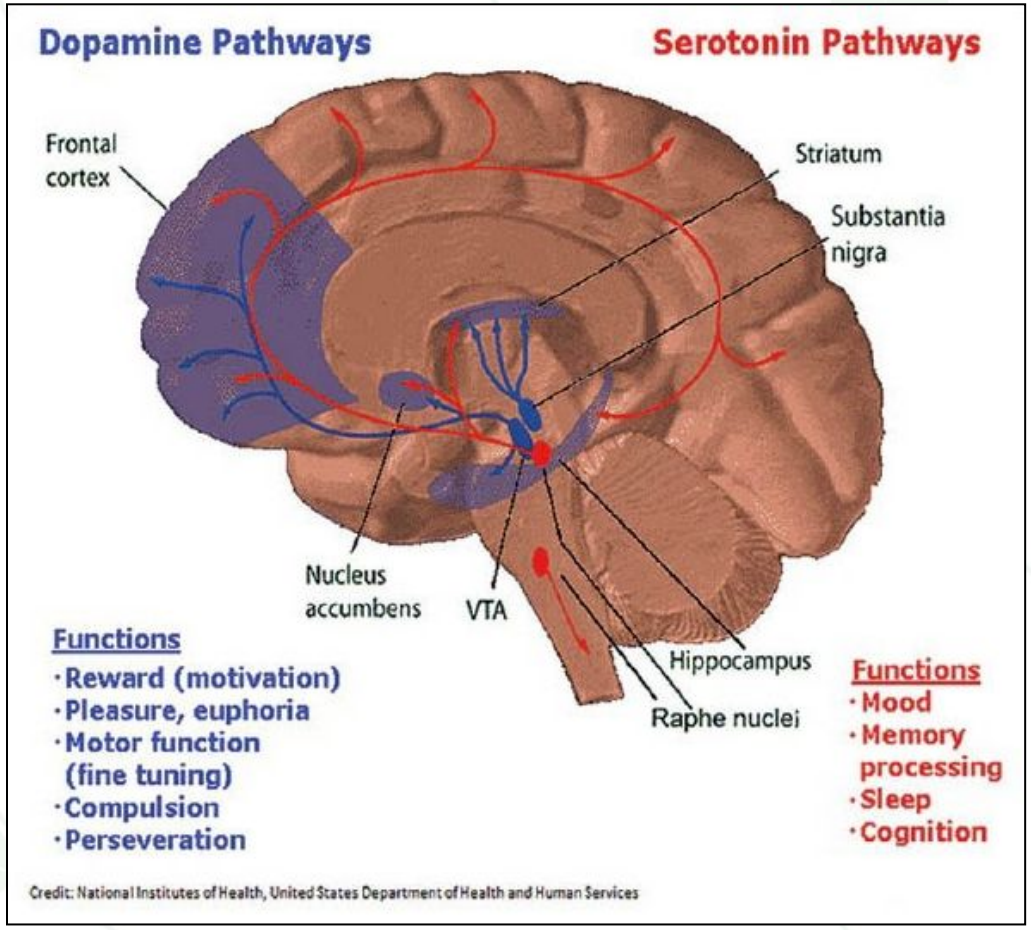
- Alcohol causes short term increase in dopamine
- Reduced dopamine receptors with long-term use

Valenzuela CF. Alcohol and neurotransmitter interactions. Alcohol Health & Research World. 1997;21:144–148
Sharrett-Field L, Butler TR, Reynolds AR, Berry JN, Prendergast MA. Sex differences in neuroadaptation to alcohol and withdrawal neurotoxicity. *Pflugers Arch*. 2013;465(5):643-654. doi:10.1007/s00424-013-1266-4
Image: https://www.dovemed.com/common-procedures/radiology-procedures/positron-emission-tomography-computed-tomography-petct-scan/

Serotonin

- Serotonin is inhibitory and regulates sleep, appetite and aggression
- When out of range, can lead to depression, anxiety, difficulty with pain control

- Alcohol causes short term serotonin production increase
- Chronic alcohol use can decrease brain levels of serotonin



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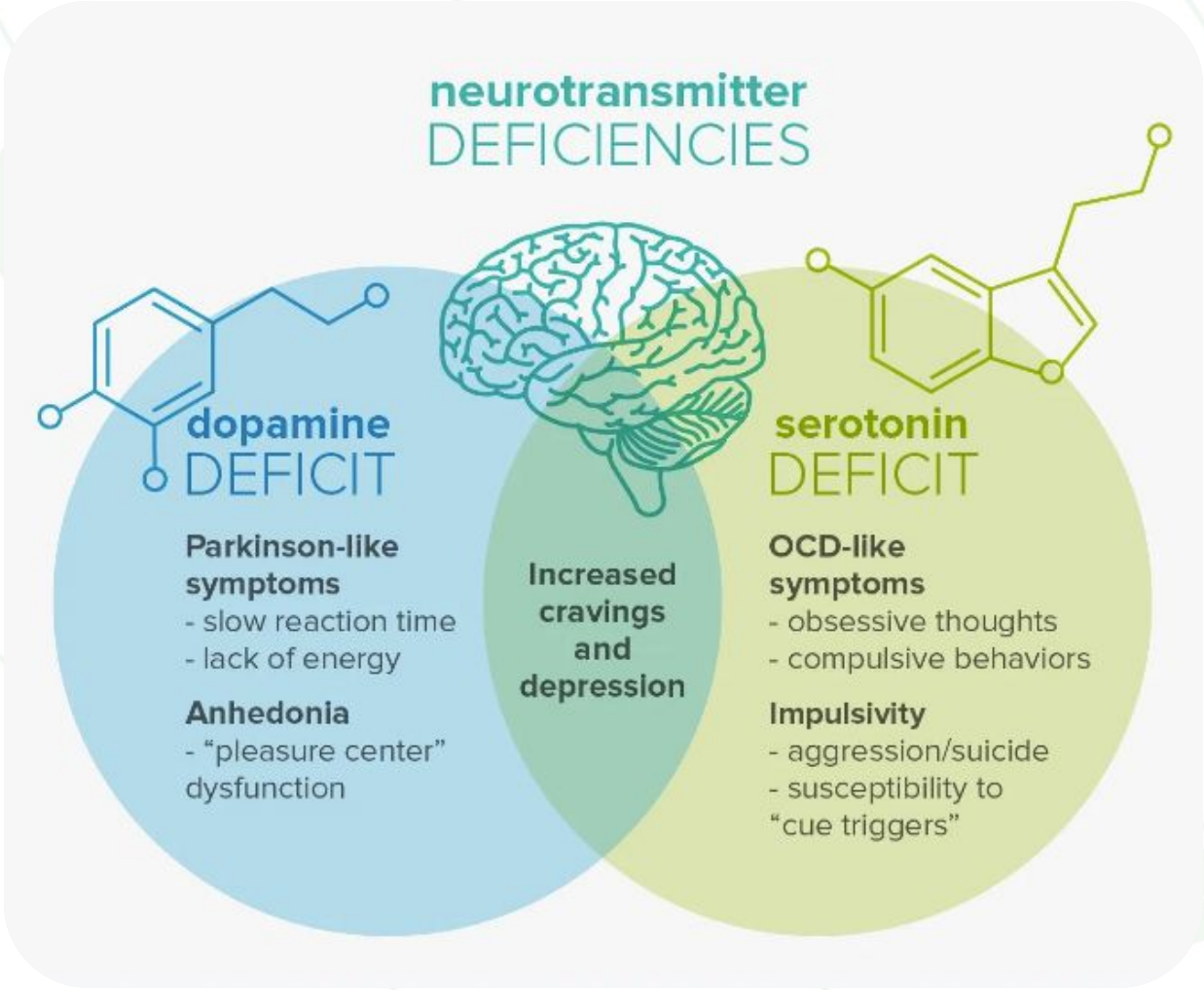
Sharrett-Field L, Butler TR, Reynolds AR, Berry JN, Prendergast MA. Sex differences in neuroadaptation to alcohol and withdrawal neurotoxicity. *Pflugers Arch*. 2013;465(5):643-654. doi:10.1007/s00424-013-1266-4
Lovinger DM. Serotonin's role in alcohol's effects on the brain. *Alcohol Health Res World*. 1997;21(2):114-120.
Banerjee N. Neurotransmitters in alcoholism: A review of neurobiological and genetic studies. *Indian J Hum Genet*. 2014;20(1):20-31. doi:10.4103/0971-6866.132750



Chronic EtOH use depletes serotonin and dopamine in the brain

https://www.healthline.com/health-news/how-nutritional-therapy-is-helping-people-overcome-alcohol-addiction. Accessed 12/2/2020.

