ALCOHOL USE DISORDER REVIEW, PHARMACOLOGIC TREATMENTS/PITFALLS & CO-OCCURRING DISORDERS

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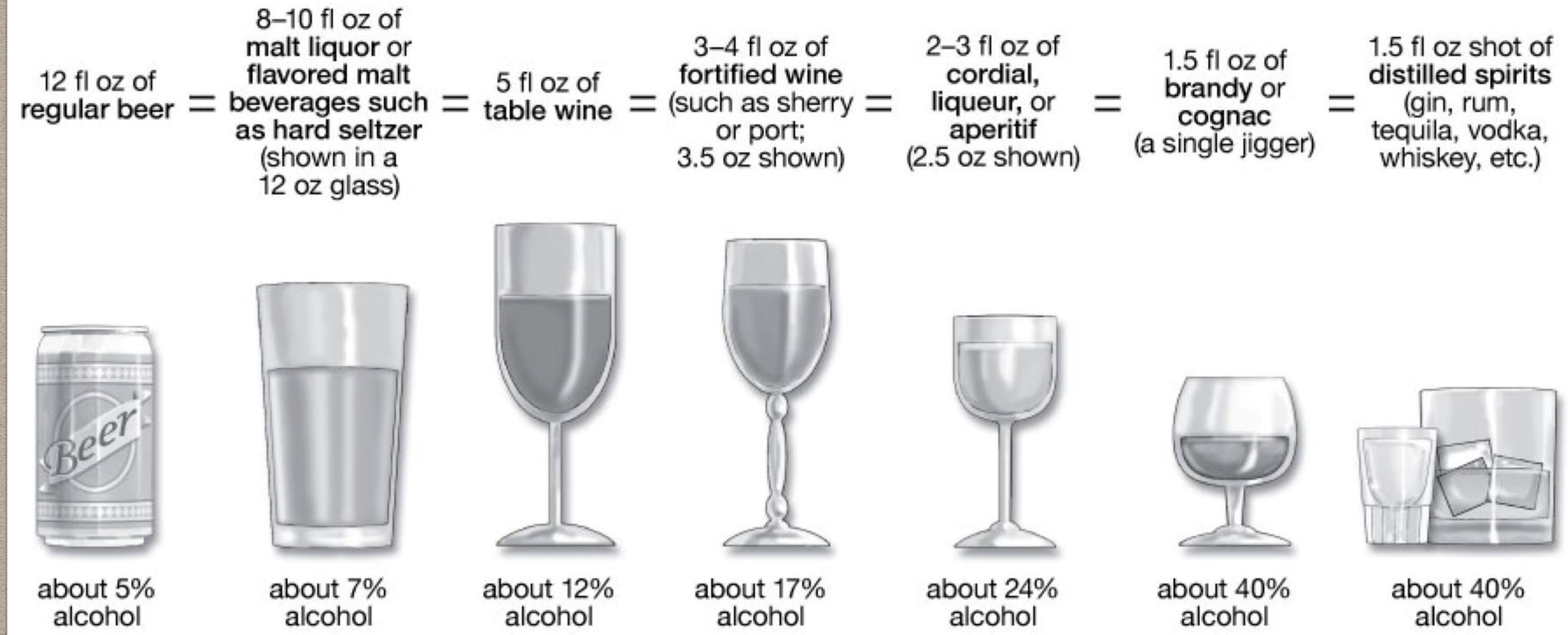
OBJECTIVES

- To define alcohol use disorder and to understand what are recommended daily and weekly drink limits
- Be able to list the 3 FDA approved medications for alcohol use disorder and their relative indications/contraindications
- To understand common co-occurring disorders and how to understand and address them in the context of alcohol use



WHAT IS A "STANDARD DRINK"?

NOT A STANDARD DRINK…

A "STANDARD DRINK"

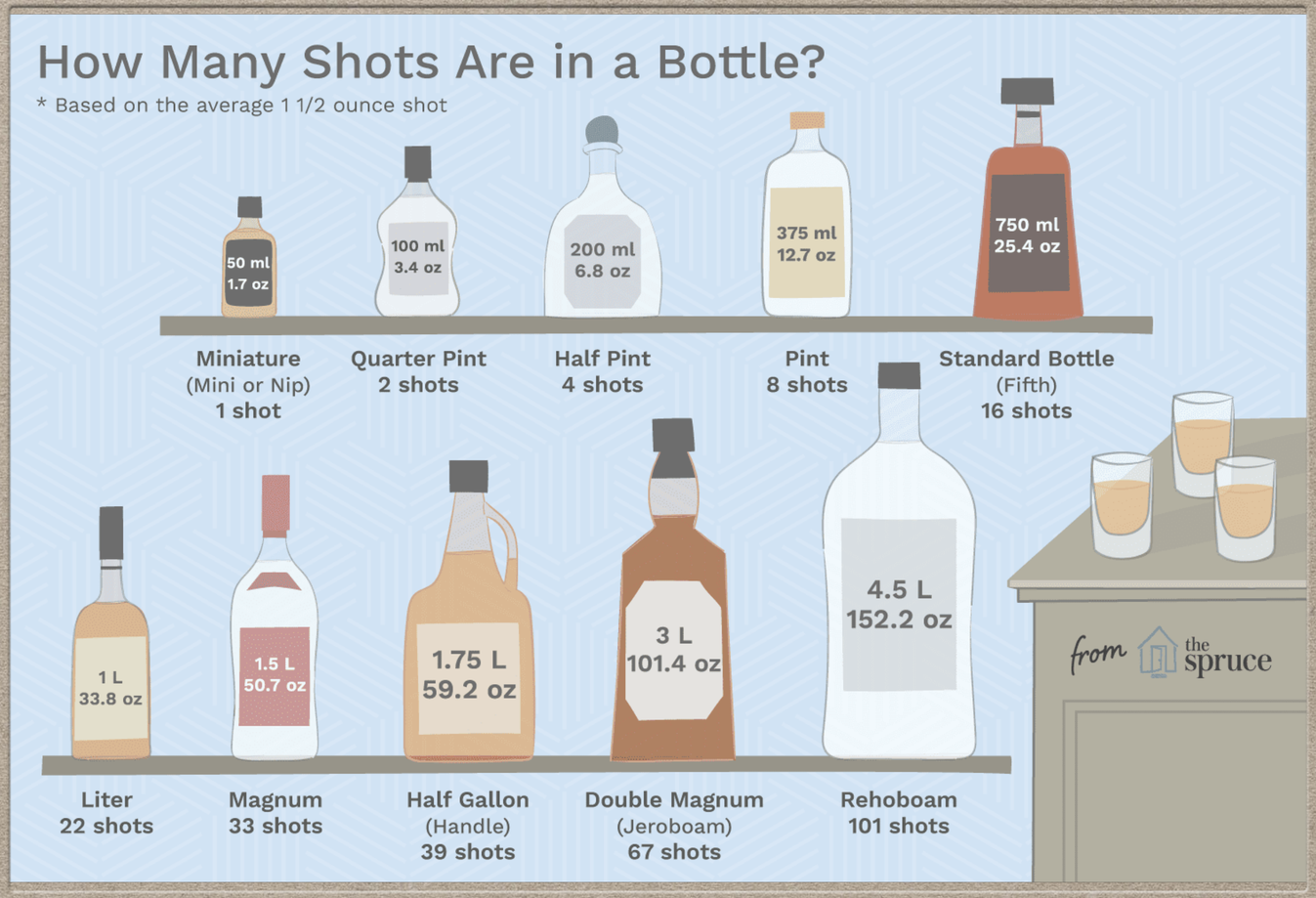
(a standard drink contains approximately 12-14 grams or 0.5-0.6 oz of pure alcohol)

Beer (3-5%) (Budweiser, Miller, Coors, Michelob, Heineken, Corona)	Malt Liquor (7-10%) (Steele Reserve, Colt 45, King Cobra, Camo 40, Black Bull, Hurricane, Mickey's, Private Stock)	Table Wine (12-13%) (Chardonnay, Merlot, Pinot Grigio, Reisling, Sangria)	Fortified Wine (FW), Port, Sherry (17-20%) (Mad Dog 20/20, Night Train Express, Richard's Wild Irish Rose, Thunderbird)	Brandy (37-40%) (Cognac, Martell, Hennessy, E & J, Courvoisier, Remy Martin)	Liquor/Distilled "Spirits" (40%) (vodka, gin, rum, scotch, whiskey, bourbon, tequila)
					
12oz.	6-8oz.	5oz.	3.5 oz.	1.5 oz.	1.5 oz.

