

Alcohol and benzodiazepine dependence

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Disclosures

- I am employed by the HealthEast Care System
- I do not have any financial relationships with the pharmaceutical or medical device industries



Unapproved ("off label") uses

- Baclofen (Lioresal)
- Ondansetron (Zofran)
- Topiramate (Topamax)
- Varenicline (Chantix)



New thoughts about something old

- What does phenotype (observable traits and behaviors) tell us about:
 - Neurologic (brain) disease
 - Treatment matching, both for psychosocial interventions and medications (addiction pharmacotherapy)



Substance dependence

- Tolerance
- Withdrawal
- Impaired control



Tolerance

- Need for markedly increased amounts of the substance to achieve intoxication or desired effect
- Markedly diminished effect with continued use of the same amount of the substance

DSM-IV-TR, 2000:197.



Withdrawal

- The characteristic withdrawal syndrome for the substance
- The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

DSM-IV-TR, 2000:197.



Impaired control

- The substance 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 substance use
- A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects

DSM-IV-TR, 2000:197.



Impaired control (cont)

- Important social, occupational, or recreational activities are given up or reduced because of substance use
- The substance use is continued despite having knowledge of a persistent or recurrent physical or psychological problem that is likely caused or exacerbated by the substance

DSM-IV-TR, 2000:197.



Alcohol withdrawal syndrome

- Autonomic hyperactivity (e.g., tachycardia, diaphoresis)
- Postural tremor
- Insomnia
- Nausea or vomiting
- Transient visual, tactile, or auditory hallucinations or illusions

DSM-IV-TR, 2000:216.



Alcohol withdrawal syndrome (cont)

- Psychomotor agitation
- Anxiety
- Seizures

DSM-IV-TR, 2000:216.



Alcohol dependence phenotypes

- There can be remarkable clinical texture and variability which we often discount and ignore
- This variability may suggest that alcohol dependence isn't a single disease entity but rather a spectrum or family of disorders
- This variability may suggest that different treatments are indicated or needed for different forms of alcohol dependence

Unreasonable?

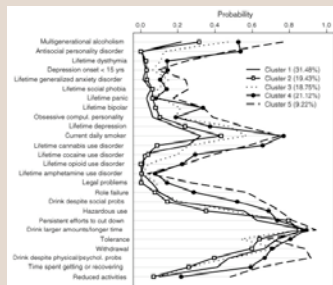
- The cardinal feature of diabetes is hyperglycemia (elevated blood glucose [sugar])
- The different forms of diabetes are due to different underlying problems and require specific treatments:
 - Type 1 diabetes
 - Type 2 diabetes
 - Gestational diabetes
 - Other forms of diabetes

Alcohol dependence phenotyping

- Cloninger type I and II
- Barbor type A and B
- Apollonian-Dionysian hypothesis

Some features

	Apollonian	Dionysian
Cloninger	Type I	Type II
Barbor	Type A	Type B
Onset	Older	Younger
Family history	Negative	Positive
Treatment occurs	Later	Sooner
Social problems	Less	More
Other features	Emotional problems	Disinhibited



More real world complexity

Dimension	Defined as	DSM-IV-TR
1	Intoxication, withdrawal	Axis I
2	Biomedical conditions	Axis III
3	Emotional, behavioral, cognitive	Axis I and II
4	Readiness to change	—
5	Relapse, continued use	—
6	Recovery environment	Axis IV

What does this mean?

- I don't know
- Diagnosis of and therapies for alcohol dependence are a bit crude and non-specific



Phases of treatment

- Medically supervised withdrawal ("detoxification")
- Maintenance of abstinence



Medically supervised withdrawal

- Does not, unless coupled with measures to maintain abstinence, lead to durable clinical success
- 100 alcohol dependent patients with over 1,500 hospital-based detoxification episodes:
 - Only 3% of treatment episodes were followed by 1 year of abstinence
- Is a necessary prelude to substance abuse treatment

Br J Addict 1988;83:1147 [PMID = 3191263]



Traditional detoxification regimens

- Diazepam in fixed, tapering doses:
 - 10 mg every 6 hours for 24 hours; then
 - 10 mg every 8 hours for 24 hours; then
 - Et cetera
- Problems:
 - Too much = medication toxicity
 - Too little = unrelieved symptoms of withdrawal, complicated withdrawal



Scoring severity

- Revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)
- Combination of symptoms and signs rated by trained personnel

Br J Addict 1989;84:1353 [PMID = 2597811]



CIWA-Ar

Item (points)	
Nausea and vomiting (0–7)	Tactile disturbances (0–7)
Tremor (0–7)	Auditory disturbances (0–7)
Paroxysmal sweats (0–7)	Visual disturbances (0–7)
Anxiety (0–7)	Headache (0–7)
Agitation (0–7)	Orientation (0–4)

Br J Addict 1989;84:1353 [PMID = 2507811].