Alcohol and Depression

- The female:male ratio of global disability from major depression is 1.7:1[1]
- Long-term overuse of alcohol can lead to depression and anxiety. Existing mental health conditions may worsen, be prolonged and are harder to treat.[2]
- Over 40% of those with MDD in their lifetime had a co-ocurring alcohol use disorder

1. Albert PR. Why is depression more prevalent in women?. *J Psychiatry Neurosci*. 2015;40(4):219-221. doi:10.1503/jpn.150205
2. Castaneda R, Sussman N, Westreich L, Levy R, O'Malley M. A review of the effects of moderate alcohol intake on the treatment of anxiety and mood disorders. *J Clin Psychiatry* 1996;57(5):207–212.

Imbalance between excitatory and inhibitory NTs

Kate - Postmenopausal female, 7-10 drinks weekly

NT Treatment:

1. Catecholamine support supplement containing tyrosine, P5P, velvet bean, zinc. 2. Check and treat D3 and Iron levels. 3. L-histidine and phenethylamine. 4. Optimize gut function (↓ EtOH)

Analyte	Result	Unit per Creatinine	L WRI H	Reference Interval
Serotonin	78.4	µg/g		60 – 125
Dopamine	118	µg/g		125 – 250
Norepinephrine	15.2	µg/g		22 – 50
Epinephrine	1.7	µg/g		1.6 – 8.3
Norepinephrine / Epinephrine ratio	8.9			< 13
Glutamate	22	µmol/g		12.0 – 45.0
Gamma-aminobutyrate (GABA)	3.5	µmol/g		2.0 – 5.6
Glycine	682	µmol/g		450 – 2200
Histamine	10	µg/g		14 – 44
Phenethylamine (PEA)	20	nmol/g		32 – 84
Creatinine	60.1	mg/dL		30 – 225

NT Support Considerations for long term changes dt EtOH

- L-theanine
- Meditation[1], Forest Bathing, regular exercise[2] (promotes new brain cell growth and helps maintain abstinence), optimize sleep, nutrient rich diet, social connection
- **Low GABA?** GABA supplementation or cofactors P5P, taurine (lysine and P5P to support GAD and sensitize receptors), fermented foods, probiotics
- **High glutamate?** Taurine, NAC, B3, P5P, Mg. Avoid fast food, processed food.
- **Low serotonin?** Normalize vit D and iron levels, P5P, B3, C, SAMe, Molybdenum, Zn; Tryptophan, 5-HTP, light therapy (10,000 lux)[3]
- **To help prevent withdrawal**: "Early research shows that taking 5-HTP with D-phenylalanine and L-glutamine for 40 days can reduce alcohol withdrawal symptoms."[4]

1. Kjaer TW, Bertelsen C, Piccini P, Brooks D, Alving J, Lou HC. Brain Res Cogn Brain Res. 2002 Apr; 13(2):255-9.
2. *Salmon P*. Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. *Clin Psychol Rev. 2001 Feb; 21(1):33-61.*
3. Young SN. How to increase serotonin in the human brain without drugs. *J Psychiatry Neurosci*. 2007;32(6):394-399.
4. Jukić T, Rojc B, Boben-Bardutzky D, Hafner M, Ihan A. The use of a food supplementation with D-phenylalanine, L-glutamine and L-5-hydroxytriptophan in the alleviation of alcohol withdrawal symptoms. *Coll Antropol*. 2011;35(4):1225-1230.

Pop Quiz!

Question:

Chronic alcohol use decreases brain levels of which of the following neurotransmitters?

A) Serotonin
B) Dopamine
C) Both A and B

Answer:

C) Both serotonin and dopamine

Alcohol Use Screening Tools and Next steps

Single Alcohol Screening Question (SASQ):

How many times in the past year have you had *X* or more drinks in a day?

- *X* = 4 for women or 5 for men

AUDIT-C - Identifies at-risk drinkers who may not be alcohol dependent

Bradley KA, DeBenedetti AF, Volk RJ, Williams EC, Frank D, Kivlahan DR. AUDIT-C as a brief screen for alcohol misuse in primary care. Alcohol Clin Exp Res. 2007 Jul;31(7):1208-17. doi: 10.1111/j.1530-0277.2007.00403.x. Epub 2007 Apr 19. PMID: 17451397.
https://www.cdc.gov/chronicdisease/resources/publications/factsheets/alcohol.htm. Accessed 12/1/20.

AUDIT-C (3 questions)

1. How often did you have a drink containing alcohol in the past year?

Never	0
Monthly or less	+1
2 to 4 x /month	+2
2 to 3x /week	+3
4 or more x/week	+4

2. How many alcoholic drinks did you have on a typical day that you drank in the past year?

1 or 2 drinks	0
3 or 4	+1
5 or 6	+2
7 to 9	+3
10+	+4

3. How often did you have 6+ drinks on one occasion in the past year?

Never	0
Less than monthly	+1
Monthly	+2
Weekly	+3
Daily or almost daily	+4

Scoring the AUDIT-C:

Females

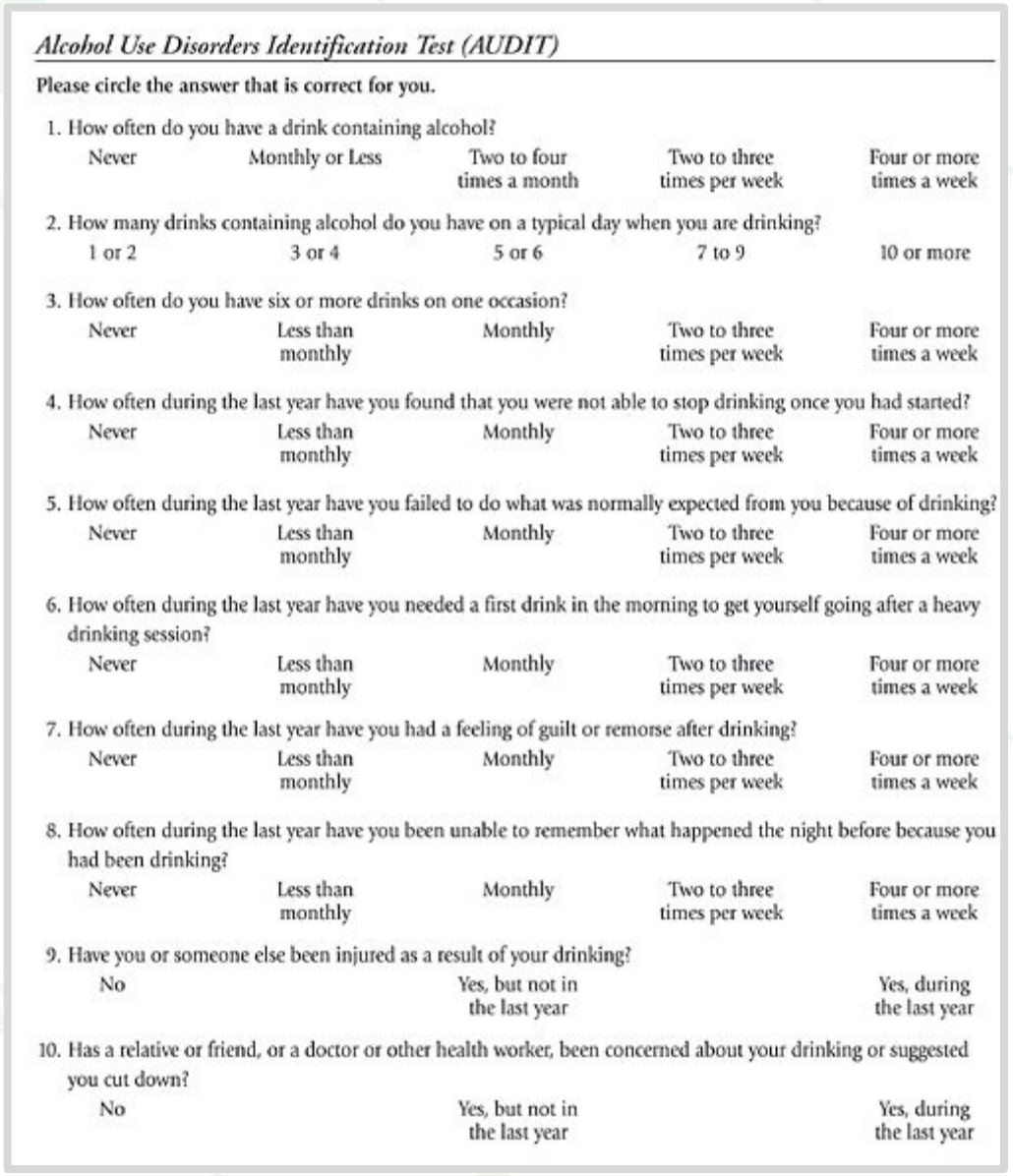
- < 3 = normal alcohol consumption
- 3 and above = alcohol misuse
  - If points are only from Q#1 – review intake over the last month
- 5 and above = possible liver damage