"Double Deuce"= 2 drinks	"Pint"= 2 ½ drinks	"Half Pint"= 4 ½ drinks
"Quart"= 2 ½ drinks	"Pint" of FW = 4 drinks	"Pint"= 8 ½ drinks
"40" of beer = 3-4 drinks	"Fifth"= 5 drinks	"Fifth"= 17 drinks
"40" of malt liquor = 6-7 drinks	"Fifth" of FW = 7 ½ drinks	"Handle"= 40 drinks

ASSESSING ALCOHOL QUANTITY

- Ask about beer and wine specifically.
- Ask if the “bottle” (pint, fifth, etc.) is beer, wine or liquor.
- Ask how many ounces or how big “a drink” is (can have patient gesture with hands).
- Beer bottles/cans come in ounces and mls/liters.
- Wine and liquor bottles come in mls/liters.
- Several names are often used to describe different sizes of bottles
    - 1 fluid ounce ≈ 30mL



LEVELS OF RISK FOR ALCOHOL USE

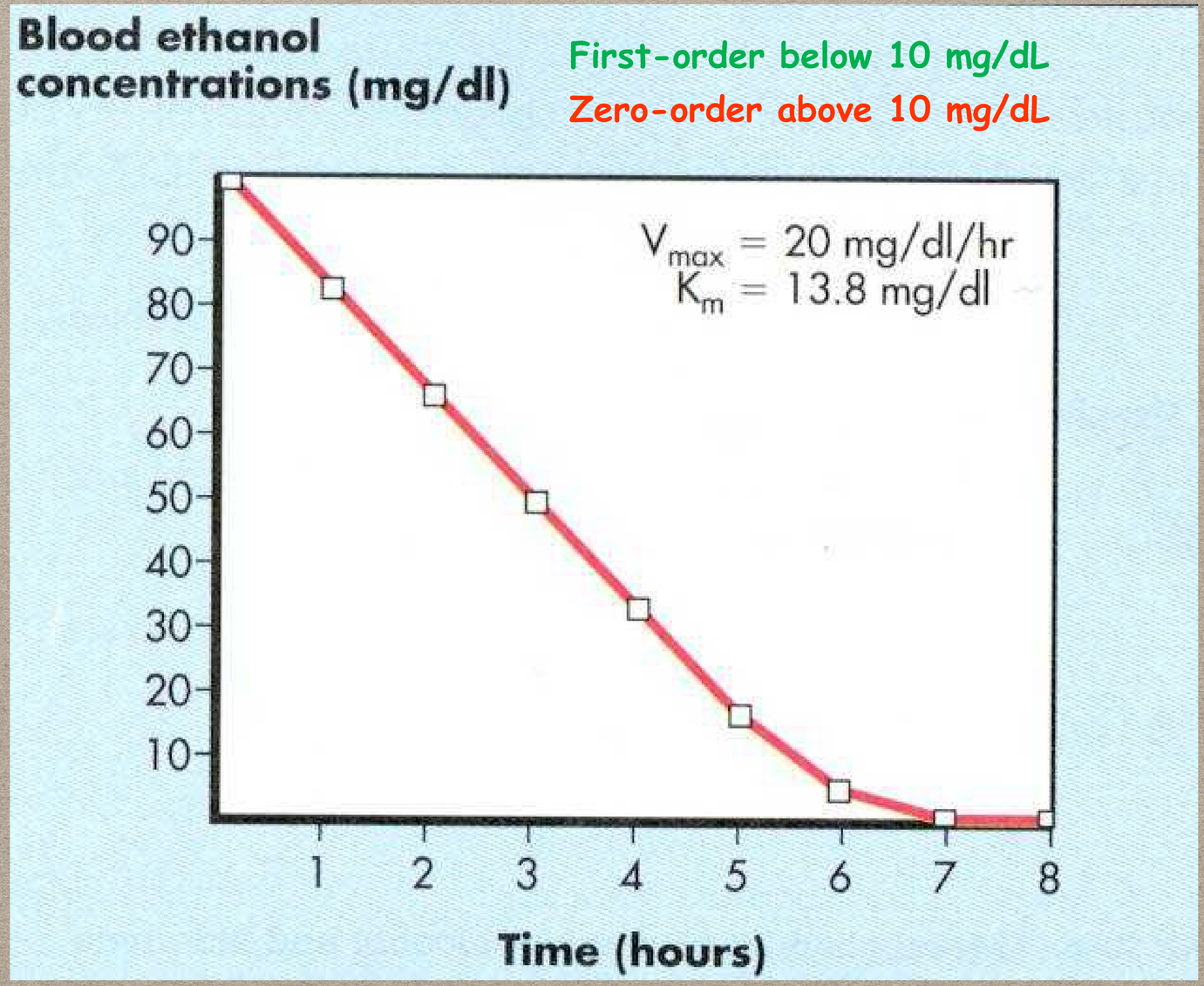
- Patients drinking above these recommended levels could be putting themselves at risk for illness or injury.
  - Their alcohol use should be addressed with a secondary screen and/or a brief intervention/advice.
- Patients with high physical dependence may need medication to manage withdrawal.
  - "Dietary Guidelines for Americans 2020-2025" (HHS); National Institute on Alcohol Abuse & Alcoholism (NIH)

Groups	Drinks/Week	Drinks/Occasion
Men	More than **14**	More than **4**
Women	More than **7**	More than **3**
65+	More than **7**	More than **3**

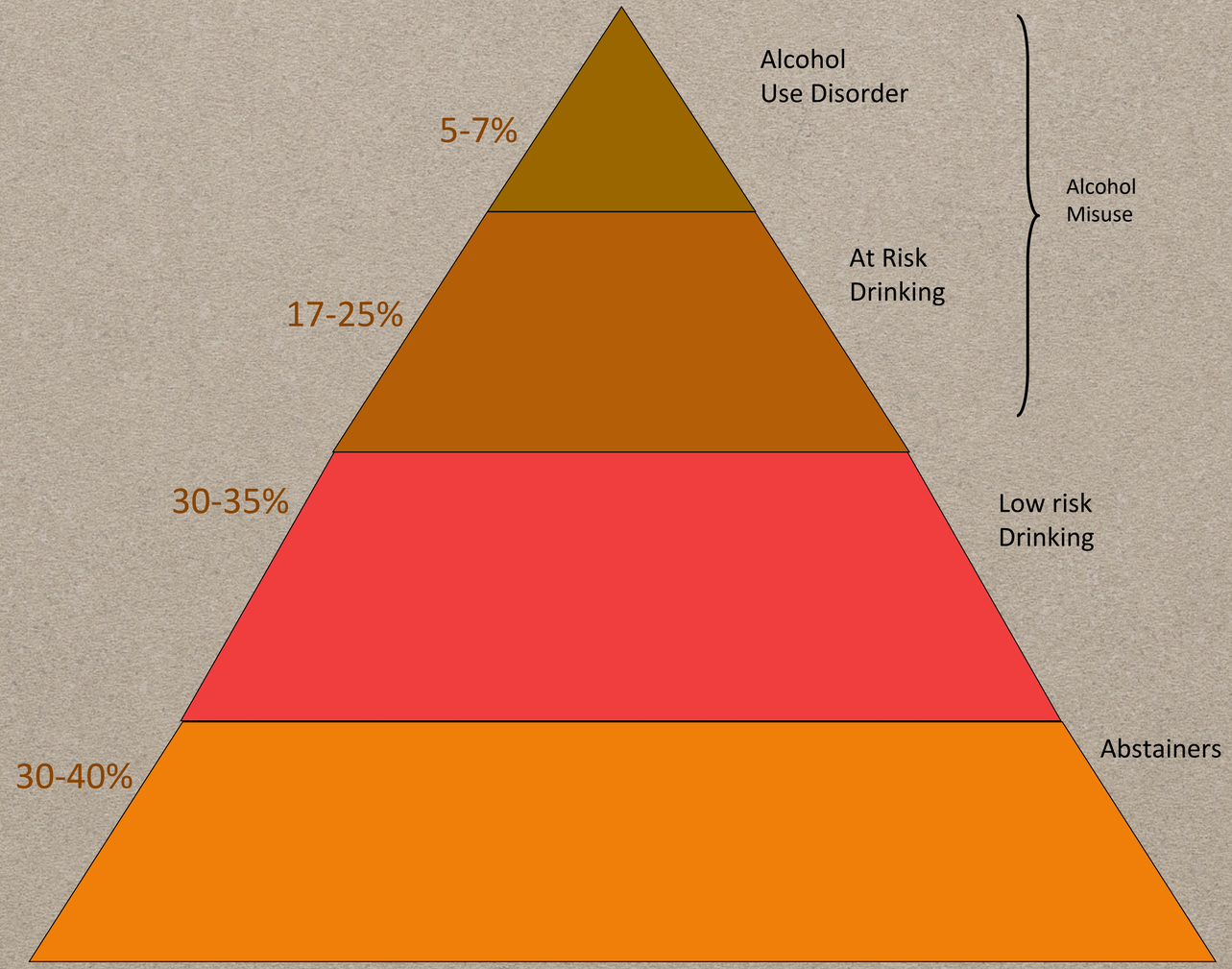
CONCENTRATION-EFFECT RELATIONSHIP

BAC [%]	EFFECTS
0.02-0.03	Mood elevation. Slight muscle relaxation.
0.05-0.06	Relaxation and Warmth. Increased reaction time. Decreased fine muscle coordination.
0.08-0.09	Impaired balance, speech, vision, hearing, muscle coordination. Euphoria.
0.14-0.20	Slurred speech, ataxia, impaired motor function
0.20-0.30	Confusion, hypotension, unconscious
0.30-0.50	Respiratory depression, Coma
>0.50	Death from respiratory depression

PHARMACOKINETICS AND ELIMINATION



PREVALENCE OF ALCOHOL MISUSE IN PRIMARY CARE… HAS THIS CHANGED SINCE COVID?



Source: Manwell, Fleming, Johnson, & Barry (1998)

PRIMARY SCREEN: ALCOHOL

- “How often did you have a drink containing alcohol, even beer or wine, in the past year?”
- *If any at all, ask:*
    - “How many drinks containing alcohol do you have on a typical day when you do drink?” **OR**
    - “How often did you have 5 (for men)/4 (for women & elderly) or more drinks on one occasion in the past year?”

