

# Why Does Cocaine Cause Fatal Heart Attacks?

- **Mental stimulation:** Cocaine encourages vigorous activity
- **Sympathetic stimulation:** Cocaine speeds heart rate directly
- **Vasoconstriction:** Impairs blood flow to heart
- **Numbing:** Blocks signals in heart

# The Action Potential

- How does it work?
- Epilepsy and anticonvulsants
- Local anesthetics (e.g. Novocaine)
- Alcohol and alcohol antagonists
- Shock therapies

# Don't worry

- Don't worry – this is the most confusing, complex, and technical bit of the whole class. I *promise* we won't do this again.
- This is important, so please pay attention and ask questions whenever you don't understand.

# Plan of action:

- Electric cells? What?
- How batteries work
- The four batteries inside every neuron
- Channels opening and closing
- Putting it all together: The Action Potential

# The potassium battery (The resting potential)

- Draw it on the board (outside cell on top, draw leak channels)
- Which way does the diffusion force point?
- Which way does the electric force point?
- What equilibrium does it eventually settle into?

# Ion concentrations in and around axons:

Ion	Concentration outside (in mM)	Concentration inside (in mM)	Ratio Out:In	$E_{ion}$ (at 37 C, in mV)
K <sup>+</sup>	5	100	1 : 20	-80
Na <sup>+</sup>	150	15	10 : 1	+62
Ca <sup>++</sup>	2	0.0002	10,000 : 1	+123
Cl <sup>-</sup>	150	13	11.5 : 1	-65

# What happens if we open and close channels?

- Whenever you open a channel, you pull the voltage CLOSER to that channel's REVERSAL POTENTIAL. The reversal potential is simply the Nernst potential for the one ion in question if only one ion passes through the channel.
- Whenever you close a channel, you push the voltage FARTHER from the reversal potential (this is actually just the absence of the pull from open channels).

# Types of channels

- There are a few types of ion channels:
  - Leak channels: These are always open, there are a number of  $K^+$  leak channels and they are responsible for the resting potential
  - Voltage-gated: Open or close at specific voltages, very important for action potentials
  - Ligand-gated: Open or close when exposed to chemicals
  - Second-messenger-gated: Similar to ligand-gated, these open or close depending on chemicals called second messengers inside the cell, or they open or close when phosphorylated or dephosphorylated
  - Combined type: NMDA receptors have multiple agonists that must bind simultaneously for opening, PLUS they only open when the membrane is depolarized

# Electrical synapses

- There are electrical synapses. They are simply holes/tubes/ducts that connect one neuron directly to another.

# Local anesthetics

- Mechanism: They completely plug up the voltage-gated sodium channel (similar to anticonvulsants but a much more complete blockage)
- Cocaine was the first, but it has other effects too.
- Then came procaine, marketed as Novocaine. It is now deprecated for safety reasons.
- Today dentists and doctors use: lidocaine, benzocaine

# Epilepsy

- Seizures are caused by excessive and disorganized action potentials
- Seizures are treated with anticonvulsants:
  - Phenytoin and carbamazepine help inactivate sodium channels (these drugs put channels in the refractory state). In small doses, this ensures that rapid sequences of spikes can't occur
  - Phenobarbital (a barbiturate), benzodiazepines, and valproate (Depakote) increase GABA-mediated inhibition in various ways

# More anticonvulsants

- Gabapentin (Neurontin) probably inhibits voltage-gated  $\text{Ca}^{++}$  channels. This drug was marketed using very sleazy and aggressive practices.
- Lamotrigine (Lamictal) unknown mechanism. Possibly similar to phenytoin and carbamazepine (voltage-gated  $\text{Na}^{+}$  channel inactivation). Often used off-label for bipolar disorder, other psychiatric disorders.

# Alcohol

In many ways, alcohol is the most dangerous drug I will talk to you about.