Males

- ≤ 3 = normal alcohol consumption
- 4 and above = alcohol misuse
- 5 and above = possible liver damage

NEXT Steps

- Normal consumption: Encourage continued moderation
- Counsel abstinence in these cases:
  - Pregnancy
  - Under legal drinking age
  - Contraindicated medication
  - Medical/psychiatric disorder caused or exacerbated by EtOH
  - Alcohol use disorder
- Unhealthy alcohol use or liver damage: follow-up with a more in-depth risk assessment (AUDIT – 10 questions) to confirm unhealthy alcohol use and determine the next steps of care
  - For Q#1-8 – answers are 0 to 4 points (from left to right); for Q#9 and 10 – answers are 0,2, and 4 points.
  - Score of 8+ suggests hazardous alcohol use
  - 15+ indicates likely alcohol dependence



Alcohol Use Disorders Identification Test (AUDIT)

Please circle the answer that is correct for you.

1. How often do you have a drink containing alcohol?

Never	Monthly or Less	Two to four times a month	Two to three times per week	Four or more times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?

1 or 2	3 or 4	5 or 6	7 to 9	10 or more

3. How often do you have six or more drinks on one occasion?

Never	Less than monthly	Monthly	Two to three times per week	Four or more times a week

4. How often during the last year have you found that you were not able to stop drinking once you had started?

Never	Less than monthly	Monthly	Two to three times per week	Four or more times a week

5. How often during the last year have you failed to do what was normally expected from you because of drinking?

Never	Less than monthly	Monthly	Two to three times per week	Four or more times a week

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

Never	Less than monthly	Monthly	Two to three times per week	Four or more times a week

7. How often during the last year have you had a feeling of guilt or remorse after drinking?

Never	Less than monthly	Monthly	Two to three times per week	Four or more times a week

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

Never	Less than monthly	Monthly	Two to three times per week	Four or more times a week

9. Have you or someone else been injured as a result of your drinking?

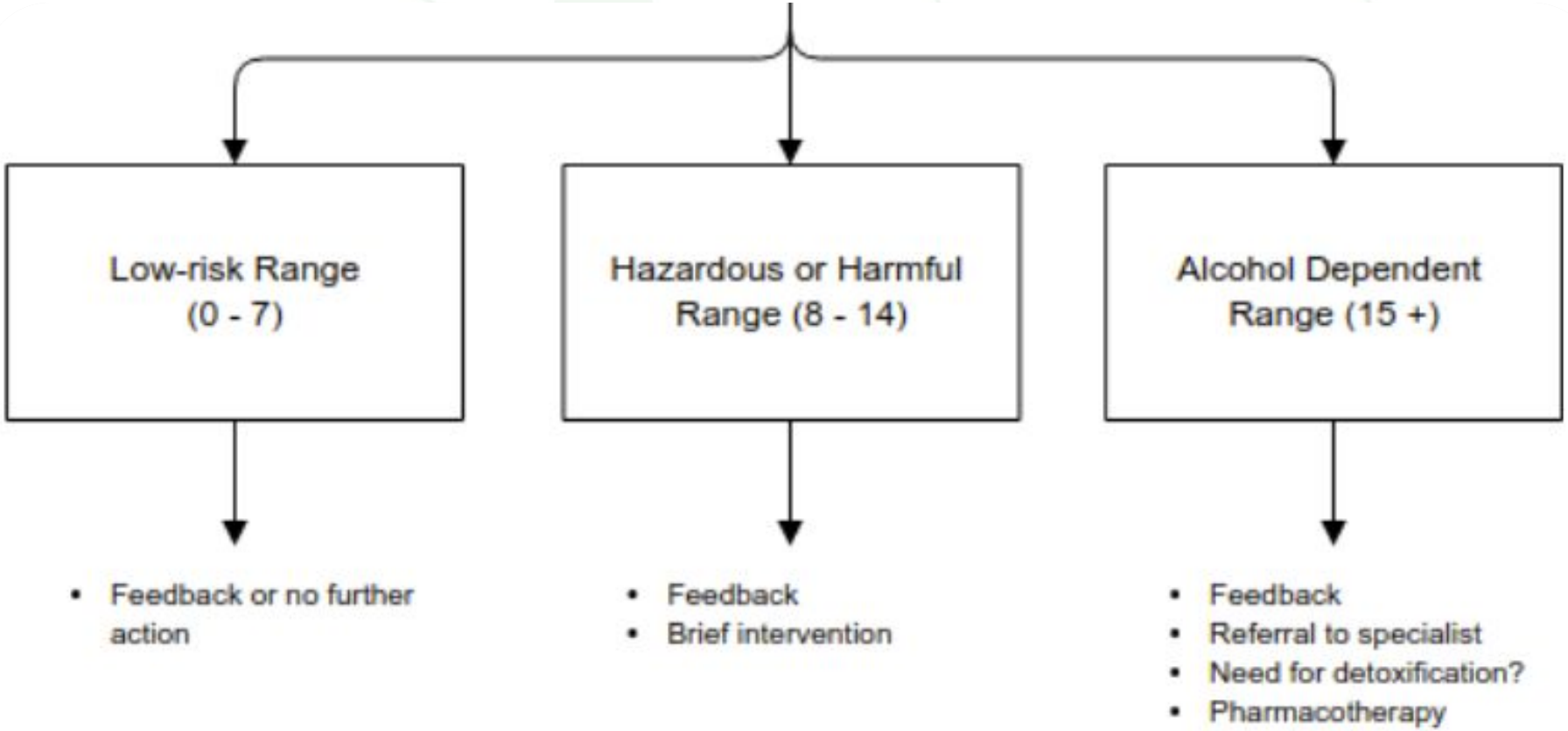
No	Yes, but not in the last year	Yes, during the last year

10. Has a relative or friend, or a doctor or other health worker, been concerned about your drinking or suggested you cut down?