ALCOHOL USE DISORDER (AUD)

2-3 symptoms for mild AUD ——— 4-5 for moderate AUD ——— >6 for severe AUD

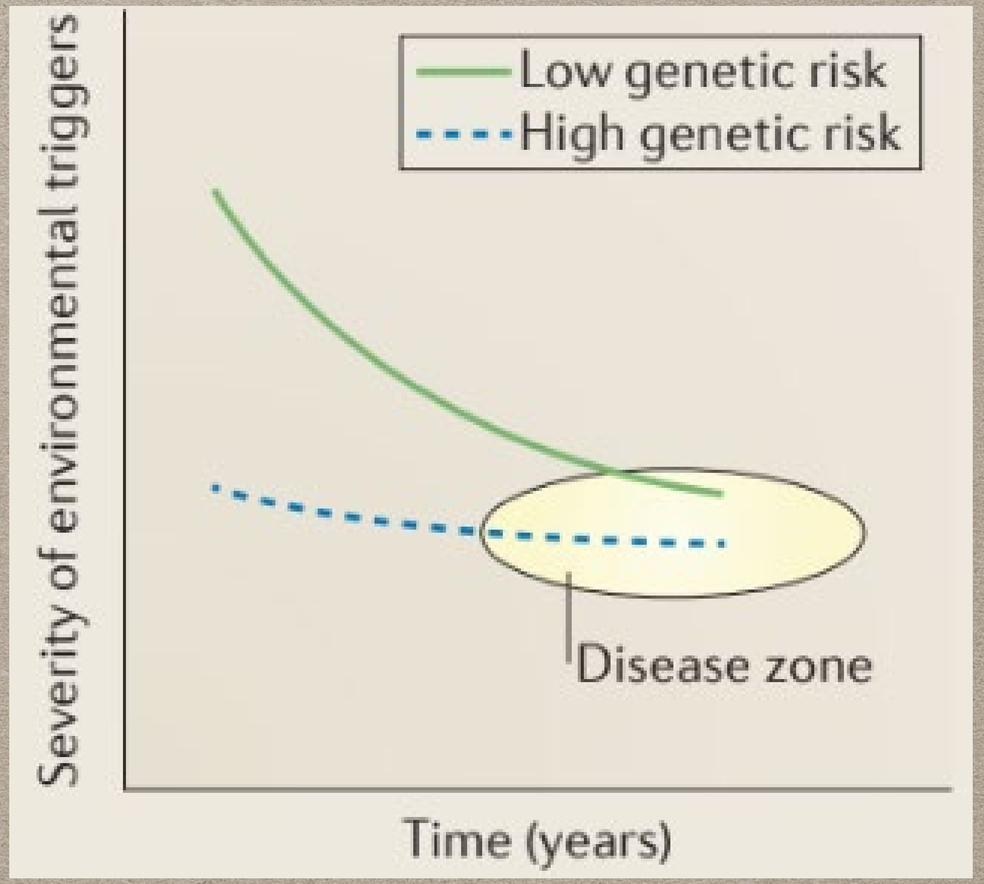
- Alcohol is often taken in larger amounts or over a longer period than was intended.
- There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
- A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
- Craving, or a strong desire or urge to use alcohol.
- Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
- Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.

ALCOHOL USE DISORDER (AUD)

- Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
- Recurrent alcohol use in situations in which it is physically hazardous.
- Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
- **Tolerance**, as defined by either of the following:
  - A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
  - A markedly diminished effect with continued use of the same amount of alcohol.
- **Withdrawal**, as manifested by either of the following:
  - The characteristic withdrawal syndrome for alcohol
  - Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

ALCOHOL USE DISORDER (AUD)

- AUD can present as similar phenotypes in different individuals, but the disease state has been arrived at through very different trajectories



From: Heilig et al., *Nature Reviews Neuroscience*, 2011

TYPES OF ALCOHOLISM

- Thomas Babor et al., *Arch Gen Psychiatry*, 1992
  - Type A
    - Later onset (after 25yo)
    - Less severe dependence
    - Fewer childhood risk factors
    - Less psychopathology

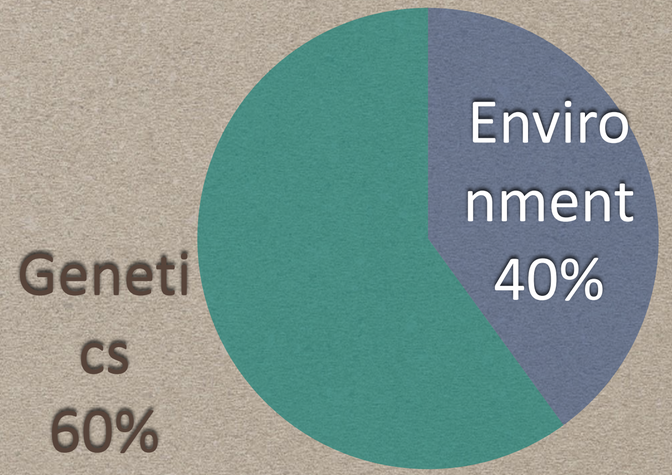
TYPES OF ALCOHOLISM

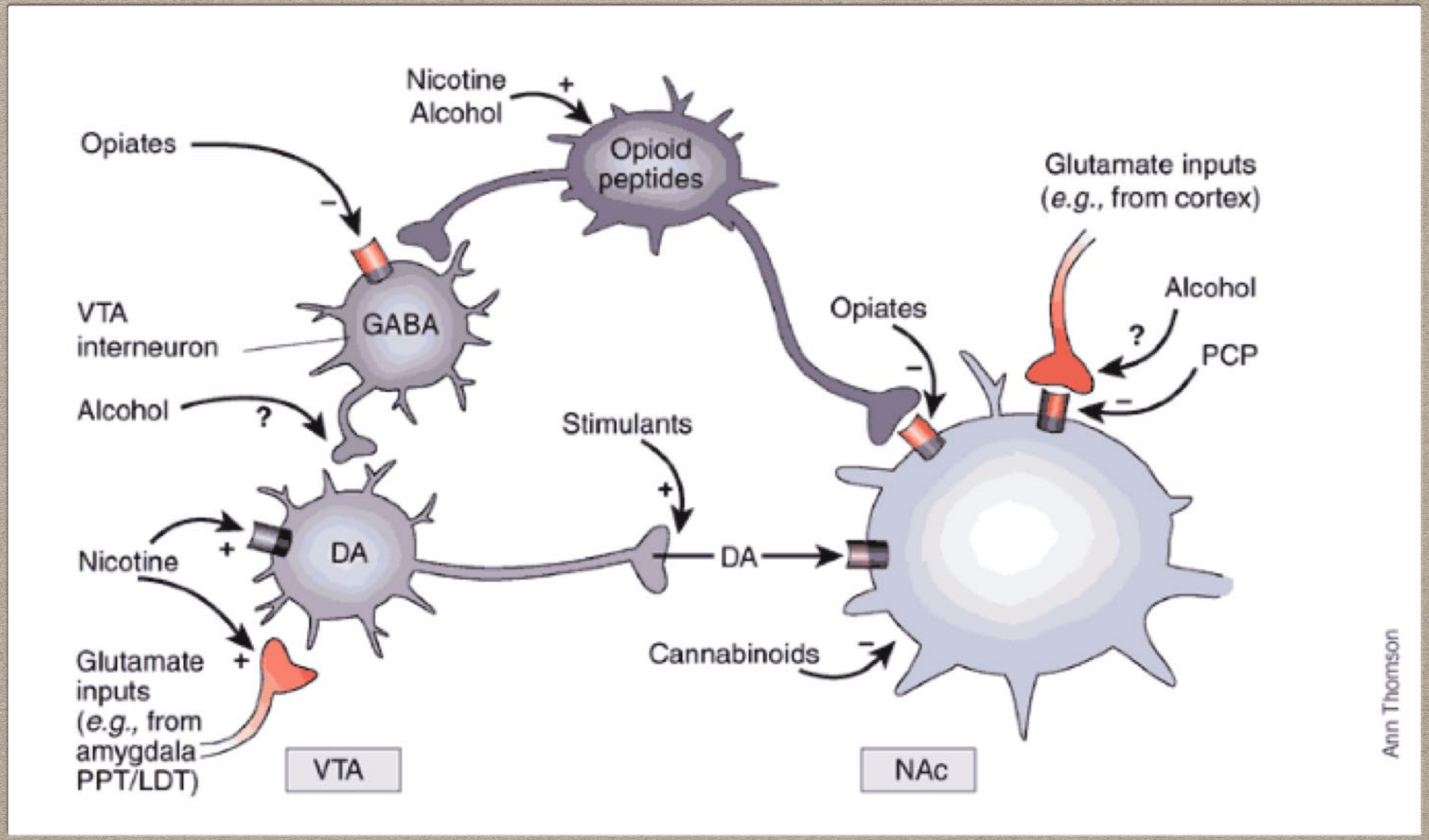
- Type B
  - Increased familial alcoholism
  - Polysubstance use
  - Younger age of onset (alcohol use and related issues) – before 25yo
  - Greater comorbidity with cluster B psychopathology[1]

- Genetic factors account for **50-60% of disease risk** in AUD

GENETIC FACTORS ASSOCIATED WITH AUD

- 3-4x higher risk in close relatives of people with AUD
- Higher risk associated with:
  - Greater number of affected relatives
  - Closer genetic relationships
  - Severity of alcohol-related problems in affected relative(s)
- Significantly higher risk in monozygotic twin than dizygotic twin of a person with alcohol dependence
- 3-4x increase in risk in adopted children with a natural parent who is alcohol dependent despite being raised by adoptive parents without the disorder