CDC: 76,000 Americans a year die because of alcohol (conservative estimate)

NIAAA: 110,000 Americans per year die because of alcohol (commonly cited estimate)

Alcohol causes car accidents, violence, exacerbates other conditions, and breaks up families – all these harms are not included in the death tolls above.

# Alcohol

How does alcohol work?

It is not understood which mechanisms are important, and alcohol does many things to the brain. Here are a few things it does:

- Opens BK potassium channels

- Closes SK potassium channels, which are found on DA-releasing cells in the VTA

- Activates GABA<sub>A</sub> and GABA<sub>B</sub> receptors

- Lets calcium into cells, causing cell death

# Alcohol

## BAC and effects:

- .03 Mild euphoria, relaxation, talkativeness, decreased inhibition, coordination and judgment impaired
- .06 Reflexes, senses, and reasoning impaired
- .10 Emotional swings, staggering, slurred speech
- .20 Memory blackout, possible unconsciousness, highly impaired thought, movement, and perception, gag reflex is suppressed
- .30 Unconsciousness, impaired breathing and heart rate, death possible
- .40 Death likely if untreated

## Gender and alcohol tolerance

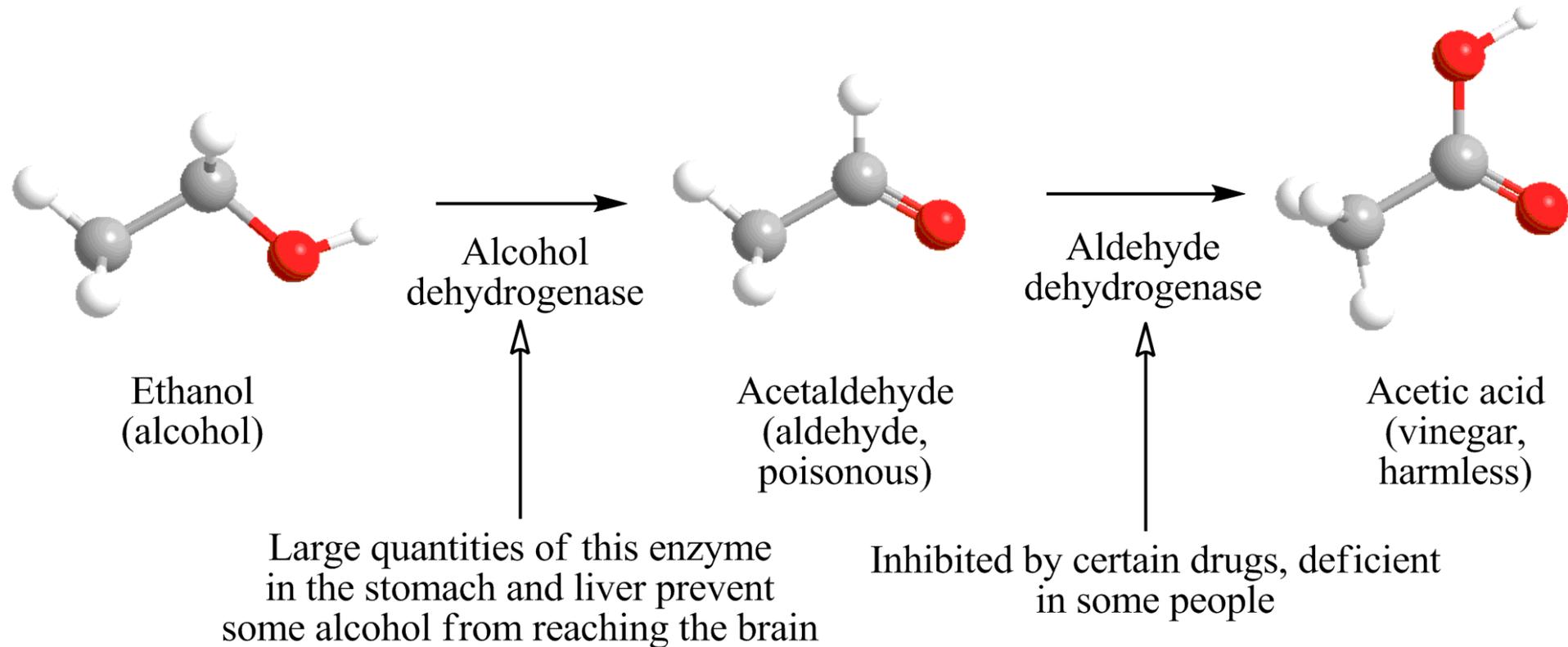
# Alcohol

Hilarious study correlating alcohol consumption to enjoyment.