No	Yes, but not in the last year	Yes, during the last year

https://pubs.niaaa.nih.gov/publications/practitioner/cliniciansguide2005/guide.pdf. Accessed 12/29/2020.

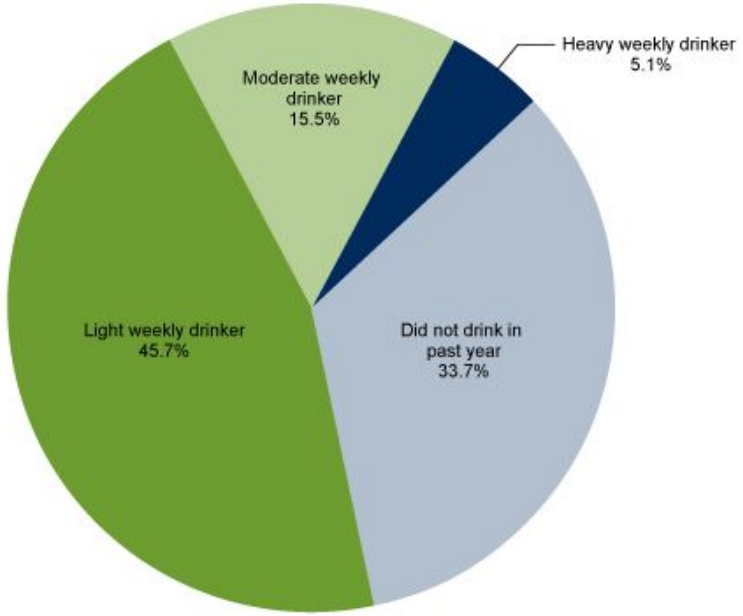
AUDIT Decision Tree



https://auditscreen.org/about/audit-decision-tree Accessed 11/20/20.

Brief Intervention: the Drink Less Program

- Give feedback on drinking risk and how drinking habits compare to others
- Ask patient “Have you thought about changing your drinking?”
- Discuss benefits of drinking less
  - Abstinence from alcohol in moderate-heavy drinkers improves insulin resistance, weight, BP and cancer-related growth factors
  - Quitting is associated with improved mental wellbeing
- Set goals
- Discuss strategies for staying on track
  - Exercise can increase abstinence, ease withdrawal sx, improve depression and anxiety in those recovering from SUD



https://auditscreen.org/drink-less-program/ Accessed 12/29/2020
https://www.rethinkingdrinking.niaaa.nih.gov/Tools/Interactive-worksheets-and-more/Default.aspx
Mehta G, Macdonald S, Cronberg A, et al. Short-term abstinence from alcohol and changes in cardiovascular risk factors, liver function tests and cancer-related growth factors: a prospective observational study. *BMJ Open*. 2018;8(5):e020673. Published 2018 May 5. doi:10.1136/bmjopen-2017-020673
Wang D, Wang Y, Wang Y, Li R, Zhou C. Impact of physical exercise on substance use disorders: a meta-analysis. PLoS One. 2014 Oct 16;9(10):e110728. doi: 10.1371/journal.pone.0110728. PMID: 25330437; PMCID: PMC4199732.
CMAJ July 08, 2019 191 (27) E753-E760; DOI: https://doi.org/10.1503/cmaj.181583

Strategies to cut down or quit

<u>To cut down:</u>

- Keep track
- Count and Measure – learn to measure a standard drink so you can accurately keep track
- Set goals

<u>To cut down or quit:</u>

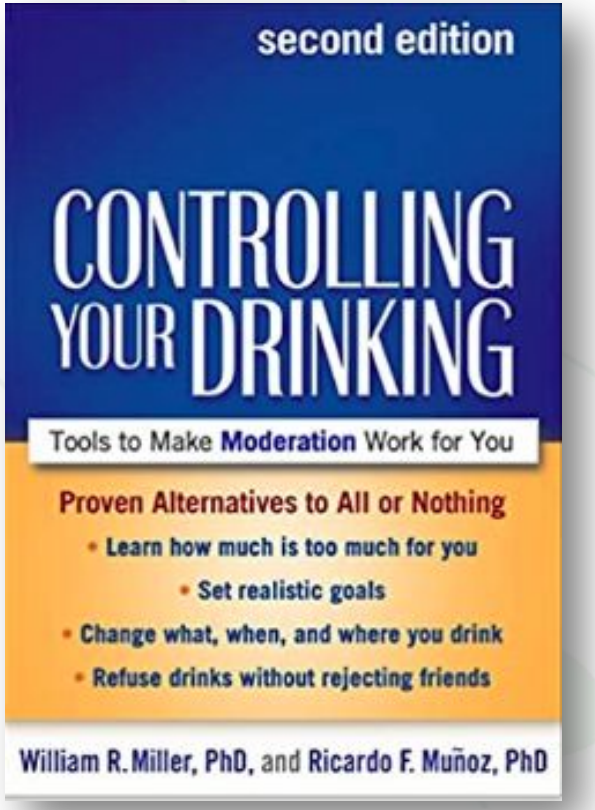
- Find alternatives – new healthy activities, manage stress/emotions/social anxiety
- Avoid triggers – certain people or settings, a specific time of day – plan a different activity at that time.
- Plan to handle urges: https://www.rethinkingdrinking.niaaa.nih.gov/Tools/Interactive-worksheets-and-more/Stay-in-control/Coping-With-Urges-To-Drink.aspx
- Learn drink refusal skills: https://www.rethinkingdrinking.niaaa.nih.gov/Tools/Interactive-worksheets-and-more/Stay-in-control/Drink-Refusal-Skills.aspx

https://www.rethinkingdrinking.niaaa.nih.gov/Thinking-about-a-change/Strategies-for-cutting-down/Tips-To-Try.aspx Accessed 6/29/2021

Controlling Your Drinking, Second Edition: Tools to Make Moderation Work for You

by William R. Miller and Ricardo F. Muñoz

Interested in cutting down on your drinking without giving it up altogether? This encouraging, science-based book can help make that goal a reality. Distinguished clinician-researchers William R. Miller and Ricardo F. Muñoz have spent more than 40 years studying whether moderation works, who it works (and doesn't work) for, and how to achieve it. They give you tools to evaluate your alcohol consumption, decide what changes you want to make, and create a doable plan of action. Learn new ways to enjoy social events, defuse tension and stress, and cope with difficult emotions--with or without a glass in hand. The updated second edition incorporates the latest scientific data and features a new chapter on mindfulness. Helpful forms and worksheets can be downloaded and printed in a convenient 8 1/2" x 11" size.



Psychosocial support

- Motivated, capable patients: Combination of **CBT, 12-step facilitation, motivational interviewing**
- Limited cognitive ability:
  - 12-step
  - Mutual support groups – AA, Secular Organizations for Sobriety...
  - Contingency management - offering incentives to encourage abstinence or discourage use
- Significant social needs:
  - Community reinforcement approach – involves the spouse or a close contact; skills training for problem solving, drink refusal, job hunting; recreational counseling to help identify sober activities
- Relationship problems: Couples or family therapy

Saitz R. (Jan 2021) Approach to treating alcohol use disorder. In Saxon AJ & Friedman N (Eds.), UptoDate. Available from https://www.uptodate.com/contents/approach-to-treating-alcohol-use-disorder.
1. https://pubs.niaaa.nih.gov/publications/practitioner/cliniciansguide2005/guide.pdf Accessed 1/2/20
2. Magill M, Ray L, Kiluk B, et al. A meta-analysis of cognitive-behavioral therapy for alcohol or other drug use disorders: Treatment efficacy by contrast condition. *J Consult Clin Psychol*. 2019;87(12):1093-1105. doi:10.1037/ccp0000447
3. Kelly JF, Humphreys K, Ferri M. Alcoholics Anonymous and other 12-step programs for alcohol use disorder. *Cochrane Database Syst Rev*. 2020;3(3):CD012880. Published 2020 Mar 11. doi:10.1002/14651858.CD012880.pub2