ACTIONS OF ALCOHOL ON REWARD CIRCUITS

NEUROPHARMACOLOGY: SUMMARY

EXPERIENCE	TRANSMITTER/RECEPTOR
Euphoria/pleasure	**Dopamine, Opioids**
Anxiolysis/ataxia	GABA
Sedation/amnesia	GABA + ↓ NMDA
Nausea	5HT3
Neuroadaptation	NMDA, 5HT
Stress	CRF
Withdrawal	**GABA, glutamine, NMDA (Ca, ↓Mg)**

MEDICATIONS FOR AUD

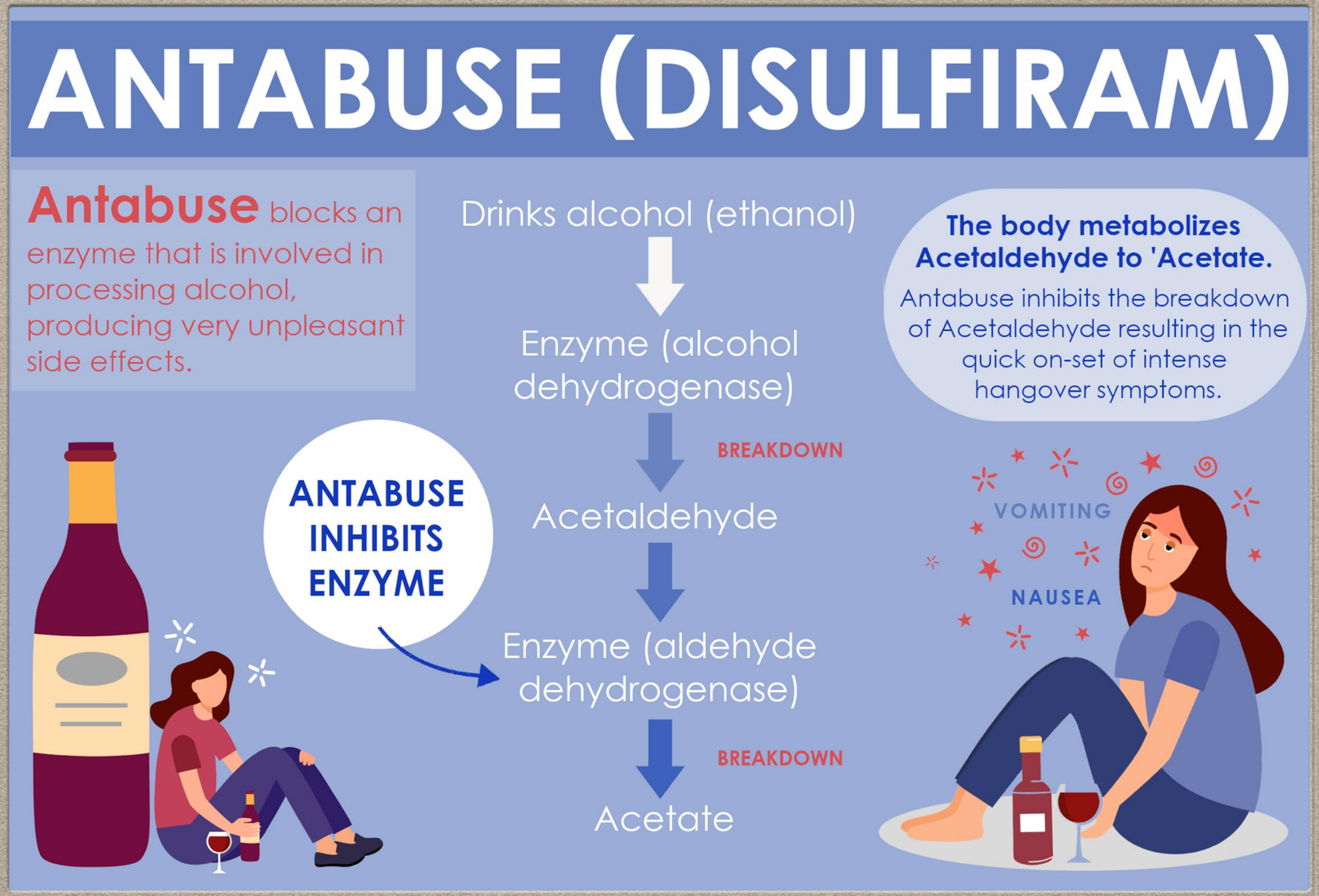
- **FDA Approved**
  - **Disulfiram** (Antabuse)
  - **Naltrexone** (Revia; Vivitrol LAI)
  - **Acamprosate** (Campral)

Experimental/Not Approved

- Ondansetron (5-HT3 receptor antagonist)
- Calcium carbimide (acetaldehyde dehydrogenase inhibitor)
- Gabapentin (calcium channel GABAergic modulator)
- Topiramate (non-NMDA glutamate & GABA receptor modulator)
- Tiapride (D2 and D3 antagonist, not approved in USA)
- Varenicline (acetylcholine α4β2 receptor partial agonist)
- Psilocybin
- Oxytocin
- Semaglutide/GLP-1s?

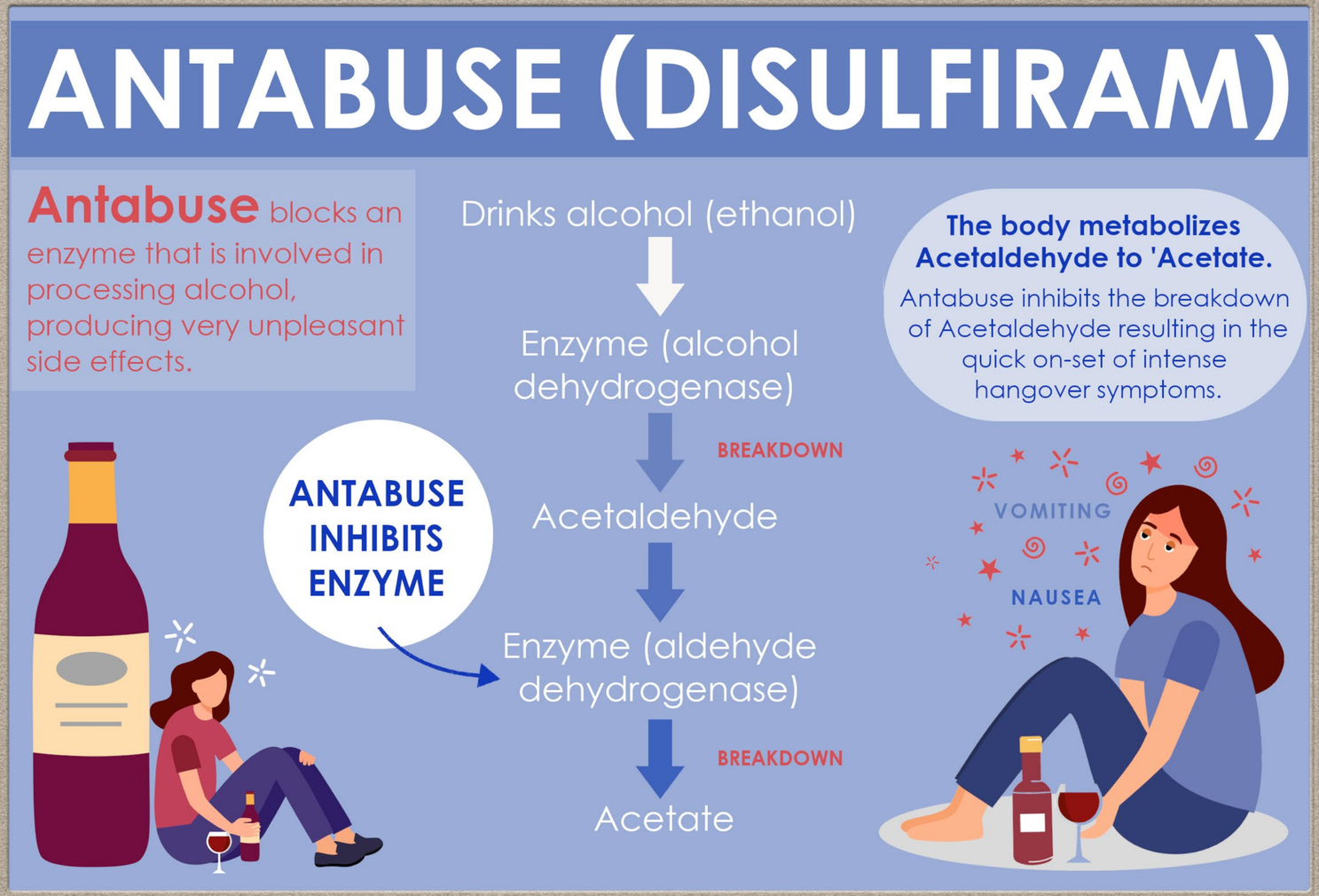
DISULFIRAM (ANTABUSE)

- **First medication for AUD, approved in 1951**
- **Irreversibly binds and inhibits aldehyde dehydrogenase**
  - No effects on brain opioid, GABA or glutamate receptors
  - But can inhibit dopamine B-hydroxylate which can affect serotonin..
- When taken with alcohol, ↑ acetaldehyde leads to nausea, dizziness, headache, flushing — **aversive conditioning**



DISULFIRAM (ANTABUSE)

- Side effects - rare but serious risks of hepatotoxicity and neurologic issues
  - Drowsiness, lethargy, peripheral neuropathy
  - Completely metabolized by liver, should not be used by anyone with any liver disease per Amer College of Gastroenterology, consider CYP and DDIs
- Absolute contraindication for CHF, CAD — rarely cardiac problems, hypotension and death