Recent study from Northumbria and Kent universities shows that 3 or 4 days after having 4 or 5 shots of alcohol or nothing, the young adults who had alcohol remembered one third fewer items from a video/list than the non-alcohol subjects

University of Tokyo finds that drinking after a bad day will actually reinforce the memory – you have to start drinking BEFORE an event to forget it, getting hammered after being fired or dumped will only make your psychological pain and memories worse.

# Alcohol metabolism



# Alcohol

Why does it make you nauseous?

How do Antabuse and Temposil work?

How can you avoid nausea and improve bioavailability?

- Other routes of administration (bad idea)
- Become an alcoholic and destroy your GAD and liver (also a bad idea, especially since it masks the development of tolerance which would have otherwise required larger doses, and it removes the disincentive to drinking caused by nausea and hangovers)

# Alcohol

Why does it cause brain damage?

What else does it cause?

- Cancer from the lips to the anus, hepatitis, pancreatitis, gastritis, anxiety, depression, phobias, sleep disorders, liver cirrhosis, Korsakoff's syndrome, Wernicke's encephalopathy, alcoholic dementia, heart disease, epilepsy, polyneuropathy, malnutrition, and sexual dysfunction

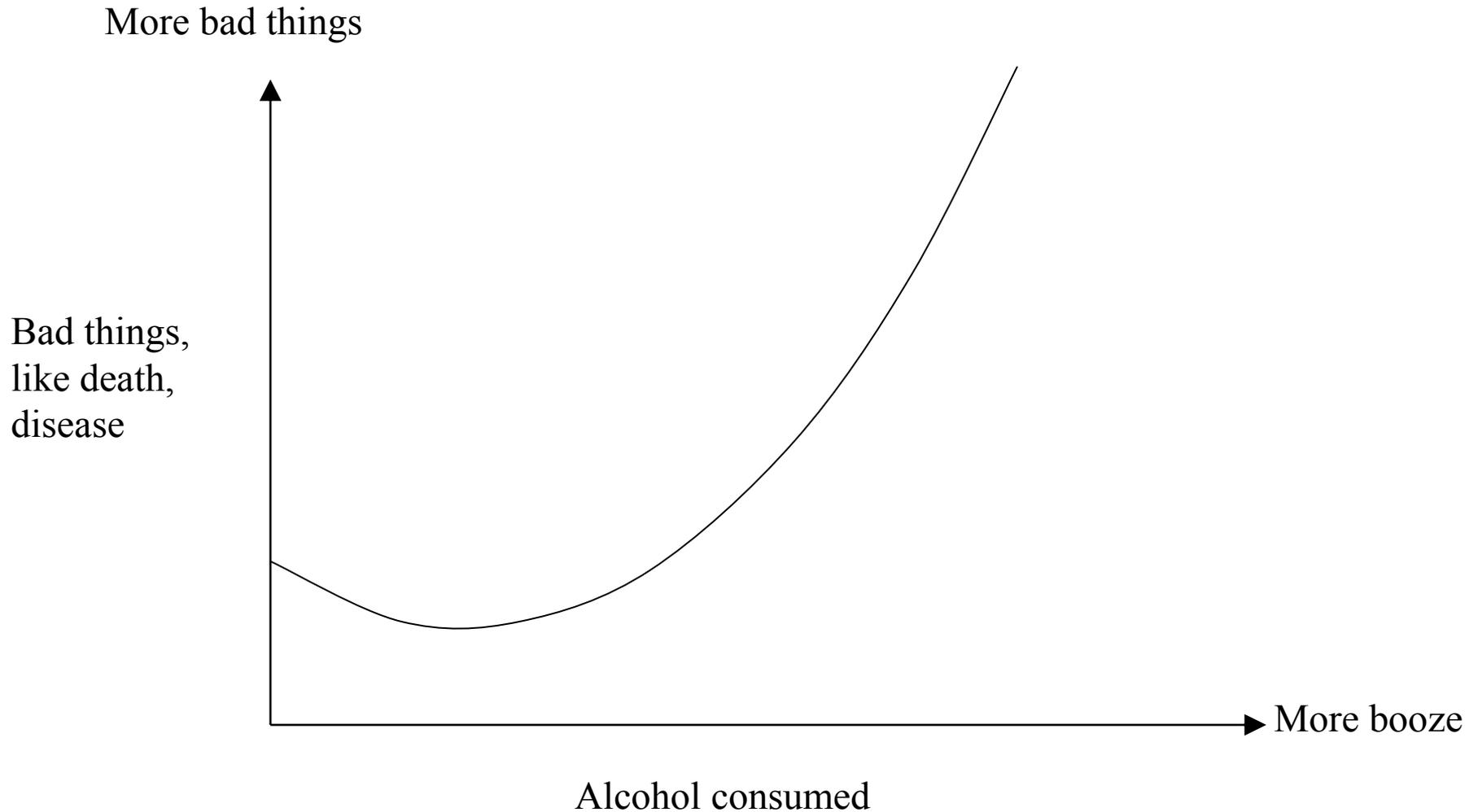
What blocks the effects of alcohol?