Virtual Support

- Alcoholics Anonymous has been running virtual support groups
- https://checkupandchoices.com/ - digital program funded by NIAAA and recommended by the American Society of Addiction Medicine's COVID-19 Task Force. Provides online or smartphone - based screening for unhealthy alcohol use and a program to support developing skills for recovery
- More Apps
  - Recovery Box
  - SoberTool
  - I am Sober

Referrals

Behavioral Health Treatment Services Locator:
https://findtreatment.samhsa.gov/

American Society of Addiction Medicine

301-656-3929

Ask for your state chapter's phone number for referrals.

https://www.rethinkingdrinking.niaaa.nih.gov/Help-links/

Qigong to help prevent relapse

- One study found that people with an addiction who tried qigong meditation had a 92% completion rate, versus the 78% completion rate for people who focused primarily on stress management and relaxation training.
- Qigong and Tai Chi Chuan worked better than yoga (as adjunctive therapy for alcoholism) in 1 study – better executive functioning and affect regulation and lower relapses at 6 month

Chen KW, Comerford A, Shinnick P, Ziedonis DM. Introducing qigong meditation into residential addiction treatment: a pilot study where gender makes a difference. *J Altern Complement Med*. 2010;16(8):875-882. doi:10.1089/acm.2009.0443
Kumar R, Kumar KJ, Benegal V, Roopesh BN, Ravi GS. Effectiveness of an Integrated Intervention Program for Alcoholism (IIPA) for enhancing self-regulation: Preliminary evidence. Asian J Psychiatr. 2019;43:37-44. doi:10.1016/j.ajp.2019.05.006

Pop Quiz!

Question:

After completing the AUDIT-10, your patient's alcohol use was considered to be in the hazardous range.

True or False? Providing feedback and a brief in-office intervention would be appropriate.

Answer:

True

Pharmacotherapy for Alcohol Use Disorder

Indications for medication

- Optimally use a combination of medication, evidence-based psychosocial treatment, social services if necessary, and a support group
- Medications (ideally with psychosocial interventions) can be used for:
  - Moderate to severe AUD (DSM-5) = current heavy use and risk for consequences
  - Patient motivation to reduce intake, patient preference for medication
- Medication not recommended for mild AUD: psychosocial interventions preferred as medication efficacy has not been determined

Saitz R. (Jan 2021) Approach to treating alcohol use disorder. In Saxon AJ & Friedman N (Eds.), UptoDate. Available from https://www.uptodate.com/contents/approach-to-treating-alcohol-use-disorder.

Address withdrawal first

- Based on the 2018 American Psychiatric Association practice guidelines:
- Evaluate for withdrawal – sx or history indicating high risk inpatient treatment, maybe ambulatory
- Withdrawal must be managed in order for patients to be willing to undergo treatment

Clinical Institute Withdrawal Assessment for Alcohol – revised (CIWA-Ar) scale

Clinical Institute Withdrawal Assessment for Alcohol revised	
Symptoms	**Range of scores**
Nausea or vomiting	0 (no nausea, no vomiting) –7 (constant nausea and/or vomiting)
Tremor	0 (no tremor) – 7 (severe tremors, even with arms not extended)
Paroxysmal sweats	0 (no sweat visible) – 7 (drenching sweats)
Anxiety	0 (no anxiety, at ease) – 7 (acute panic states)
Agitation	0 (normal activity) – 7 (constantly trashes about)
Tactile disturbances	0 (none) – 7 (continuous hallucinations)
Auditory disturbances	0 (not present) – 7 (continuous hallucinations)
Visual disturbances	0 (not present) – 7 (continuous hallucinations)
Headache	0 (not present) – 7 (extremely severe)
Orientation/clouding of sensorium	0 (orientated, can do serial additions) – 4 (Disorientated for place and/or person)

Saitz R. (Jan 2021) Approach to treating alcohol use disorder. In Saxon AJ & Friedman N (Eds.), UptoDate. Available from https://www.uptodate.com/contents/approach-to-treating-alcohol-use-disorder.
Clinical Institute Withdrawal Assessment for Alcohol (CIWA -A) scale. GP notebook. Available from https://gpnotebook.com/simplepage.cfm?ID=x20201007173622554 60. Accessed 3/24/2021.

Withdrawal Treatment Goals

- Determine if inpatient or outpatient treatment is more appropriate
  - CIWA-Ar
    - <15 and **no hx of seizures or delirium tremens** □ outpatient
    - 15+ and or hx of seizures or delirium tremens □ inpatient
- Manage symptoms
  - Tremors, sweating, elevated pulse and blood pressure, nausea, insomnia, anxiety, possibly generalized seizures
- Prevent serious events
  - Seizures
  - Delirium tremens
  - Death
- Address nutritional deficiencies

Hoffman RS & Weinhouse GL. (January 2021) Management of moderate and severe alcohol withdrawal syndromes. In Traub SJ, Grayzel (Eds.), UptoDate. Available from https://www.uptodate.com/contents/management-of-moderate-and-severe-alcohol-withdrawal-syndromes
Muncie HL, Yasinian Y, Ogé L. Outpatient Management of Alcohol Withdrawal Syndrome. *Am Fam Physician.* 2013 Nov 1;88(9):589-595

Ambulatory Treatment

- Ambulatory treatment for withdrawal lasts from 1 to 7 days.
- Follow up with patients **daily** – can alternate in-person and phone consult days if appropriate.
- Patient needs to be monitored frequently by a friend/family member who stays with them during this time for worsening symptoms or respiratory depression

Hoffman RS & Weinhouse GL. (January 2021) Management of moderate and severe alcohol withdrawal syndromes. In Traub SJ, Grayzel (Eds.), UptoDate. Available from https://www.uptodate.com/contents/management-of-moderate-and-severe-alcohol-withdrawal-syndromes

Medications for Withdrawal

- Gabapentin
- Carbemazepine
- Diazepam
- Lorazepam
- Chlordiazepoxide
- Oxazepam

Hoffman RS & Weinhouse GL. (January 2021) Management of moderate and severe alcohol withdrawal syndromes. In Traub SJ, Grayzel (Eds.), UptoDate. Available from https://www.uptodate.com/contents/management-of-moderate-and-severe-alcohol-withdrawal-syndromes

Benzodiazepines for withdrawal

- MOA: Stimulate GABA receptors.
- Treats psychomotor agitation and prevents progression to worsening symptoms like seizures and delirium.
- Warning: **Excessive doses can lead to respiratory depression**. Risk of misuse and addiction.
- Longer acting benzos are generally preferable – chlordiazepoxide
- Shorter acting can be used for those with liver disease, delirium or dementia – lorazepam or oxazepam.

Hoffman RS & Weinhouse GL. (January 2021) Management of moderate and severe alcohol withdrawal syndromes. In Traub SJ, Grayzel (Eds.), UptoDate. Available from https://www.uptodate.com/contents/management-of-moderate-and-severe-alcohol-withdrawal-syndromes

Symptom-triggered dosing for very mild withdrawal (CIWA-Ar<10)

- Medication taken only if patient experiences withdrawal symptoms.
- Longer-acting benzo: chlordiazepoxide
  - Day 1: 50 mg q 6 to 12 hrs prn
  - Days 2 to 5: 25 mg q 6 hrs prn
- Shorter-acting benzo: oxazepam
  - Day 1: 30 mg every 6 hours prn
  - Days 2 to 5 : 15 mg q 6 hrs prn

Hoffman RS & Weinhouse GL. (January 2021) Management of moderate and severe alcohol withdrawal syndromes. In Traub SJ, Grayzel (Eds.), UptoDate. Available from https://www.uptodate.com/contents/management-of-moderate-and-severe-alcohol-withdrawal-syndromes

Fixed* dosing for mild withdrawal (CIWA-Ar 10 to 15)

Longer-acting benzodiazepine – chlordiazepoxide

- Day 1 - 50 mg q 6 to 12 hours
- Day 2 - 25 mg q 6 hours
- Day 3 - 25 mg BID
- Day 4 - 25 mg qhs

Shorter-acting benzodiazepine – oxazepam

- Day 1 - 30 mg q 6 hrs
- Day 2 - 30 mg q 8 hrs
- Day 3 - 30 mg q 12 hrs
- Day 4 - 30 mg qhs

*PRN dosing per the previous slide would also be appropriate.