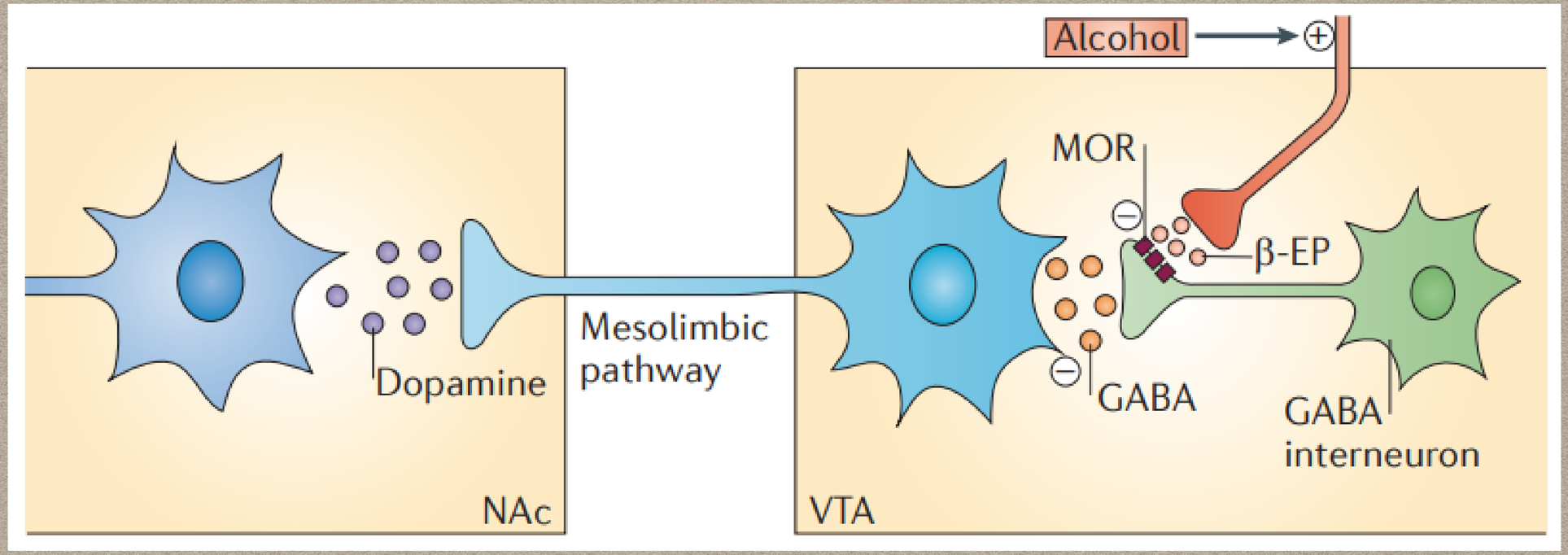
DISULFIRAM (ANTABUSE)

- Abstain for 12hrs before starting and avoid alcohol for at least 14 days after stopping (irreversible binder) — reports of disulfiram reactions in that window
    - No benefits to going beyond 500mg/day, lower doses in elderly given severity of rxn, medical comorbidities
    - Best in supervised setting with program or with partner/spouse/family - level and quality of supervision is important, optimal response best in SUD tx program
- Beware of other medications that may contain alcohol i.e. sertraline oral solution (12% alcohol solution), other OTC cough meds, vinegars, sauces

DISULFIRAM (ANTABUSE)

- Disulfiram appears to have modest clinical efficacy in maintaining alcohol abstinence in patients with AUDs, particularly when administered under supervision.
  - **Patients who are motivated for treatment, commit to total abstinence, have supervised dose administration, and are able to understand consequences of drinking and participate in their treatment/monitoring appear to derive the greatest benefits from disulfiram therapy.**

NALTREXONE (REVIA, LONG ACTING VIVITROL)



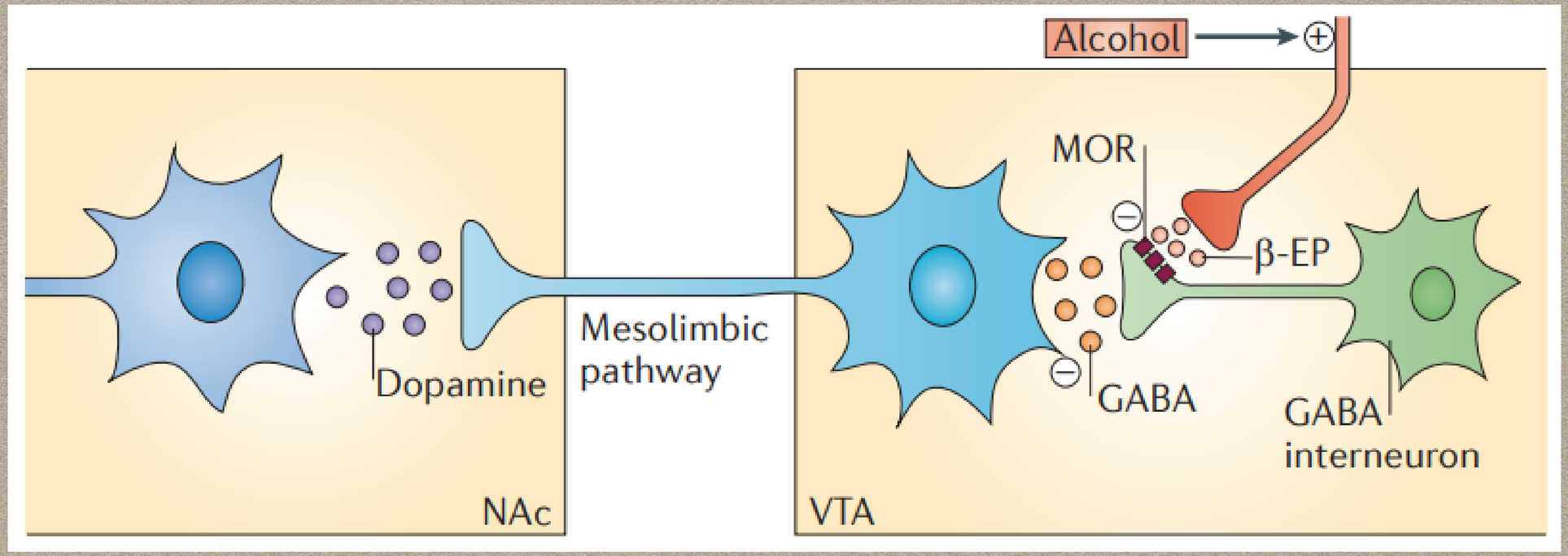
- **Approved in 1984 for moderate to severe AUD, available orally and long acting injection**
- Mu opioid antagonist - Use of NTX leads to reduction in dopamine release in NAc
- Effects through decreasing reinforcement of alcohol
  - COMBINE trial — incr % of days of abstinence, reduced risk of heavy drinking day, “good clinical outcome” i.e. no more than 2 days of heavy drinking/wk, or drinking below 14/week limit
  - Few meta-analyses, Cochrane review — superior to placebo in preventing relapse to heavy drinking after initial abstinence, and incr % of abstinent days

AUD

- Family history
  - Non-alcoholic individuals at genetic risk for AUD (i.e. positive FHx)
    - Significantly ***higher plasma endorphin release*** with alcohol use[1]

1. Gianoulakis et al., *Life Sciences*, 1989

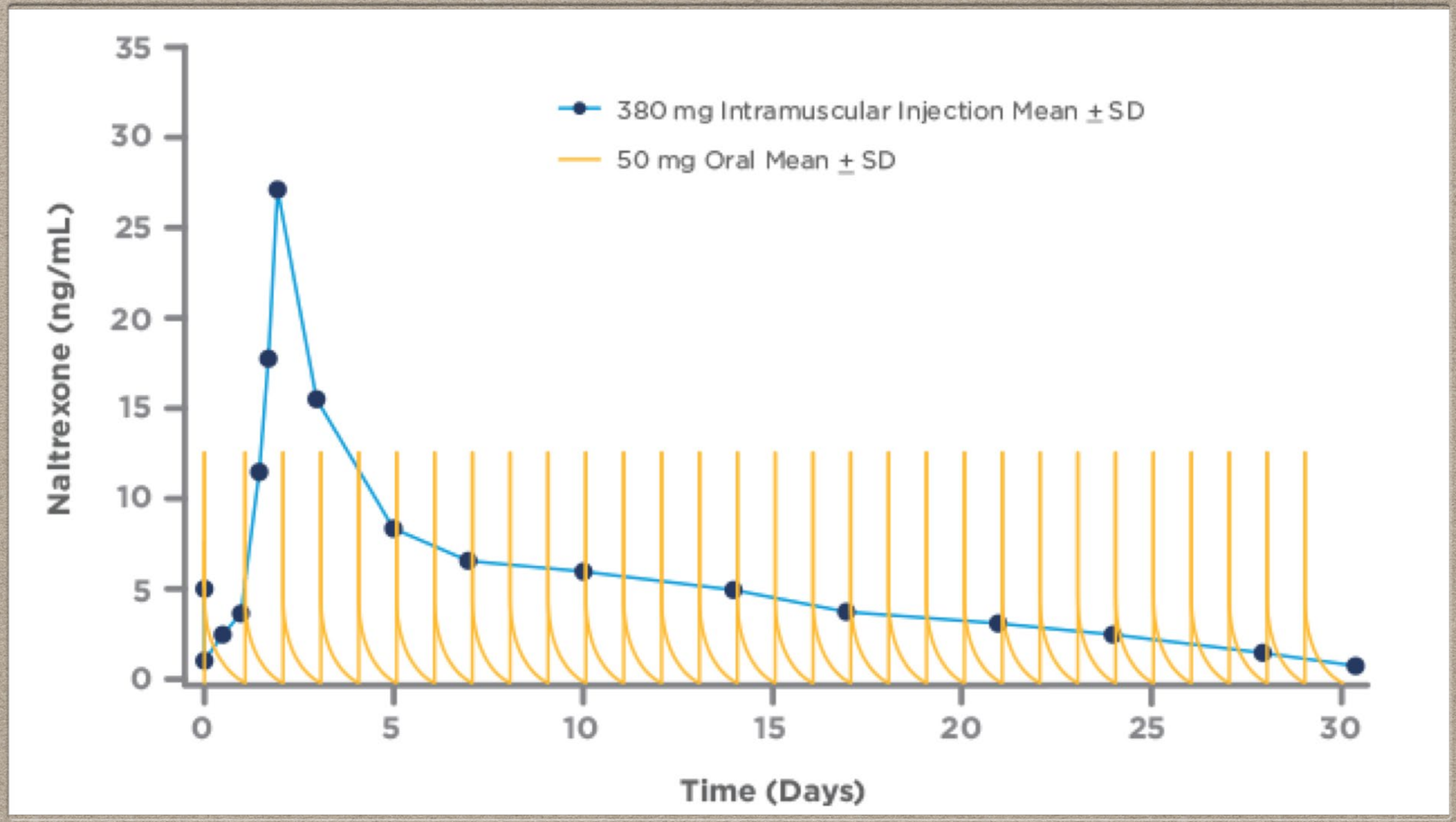
NALTREXONE (REVIA, LONG ACTING VIVITROL)