What is the alternative?

# To what extent is it OK to drink alcohol?

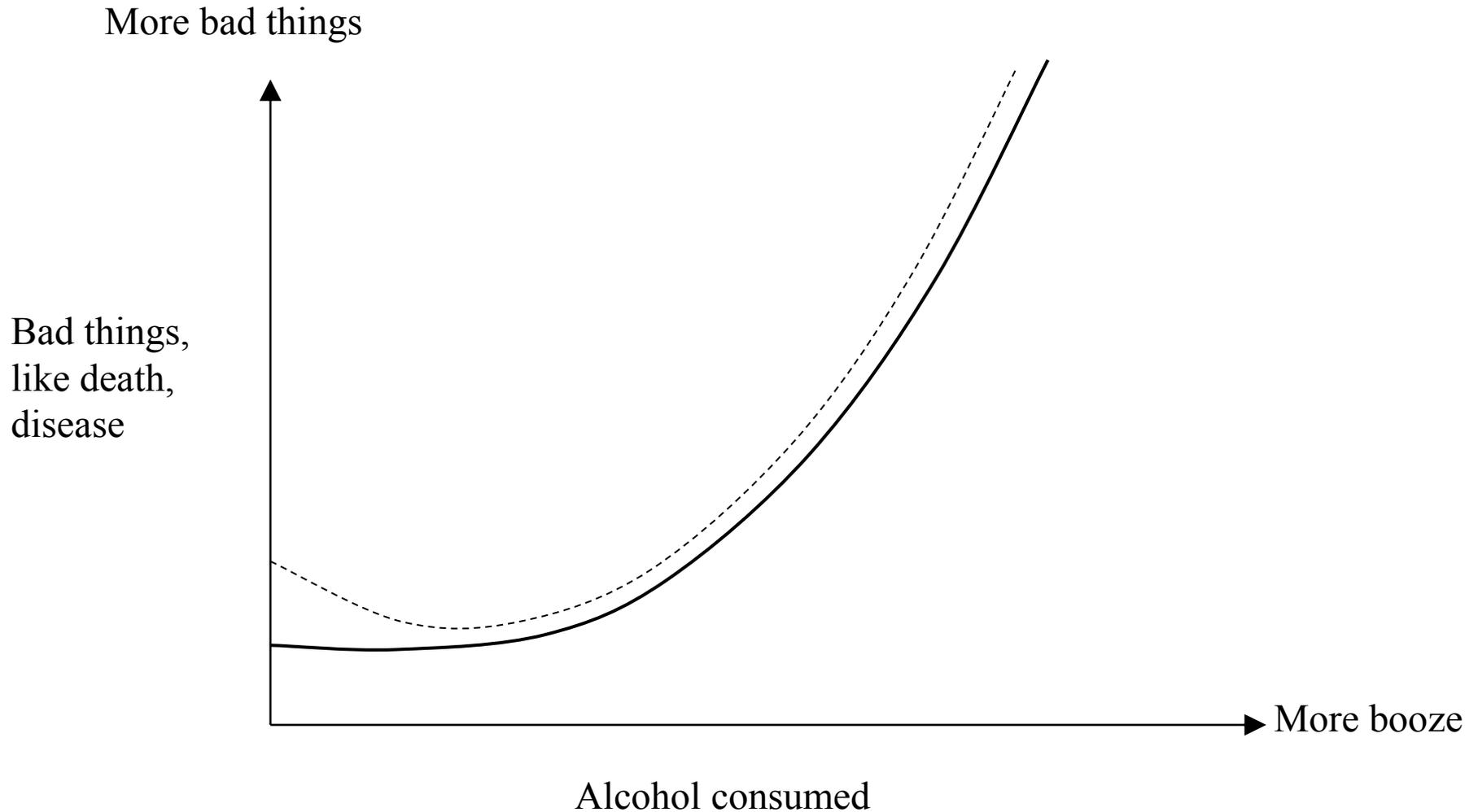
- All but the most fanatical of scientists and doctors agree that healthy adults with no history of addiction can have up to 7 drinks a week, ideally spread out.
- Some sources say up to 14 drinks a week, or up to 14 drinks a week for women and 21 drinks a week for men. (Or 10 for women, 14 for men)
- Despite what people may say about “teaching kids to drink, like they do in France,” it is a bad idea. There are a lot of alcoholics in France, and in every country where kids start drinking young. The longer you wait, the safer you are.

# Is alcohol good for you?



A number of studies produced graphs like this, but there was a problem...

# Is alcohol good for you?



If you exclude people who are already sick, alcohol doesn't look so beneficial. This is because many sick people avoid alcohol.

# Is alcohol good for you?

What kinds of people drink zero alcohol:

- Religious people
- People who have some moral or scientific objection to alcohol
- People who get nauseous when they drink
- Former alcoholics
- Former drug addicts
- People with mental health disorders
- People on medication that might interact with alcohol
- Very old people
- People with various diseases (liver disease, kidney disease, AIDS)

Reasons for not drinking which often indicate poor health are in **RED**.

There were other confounding factors as well:

- Red wine is full of good stuff, like antioxidants, but so is grape juice
- Beer is full of good stuff, like vitamins, but so is oatmeal
- Clear vs. dark liquors

# Is alcohol good for you?

A recent study (Medical University of Southern Carolina) helped to clear up this question, it included only people who began drinking for the first time during the course of the study. Beginning to drink between the ages of 45 and 64 was beneficial because it reduced coronary heart disease, but starting to drink at an earlier age was not good. Before the age of 45, the risk of heart attack is low and cannot be significantly reduced by alcohol, while the risk of alcoholism and long-term alcohol-related damage is higher.

# Is alcohol good for you?

An even more recent study

(<http://jnci.oxfordjournals.org/cgi/content/abstract/djn514> Journal of the National Cancer Institute) used a population of 1.3 million UK women, and found that drinking just 4 glasses of alcohol a week (even if it was all wine) caused an absolute increase in the risk of cancer by 1.5%. Of 1,000 women, 15 more of them will get cancer in any time period if they drink 4 glasses a week.