Hoffman RS & Weinhouse GL. (January 2021) Management of moderate and severe alcohol withdrawal syndromes. In Traub SJ, Grayzel (Eds.), UptoDate. Available from https://www.uptodate.com/contents/management-of-moderate-and-severe-alcohol-withdrawal-syndromes

Gabapentin

- Rx: 6 day taper starting with 900mg or 1200mg/day
- MOA: GABA analogue, an anticonvulsant
- Can treat **mild** alcohol withdrawal (**not involving seizures or delirium**) in the outpatient setting
- Side effects: dizziness, drowsiness (less than with benzos), ataxia, diarrhea, weakness, nausea and vomiting
- Potential for misuse but clinicians have noted that it seems less addictive than benzodiazepines.

Hoffman RS & Weinhouse GL. (January 2021) Management of moderate and severe alcohol withdrawal syndromes. In Traub SJ, Grayzel (Eds.), UptoDate. Available from https://www.uptodate.com/contents/management-of-moderate-and-severe-alcohol-withdrawal-syndromes

Massage reduces Alcohol Withdrawal Scale scores during detox

- In 50 pts undergoing alcohol detoxification, those who were randomized to massage or a “rest” control group, Those receiving massage generally showed reductions in pulse rate on 3 of the 4 days of treatment compared to the control group. Massage was also more effective in reducing Alcohol Withdrawal Scale scores in the early stages of the detoxification process. Respiration in the massage group was reduced toward the end of the detoxification admission.

"kitty back rub" by rndmcnlly is licensed with CC BY 2.0.

"'Back-rub session'" by billheng is licensed with CC BY-ND 2.0.

Reader M, Young R, Connor JP. **Massage therapy improves the management of alcohol withdrawal syndrome**. *J Altern Complement Med*. 2005;11(2):311-313. doi:10.1089/acm.2005.11.311

Medications for AUD

FDA-approved:

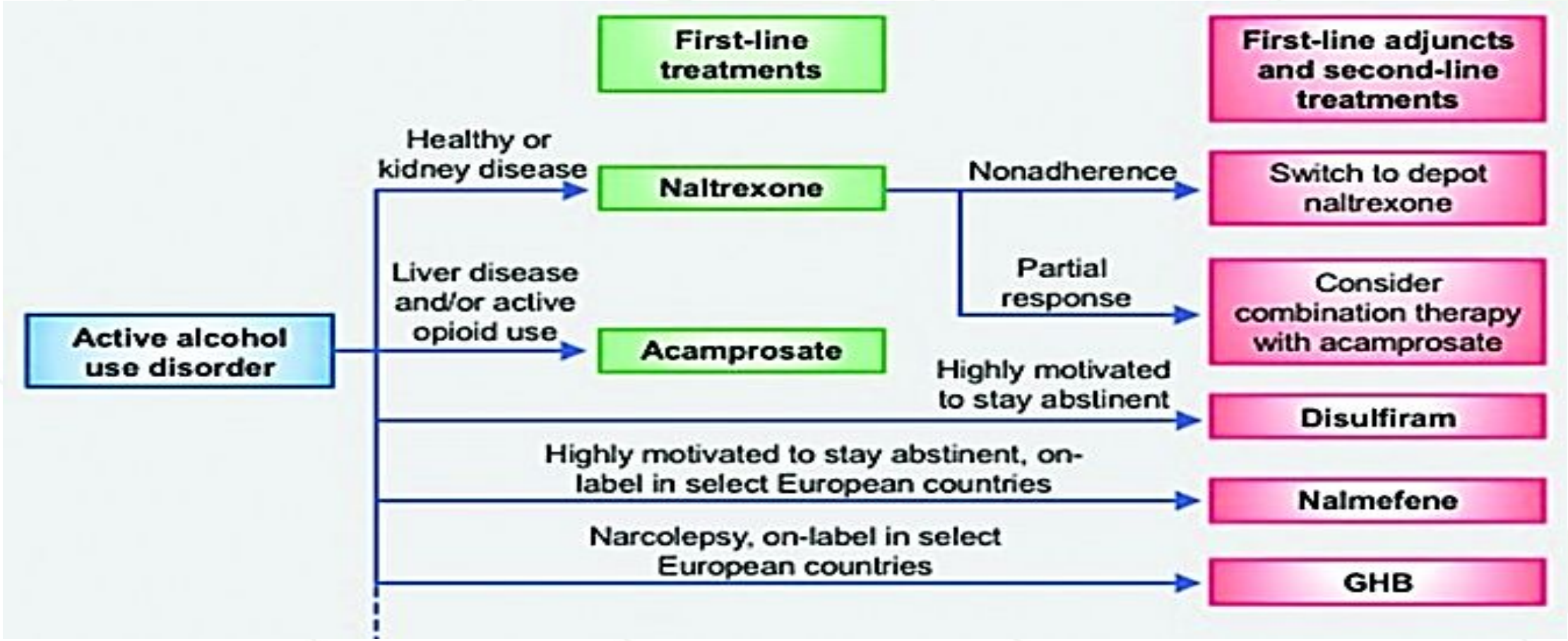
- **Naltrexone** – oral and extended release injectable (1st line)
- **Acamprosate** (1st line)
- **Disulfiram** (2nd line)

Off-label:

- Gabapentin (2nd line)
- Baclofen
- Topiramate (2nd line)
- Ondansetron

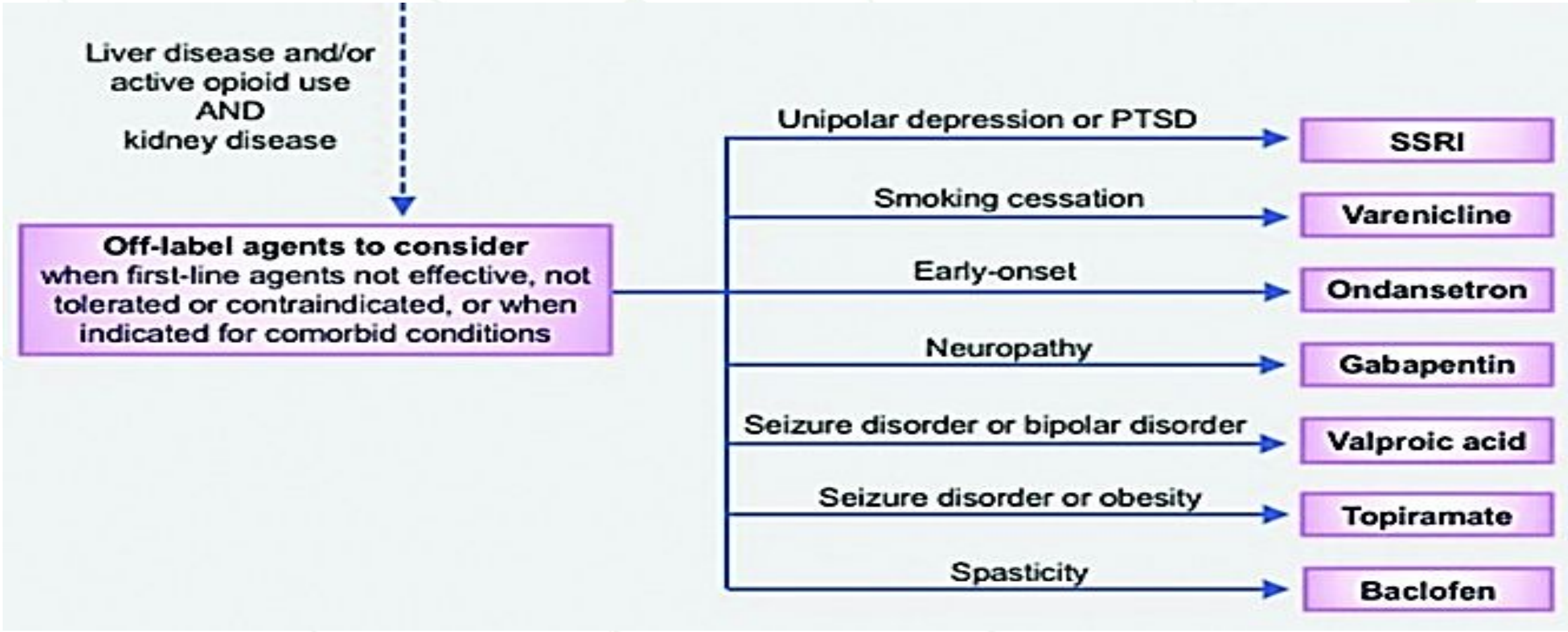
Kim T, Hack LM, Ann LS, Kim J. Practical outpatient pharmacotherapy for alcohol use disorder. *Drugs Context*. 2018;7:212308. Published 2018 Feb 7. doi:10.7573/dic.212308