- Generally well tolerated
  - Occasional nausea, headache, sedation, anxiety — opioid blocking as cause?, typically very mild
  - Very rare increase in liver function tests, contraindicated in pts who have LFTs >4-5x normal limits
  - Trials should typically last 3-4 months, if pt maintains abstinence can trial discontinuation and revisit their progress

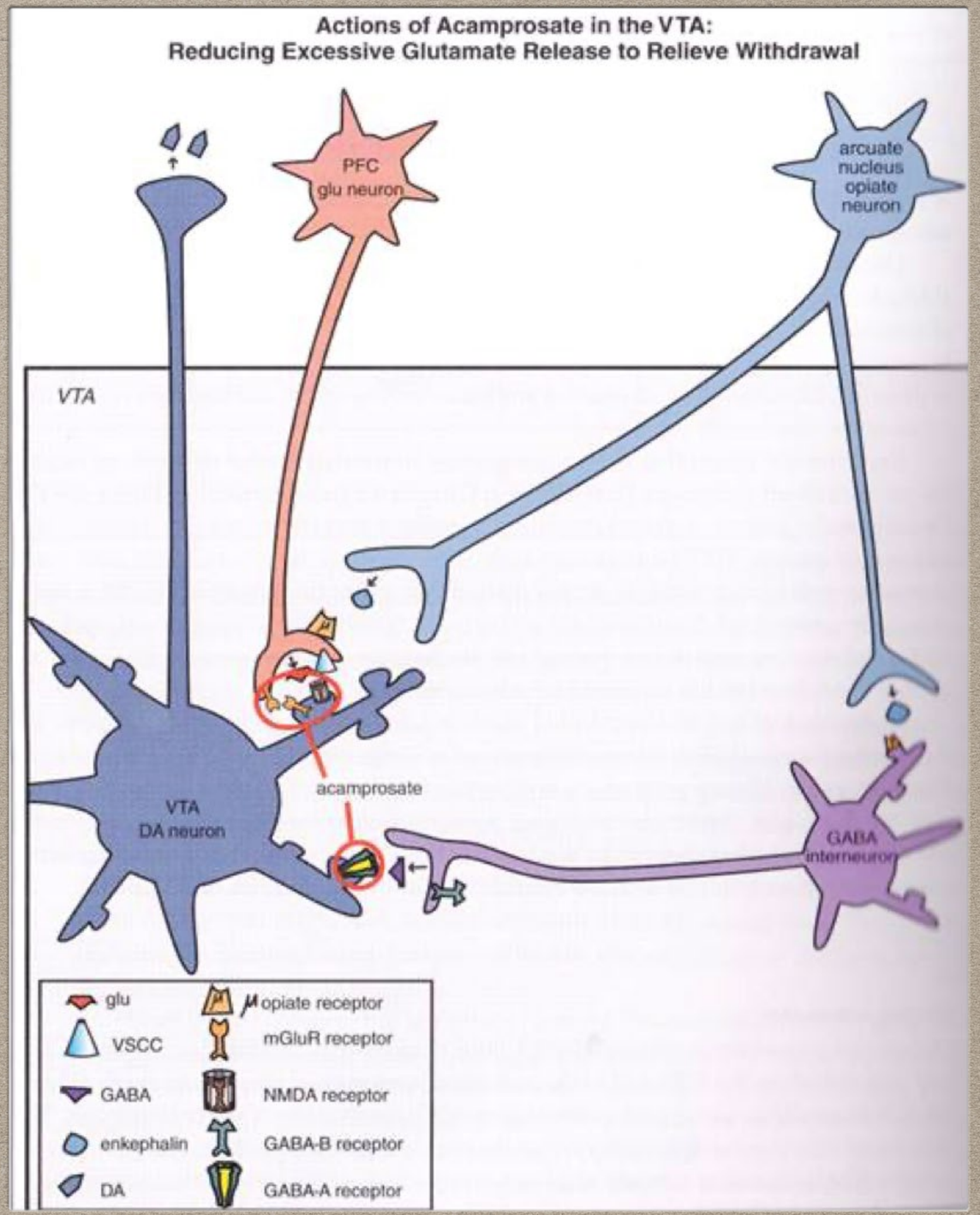
NALTREXONE

- Can consider starting at 25mg, typical dose being 50mg
  - Can consider going up to PO 100mg
  - With compliance/memory issues/pt preference can consider the LAI version of NTX (Vivitrol 380mg IM monthly)
- Once daily dosing
- Mostly well tolerated, limited side effects
- Also contraindicated in those prescribed opioids for chronic pain, currently on mOUD for opioid use disorder



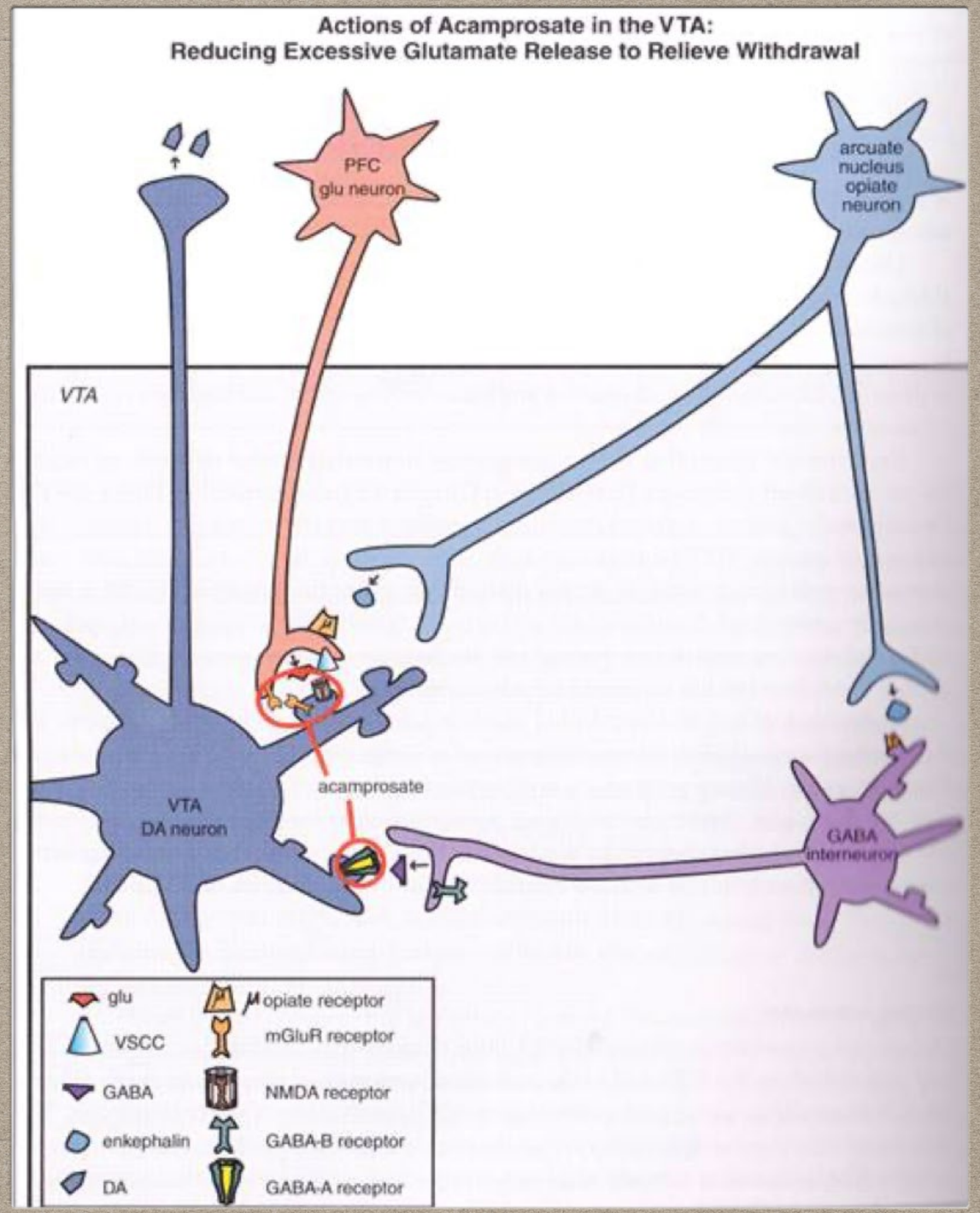
ACAMPROSATE

- **3rd AUD medication to be approved in 2004** (been used since 1989 in Europe)
- NMDA glutamate receptor modulator
- Appears to have effects through decreasing craving by normalizing glutamate levels — effective treatment for supporting abstinence after detox from alcohol dependence
- Most common side effects are GI i.e. diarrhea, nausea
  - FDA warning for increased suicide/violence
  - No liver toxicity — contraindicated in kidney disease, primarily renally cleared without being metabolized
  - Some neutral/negative studies
- TID dosing can be problematic, some studies looking at BID recently, systematic reviews typically using acamprosate for <1yr