(Notice that they define a “unit” of alcohol as 10 grams, which is less than one glass. I have converted to 17 gram glasses for you.)

Baseline lifetime risk of cancer for women is about 37.5%, so four drinks per week increases that to 39%.

# Alcohol antagonists

## Myth:

- KGB agents were given pills that blocked the effects of alcohol, they then drank Americans under the table and pumped them for secrets.

## Fact:

- The pill existed, it probably didn't work.

# Alcohol antagonists:

These drugs might actually help you win a drinking contest, or at least help you survive and feel well afterward:

- Flumazenil (benzodiazepine antagonist)
- Any benzodiazepine inverse agonist (some better for memory, or coordination, or alertness)
- Bemegride (aka megrimide, a barbiturate antagonist) is especially good at keeping you breathing, alive

# Alcohol antagonists, cont'd:

- Meclizine (an antihistamine and anticholinergic – in other words an antagonist at histamine and muscarinic ACh receptors) might help with dizziness, perhaps helps with nausea
- 5-HT<sub>3</sub> antagonists (e.g. Zofran, ondansetron) reduces nausea and vomiting (alcohol stimulates the 5-HT<sub>3</sub> receptor directly, in addition to irritating the stomach lining and intestines)

# Alcohol antagonists, cont'd:

- Pentylentetrazol (PTZ, metrazol) – this generally depolarizes neurons, probably by acting as an agonist at GABA receptors. The mechanism is not well understood. PTZ causes stimulation, anxiety, and seizures.
- Naltrexone (opioid antagonist) – blocks the euphoric feeling of alcohol, blocks some of the craving, proven effective for recovering alcoholics.

# Alcohol antagonists, cont'd:

- Disulfiram (Antabuse) inhibits the breakdown of acetaldehyde, a toxic byproduct of ethanol, leading to nausea, vomiting, headaches, flushing, sweating, fainting, tachycardia, confusion, and intensified hangover whenever alcohol is consumed. Does not inhibit the effects of alcohol, but may discourage drinking.
- Calcium carbimide (Temposil) – same mechanism as disulfiram, but less likely to kill you, especially if you take other medications or drugs.

# Shock therapies

History:

Motivation: Perhaps fever is beneficial, and syphilis patients who don't have fevers might improve if they could have a fever.

1917: Dr. Julius Wagner von Jauregg intentionally gives neurosyphilis patients malaria to cause a very high fever. He notices that if they have febrile seizures, they get less crazy and less depressed. He wins the 1927 Nobel Prize for this work.

# Shock therapies

Motivation: Maybe crazy people's brain cells are tired and need to rest. Let's induce a coma to provide that rest.

1927: Dr. Manfred J. Sakel gives schizophrenic patients insulin to induce coma, many of them are improved upon waking. Those who have seizures along with their coma improve the most.

# Shock therapies

Motivation: I've never seen a schizophrenic epileptic, therefore the diseases must be mutually antagonistic. (This theory is dead wrong and Dr. Meduna's observations were due to coincidence)

1934: Dr. Ladislav Joseph von Meduna gives schizophrenic patients various convulsants to induce seizure. He tried camphor, strychnine, thebaine, pilocarpine, and pentylenetetrazol (metrazol).

# Shock therapies

Motivation: Dr. Meduna's drug-induced seizures are incredibly dangerous. Let's try using electricity instead.

1937: Dr. Ugo Cerletti uses electric shocks to induce seizures in schizophrenic patients.

# Shock therapies

Over several decades:

- It was noticed that shock therapy is completely ineffective for schizophrenia, but it is very effective for depression
- Paralytics (including succinyl choline and vecuronium) were introduced to relax the muscles and prevent broken bones
- General anesthesia was administered before the seizure to prevent panic and pain
- The electric shock was applied only to one half of the head, or only to the front, to minimize memory loss

# ECT and Frontal Lobotomy

- Dr. Walter Freeman used ECT instead of drug-based anesthesia when performing frontal lobotomies.

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