Pharmacotherapy Algorithm



Kim Y, Hack LM, Ahn ES, Kim J. Practical outpatient pharmacotherapy for alcohol use disorder. *Drugs Context*. 2018;7:212308. Published 2018 Feb 7. doi:10.7573/dic.212308

Pharmacotherapy Algorithm (Cont'd)



Kim Y, Hack LM, Ahn ES, Kim J. Practical outpatient pharmacotherapy for alcohol use disorder. Drugs Context. 2018;7:212308. Published 2018 Feb 7. doi:10.7573/dic.212308

Naltrexone

- MOA: nonselective antagonist of μ, κ, and δ-opioid receptors, blocks rewarding effect of alcohol, reduces cravings
- Proven efficacy with minimal medical advice and no psychosocial therapy
- Considered “first-line”
- Placebo-controlled trials have shown it decreases relapse to heavy drinking and total alcohol consumption
- Can be **initiated while patient still drinking**.
- Dosing strategy: Daily pill or monthly injection
- High doses are hepatotoxic, **contraindicated in hepatic insufficiency**
- Monitor LFTs minimally at baseline, 1 month and annually
- Can treat comorbid AUD and opioid use disorder as long as a sufficient period of abstinence from opioids has been achieved

Saitz R. (Jan 2021) Approach to treating alcohol use disorder. In Saxon AJ & Friedman N (Eds.), UptoDate. Available from https://www.uptodate.com/contents/approach-to-treating-alcohol-use-disorder.

Acamprosate

- MOA: GABA-A agonist, weak antagonist of NMDA receptors and metabotropic receptor 5. Relieves some withdrawal sx, which may lesson desire to drink
- Helps those who crave alcohol in a negative mental state or when sleep-deprived, and has been shown to reverse changes to sleep architecture caused by alcohol.
- Meta-analysis found no difference in rate of return to drinking/heavy drinking vs naltrexone
- Lack of efficacy in US clinical trials; European trials have shown efficacy
- **Not compatible with drinking**, requires period of abstinence prior to initiation
- Dosing: 2 pills TID! □ poor adherence
- Excreted by kidneys and can be used in patients with liver disease
- **Contraindicated in severe renal dysfunction** (CC ≤30 mL/min) and hypercalcemia.
- Monitor renal function at baseline and at regular intervals. For moderate renal dysfunction, 1/2 dose is used initially (333mg TID)
- Appropriate choice if patient is currently taking a clinically-indicated opioid

Fairbanks J, Umbreit A, Kolla BP, et al. Evidence-Based Pharmacotherapies for Alcohol Use Disorder: Clinical Pearls. Mayo Clinic Proceedings. 2020 May;95(9):1964-1977.

Disulfiram

- Requires **abstinence prior to initiating**
- Goal to maintain abstinence
- “A meta-analysis of 22 RCTs showed an increase in total abstinence, percentage of abstinent days, mean days without alcohol, time to first drink, and a decreased likelihood of relapse” vs placebo
- MOA: Blocks aldehyde dehydrogenase 2 in liver and brain. Leads to elevated acetaldehyde levels after alcohol consumption causing adverse effects – nausea, vomiting, headache, flushing.
- Efficacy shown when taken regularly and patient being supervised.
- Contraindications: Liver disease, seizure disorder, psychotic disorder, severe myocardial disease. Avoid kombucha, vinegar, mouth wash, hand sanitizer, and some NABs. Avoid alcohol x 2 weeks after last dose.
- Monitor: LFTs baseline and monthly x 3 months, then quarterly for elevated transaminases

Fairbanks J, Umbreit A, Kolla BP, et al. Evidence-Based Pharmacotherapies for Alcohol Use Disorder: Clinical Pearls. Mayo Clinic Proceedings. 2020 May;95(9):1964-1977.

Pop Quiz!

Question:

Which medication for alcohol use disorder is available as an injection?

A) Disulfiram

B) Naltrexone

C) Acamprosate

Answer:

B) Naltrexone

Topiramate

- Off-label use for AUD, shown to reduce drinking
- Additional indications: seizure disorder, binge eating disorder, migraine prophylaxis
- Non-benzodiazepine anticonvulsant. Reduces dopamine levels in the mesocorticolimbic system and decreases rewarding effects from alcohol. Suppresses appetite.
- Side effects: cognitive impairment, paresthesias, weight loss, headache, fatigue, dizziness, depression
- **Contraindicated within 6 hours of alcohol consumption**

Fairbanks J, Umbreit A, Kolla BP, et al. Evidence-Based Pharmacotherapies for Alcohol Use Disorder: Clinical Pearls. Mayo Clinic Proceedings. 2020 May;95(9):1964-1977.

Baclofen

- Off-label. Approved in France for AUD.
- MOA: GABA-B receptor agonist, restores GABA supply which is chronically depleted in AUD.
- May be used for AUD with co-occurring liver cirrhosis. Caution in renal failure.
- Conclusion of 2018 meta-analysis:

  “associated with higher rates of abstinence than placebo. However, there is no superior effect of baclofen on increasing number of abstinent days, or decreasing heavy drinking, craving, anxiety or depression. These results suggest that the current increasing use of baclofen as a treatment for alcohol use disorders is premature.”

Rose AK, Jones A. Baclofen: its effectiveness in reducing harmful drinking, craving, and negative mood. A meta-analysis. Addiction. 2018 Aug;113(8):1396-1406. doi: 10.1111/add.14191. Epub 2018 Mar 24. PMID: 29479827.

Gabapentin

- Off-label for AUD – reduces cravings and heavy drinking, helps abstinence
- Also indicated for withdrawal
- FDA-approved for partial seizures; gabapentin enacarbil for restless legs syndrome.
- Small studies found it lead to more abstinence and reduced heavy drinking vs placebo
- Caution in renal disease.
- 1% of the population has used gabapentin recreationally or in an attempt to self-harm.

Fairbanks J, Umbreit A, Kolla BP, et al. Evidence-Based Pharmacotherapies for Alcohol Use Disorder: Clinical Pearls. Mayo Clinic Proceedings. 2020 May;95(9):1964-1977.

Course of treatment

Inadequate response after 3 to 4 months?