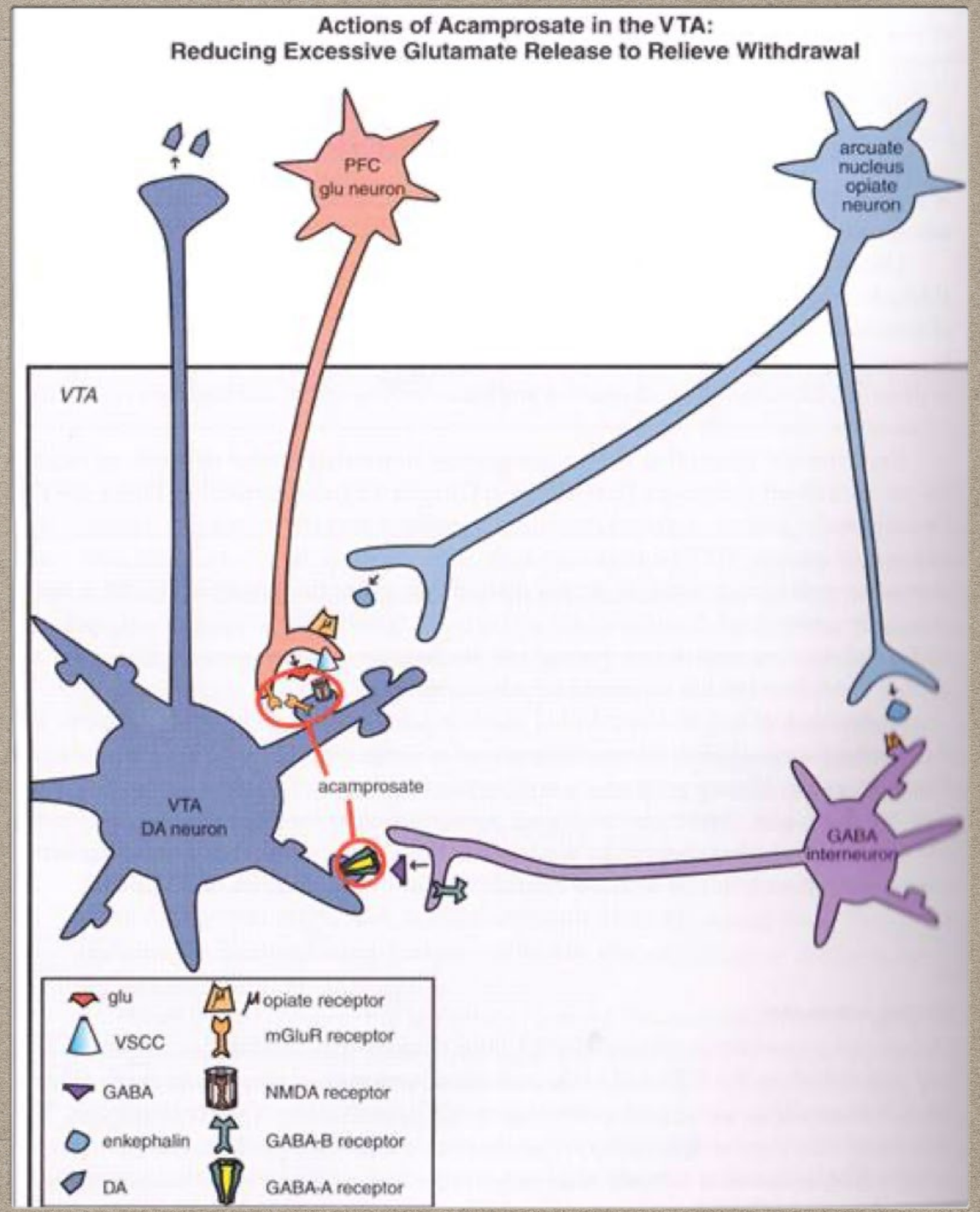
ACAMPROSATE

- Should start ASAP after assisted withdrawal, usually within 5 days after cessation, best combined with psychosocial treatments
- Most studies show effectiveness in maintaining abstinence from alcohol
- Can continue taking even with relapse!
  - Effective as NTX but with fewer adverse reactions, can consider combination



ACAMPROSATE

- Many European trials have found acamprosate more effective than placebo in reducing drinking days, increasing complete abstinence and lengthening time to relapse
  - Can use w mOUD!
  - No w/d from stopping, no taper needed
- **Acamprosate has several attractive features, including its minimal side effects, lack of negative liver effects, and drug interaction profiles.**
  - For many patients, these features make it a worthwhile agent to try despite its small therapeutic effect.



ALCOHOL AND PSYCHIATRIC COMORBIDITY

- Consider onset/chronology of symptoms
  - Having symptoms such as irritability, talkativeness, grandiosity etc only during alcohol ingestion periods could rule out other diagnoses
- 25-75% of pts with alcohol dependence have anxiety or depressive disorders, also frequently PTSD

ALCOHOL AND PSYCHIATRIC COMORBIDITY

- The self-medication hypothesis can explain the use of alcohol acutely to alleviate anxiety (thanks to its anxiolytic properties)
  - However, chronic alcohol intake will have opposite effects and worsen the disease.
- AUDs might be another symptom of an existing psychiatric disorder
- The prognosis for comorbid patients is more negative compared with that for non-comorbid patients —
  - worsens psychiatric symptoms
  - increases their frequency
  - increases the number of days of hospitalization
  - reduces life expectancy