- Judged by change to prior drinking pattern
  - Response to disulfiram can be seen in a few days; naltrexone/acamprosate can take a few weeks; topiramate takes longer as it requires tapering up. Psychosocial treatments take longer.
- Increase intensity of psychosocial therapy or add in a psychosocial treatment
- Switch from oral to injectable naltrexone for better adherence
- Clinicians might increase dose of some meds, but clinical trials do not show higher doses to work better. Theoretically might make up for missed doses.
- Change medication

Saitz R. (Jan 2021) Approach to treating alcohol use disorder. In Saxon AJ & Friedman N (Eds.), UptoDate. Available from https://www.uptodate.com/contents/approach-to-treating-alcohol-use-disorder

Next or 2nd-line Medication

- Naltrexone or acamprosate – insufficient response or contraindicated? Try the other
- Neither of the above worked or both CI?
- 2nd line: Disulfiram or topiramate
  - **Disulfiram** preferred due to worse side effect profile of topiramate
- 3rd line: ondansetron, baclofen, gabapentin – limited evidence
- Combining medications is not recommended as RCTs have failed to show improved effect with combination of naltrexone with either acamprosate or with sertraline.

Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA 2006; 295:2003.
Farren CK, Scimeca M, Wu R, Malley SO. A double-blind, placebo-controlled study of sertraline with naltrexone for alcohol dependence. Drug Alcohol Depend 2009; 99:317.

How long to continue treatment?

Good response?

- Psychosocial treatment should be continued for 6 to 12 months
- Medications x 1 year
  - Lower risk of recurrence
  - Longer if still providing benefit
  - Efficacy decreases once medications are stopped, but patients are more stable with increasing lengths of remission
  - **Topiramate** must be tapered over 2 weeks

Saitz R. (Jan 2021) Approach to treating alcohol use disorder. In Saxon AJ & Friedman N (Eds.), UptoDate. Available from https://www.uptodate.com/contents/approach-to-treating-alcohol-use-disorder.

Medication[1]	Dosing[2]	Side effects and monitoring[3]	Medicolegal tips, other indications and contraindications[4]
Naltrexone	50 mg once daily 380 mg monthly for intramuscular formulation	Nausea, vomiting, decreased appetite, anxiety, **hepatocellular injury, suicidality** Injection site reactions for the intramuscular formulation Monitor liver function	- Patient must be opioid-free for 7–10 days prior to initiation, as confirmed by negative urine test and/or naloxone challenge test - Discontinue if opioid-based anesthesia is anticipated - Warn patients of potential for hepatotoxicity - Contraindicated in acute hepatitis or liver failure
Acamprosate	333 mg tablets 2 tablets three times daily for weight ≥132 lbs and 2 tablets twice daily for weight <132 lbs *–Renal dosing	Diarrhea, nausea, flatulence, anxiety, depression, **suicidality** Monitor renal function	- Contraindicated in patients with creatinine clearance less than 30 mL per minute
Disulfiram	Begin at 250 mg daily, may increase to 500 mg daily *–Variable starting doses	Disulfiram-alcohol interaction, metallic taste, dermatitis, sedation, headache, **psychosis, hepatotoxicity, hypotension** Monitor liver function	- Patients must be educated about the effects if they drink, including potentially lethal hypotension, and that reactions may occur up to 2 weeks after discontinuing the medication, as well as with other forms of alcohol, including mouthwash and with cough syrup - Contraindicated in patients who are intoxicated with alcohol, taking metronidazole, amprenavir, ritonavir, or sertraline, have psychosis or cardiovascular disease

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Topiramate	Begin at 25 mg daily and increase to up to 150 mg twice daily *–Renal dosing	Sedation, dizziness, ataxia, paresthesia, psychomotor retardation, speech difficulties, tremor, nausea, cognitive function, **metabolic acidosis** Monitor electrolytes	- Indicated for epilepsy, migraine prophylaxis, chronic weight management - Non-FDA use for bipolar disorder, psychotropic drug-induced weight gain, binge-eating disorder - Contraindicated within 6 hours of alcohol use
Gabapentin	Begin at 300 mg once daily and increase to up to 600 mg three times daily *–Renal dosing	Sedation, dizziness, ataxia, fatigue, tremor, xerostomia, constipation, weight gain, peripheral edema, **sudden death** (when used in epilepsy) **and suicidality** Monitor renal function	- Indicated for post-herpetic neuralgia, adjunctive therapy in epilepsy, restless leg syndrome - Non-FDA use for fibromyalgia, anxiety, bipolar disorder
Baclofen	Begin at 5 mg three times daily, may increase up to 10 mg three times daily	Dizziness, drowsiness, fatigue, weakness, **CNS depression, respiratory depression, seizures**	- Indicated for spasticity - Non-FDA use for intractable hiccups
Nalmefene	18 mg daily as needed 1–2 hours prior to anticipated drinking situation or as soon as possible after drinking	Nausea, vomiting, insomnia, fatigue, dizziness, **confusion, psychosis, dissociation**	- Not available in the US but approved for AUD in the EU - Should not be chewed or crushed owing to potential for skin sensitization if medication comes in contact with skin
Gamma-hydroxybutyric acid	Administer 50–100 mg/kg daily divided into 3–6 doses *–hepatic dosing	Dizziness, vertigo, sedation, headache, nausea, vomiting, enuresis, depression, **respiratory depression in overdose, psychosis, wandering at night**	- Indicated excessive sleepiness and cataplexy in narcolepsy - Use with extreme caution given potential for abuse and/or diversion - Providers must register with Xyrem REMS Program and use pharmacy that is specially certified

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SSRI[5]	Depends on choice of the SSRI	Constipation, flatulence, insomnia, sedation, tremor, headache, dizziness, sweating, sexual dysfunction, **seizures, mania, suicidality**	Indicated for mood, anxiety, obsessive compulsive disorders, eating disorders, but depends on the choice of SSRI - Use with caution in patients with history of seizures or bipolar disorder
Varenicline	Begin at 0.5 mg daily, may increase up to 1 mg twice daily	Dose dependent nausea, vomiting, constipation, flatulence, insomnia, headache, abnormal dreams, depression, **suicidality**	- Indicated for nicotine dependence - Carefully monitor for changes in behavior, depressed mood, agitation and suicidality
Ondansetron	Studies have used low doses (4 μg twice daily) but lowest dose available is 4 mg *–hepatic dosing	Headache, fatigue, constipation, diarrhea, dizziness, **dose dependent QT prolongation** Monitor EKG in high risk patients	- Indicated for nausea/vomiting - Avoid in patients with congenital long QT syndrome - Use caution and monitor EKG in patients with electrolyte abnormalities, bradyarrhythmias, or CHF and those taking another QT prolonging agent

[1]FDA (U.S. Food and Drug Administration) approved medications for treatment of AUD indicated in bold.
[2]All dosing in oral route unless otherwise indicated.
[3]More common or notable side effects listed first, with serious but rare potential adverse effects to be aware of highlighted in bold.
[4]Specific medication allergy not listed for each medication to avoid redundancy, but prescribers should be aware of this contraindication.
[5]Selective serotonin reuptake inhibitors.
*Indicates drug dosing considerations for patients with hepatic or renal impairments.

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Pop Quiz!

Question:

Which medication is a negative reinforcement tool that causes nausea and vomiting when combined with alcohol?

A) Disulfiram
B) Topiramate
C) Baclofen

Answer:

A) DIsulfiram

Summary

- Regular alcohol consumption is associated with certain health risks and benefits for women depending on the quantity consumed.
- Moderate alcohol consumption is associated with lower risk of heart disease and stroke, decreased mortality and “successful aging.”
- It is also associated with increased risk of breast cancer, osteoporosis, hormone and neurotransmitter imbalance.
- Proper screening for alcohol use disorders is essential. Do not advise a nondrinker to start consuming alcohol for the perceived benefits. Association does not prove causation.
- Withdrawal must be addressed first, and medications include benzodiazepines and gabapentin. First-line pharmacotherapy for AUD includes naltrexone or acamprosate.

Questions?