OPPONENT PROCESS

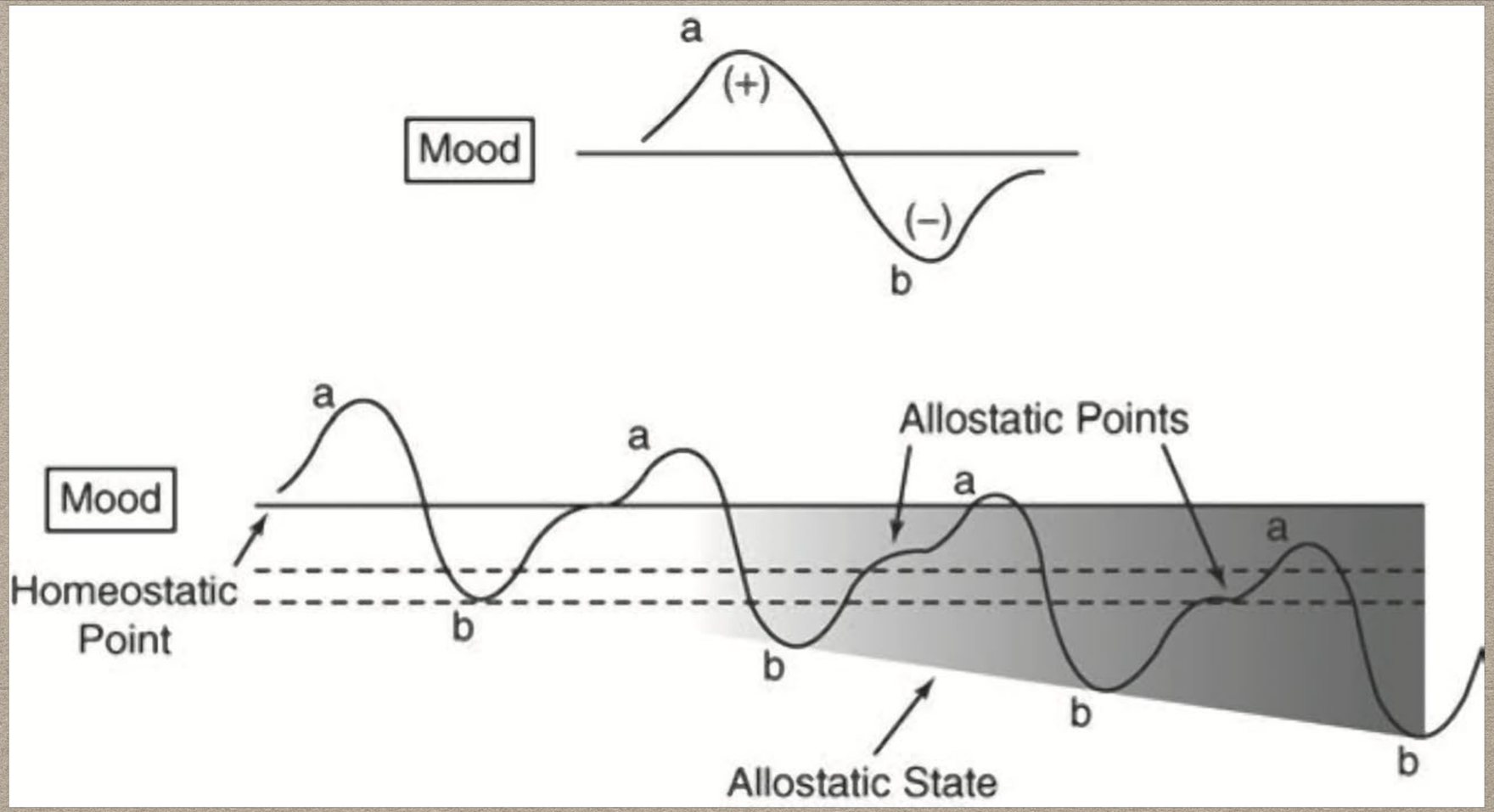
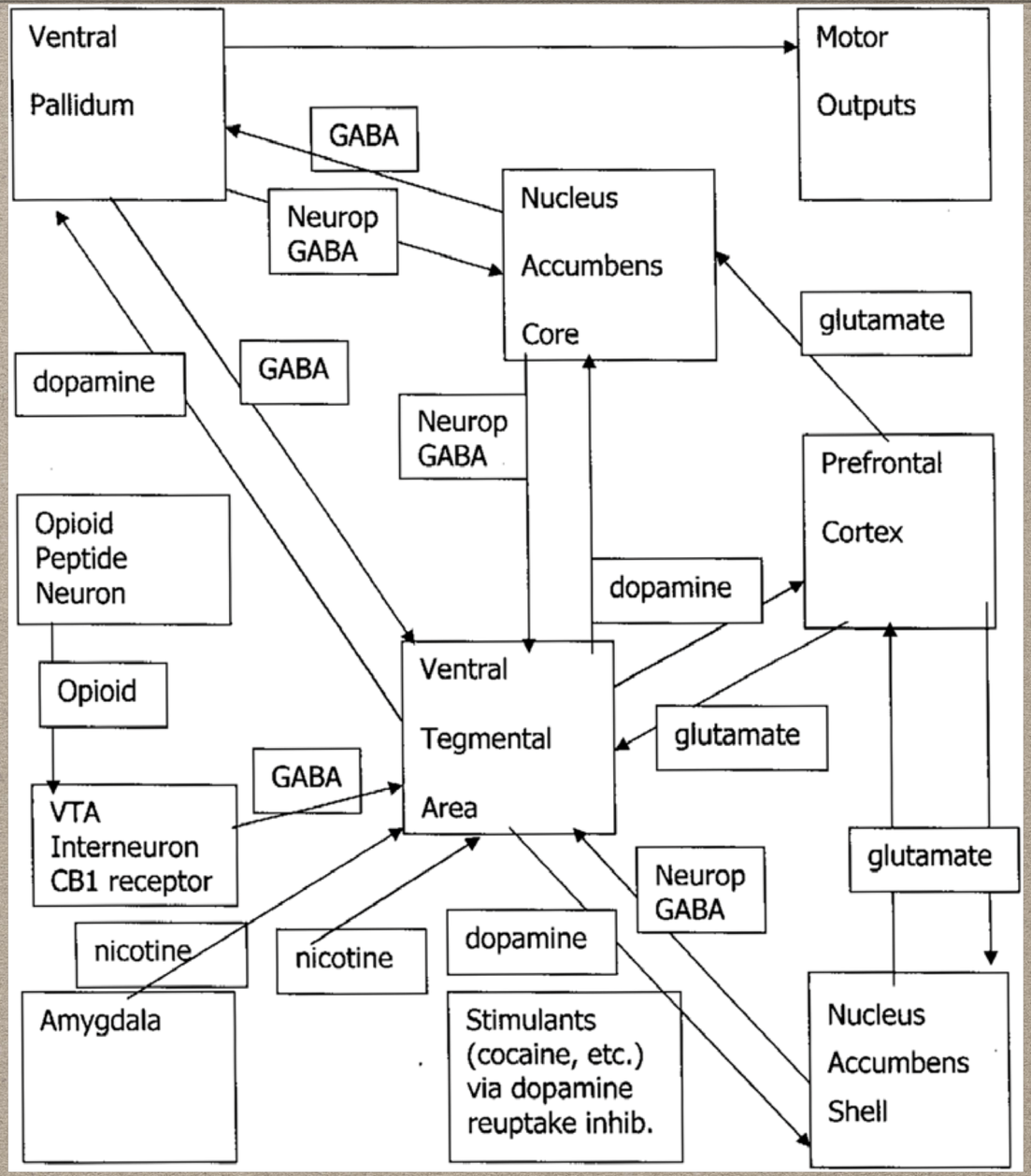


Figure 4. The "opponent process" in the central nervous system. (Reproduced by permission of Elsevier Science Inc., from G. F. Koob & M. Le Moal, "Drug Addiction, Dysregulation of Reward, and Allostasis," *Neuropsychopharmacology,* Vol. 24, 2001, pp. 97–129. © 2000 American College of Neuropsychopharmacology.)

CRAVING PATHWAYS AND CONNECTION TO "HIGHER BRAIN"



RE 1 | Craving/dreaming pathways: Neurop, neuropeptides; GABA, gamma amino butyric acid, CB, cannabinoid.

ALCOHOL AND COMORBID DEPRESSION/ANXIETY

- Lifetime prevalence of alcohol use disorder in those with lifetime MDD ranges from approximately 27% to 40% across epidemiological studies in the USA.
- Long-standing debate about whether AUD and depression are independent disorders or overlapping illnesses connected by common causative factors.
    - The use of alcohol to relieve depressive symptoms (i.e. self-medication) and the development of depression as a result of the social and biological consequences of alcohol use disorder, have both been reported.
- Comorbid alcohol use disorder and anxiety disorder is a common dual diagnosis; the estimated prevalence of AUD among people with anxiety disorders across countries ranges from 20% to 40%

ALCOHOL AND DEPRESSION/ANXIETY RX

- TCAs might be risky in overdose — consider therapeutic window w active drinking
- SSRIs likely safer — unclear how well they help w comorbid alcoholism
- Buspirone has been formally evaluated in several double-blind, placebo-controlled trials for patients with comorbid GAD and alcohol dependence. Although several of these clinical studies suggested that buspirone reduced anxiety symptoms and one suggested that it reduced alcohol use, other studies reported that it had no effect in reducing anxiety or alcohol use…
- Limit benzos — additive w alcohol intoxication
- MAOIs avoided w food and beverages, tenuous monitoring

PSYCHOTHERAPY FOR COMORBID AUD AND OTHER DISORDERS

- Psychotherapy research has led to the development of several treatments for patients with AUD — adaptations of psychodynamic approaches; CBT, such as relapse prevention and motivational enhancement therapy; and behavioral treatments, such as contingency management.
- There seems to be some consensus that tx should be viewed as occurring in stages and that immediate and short-term goals should be established and may not be identical.
    - For example, although abstinence may be a long-term goal, patients with severe mental illness may not perceive their substance abuse to be a problem.
        - The immediate goal of treatment with these patients may be stabilization of the psychiatric illness, followed by a discussion of their ambivalence about their alcohol use.
        - **Similarly, patients who achieve early abstinence from alcohol may need to be closely monitored for the emergence of symptoms of a psychiatric disorder, such as PTSD, whose presence may have been masked by their previous alcohol use.**

ALCOHOL AND COMORBID ADHD

- ADHD is a condition marked by impaired ability to maintain focus and attention as well as frequent distraction, restlessness, and impulsive behavior.
- Alcohol use disorder in people with ADHD is prevalent, ranging from 19% to 26% of young adults in different countries.
  - Early-onset ADHD has been prospectively associated with future alcohol use and AUD.
  - In two meta-analyses of longitudinal studies, the pooled odds ratio for AUD in people with ADHD in childhood ranged between 1.35 (95% CI 1·11– 1·64) and 1.74 (1·38–2·20), relative to youths without ADHD
    - Would support the hypothesis of a causal connection between these two disorders, and emphasize the importance of early detection of ADHD in childhood and adolescence.

ALCOHOL AND COMORBID PTSD

- Although studies addressing the longitudinal association between PTSD and AUD are lacking, the general consensus is that PTSD tends to precede the onset of AUD.
    - In a longitudinal study of US troops screened before and after deployment to Iraq, pre-deployment alcohol use was unrelated to the onset of PTSD; however, PTSD symptoms substantially increased the risk of screening positive for new-onset AUD.
        - For example, alcohol use is a risk factor for being victimized, including sexual victimization and aggravated assaults, and thus drinking alcohol or AUD might indirectly increase the risk of PTSD.
- AUD can also affect the psychological mechanisms used to cope with traumatic events, increasing individual vulnerability to anxiety symptoms, including PTSD.

ALCOHOL AND PSYCHIATRIC COMORBIDITY

- Overall, AUD co-occurs with a wide range of other psychiatric disorders, especially those disorders involving other substance use, mood, anxiety, and attentional issues. The causal pathways between AUD and other psychiatric disorders are heterogeneous.
- Hypotheses explaining these relationships include:
  - reciprocal direct causal associations
  - shared genetic and environmental causes
- Efforts to untangle the associations between AUD and other disorders across the lifespan remain a crucial avenue of research.

SUMMARY OF KEY POINTS

- Recommended drink limits are typically <14 drinks weekly for men, <7 drinks weekly for women
    - Binge episodes are >4 drinks for men, >3 for women
- The 3 FDA approved medications are **disulfiram**, **naltrexone** and **acamprosate** — each with differing modes of action targeting different pathways of the alcohol reward system
- Alcohol is frequently comorbid with various anxiety and mood disorders, requiring thorough clinical evaluation and consideration of all medical and psychiatric issues before deciding on treatment

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