Clinical outcomes

- Withdrawal is well managed
- Overall, less diazepam is needed compared to fixed dosing regimens



Maintenance of abstinence

- Where the battle is won or lost
- Involves a combination of psychosocial supports and medications
- Psychosocial supports take precedence:
 - Effect of medications is modest
 - Medication-assisted treatment (MAT)



Reinforcers

- Primary = substance that is abused
 - Alcohol
- Secondary = non-pharmacologic
 - “People, places, things”



Reinforcers (cont)

- Addiction pharmacotherapy (medications), at least for alcohol dependence, can alter the way that reinforcers are perceived and experienced but cannot by themselves change the context in which addiction occurs





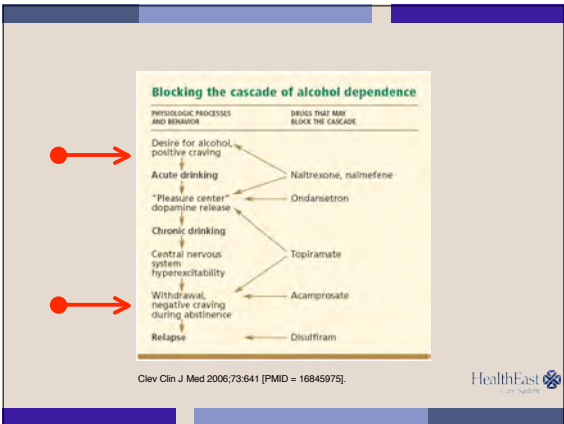
Alcohol, the substance

- Is sometimes described as a “dirty drug”
- In reality, has a complex mechanism of action

Complex mechanism of action

Neurotransmitter system	Effects of alcohol
Gamma-aminobutyric acid (GABA)	Enhance
Glycine	Enhance
Acetylcholine	Enhance
Serotonin	Enhance
Adenosine triphosphate (ATP)	Inhibit
Glutamate	Inhibit
Voltage-gated (several)	Enhance + inhibit

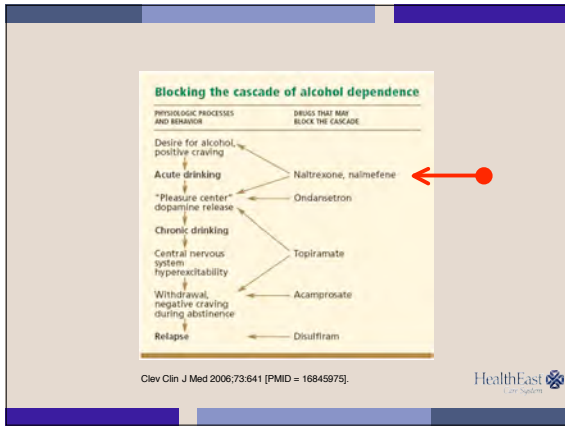
Principles of addiction medicine, 3d ed, 2003, page 104 [ISBN = 1-880425-08-4].



Cravings

- Positive = desire for reward or euphoria
- Negative = desire to relieve distress
 - “Restless, irritable, discontented”

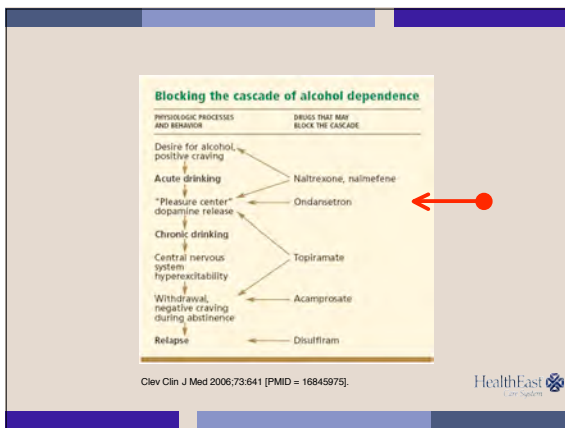
Clev Clin J Med 2006;73:641 [PMID = 16845975].



Naltrexone (ReVia, Vivitrol)

- Alcohol increases the activity of opioid pathways that affect the dopaminergic reward system
- Naltrexone blocks (antagonizes) the opioid receptor, thereby blunting (attenuating) the function of this pathway
- Most effective for patients with a positive family history

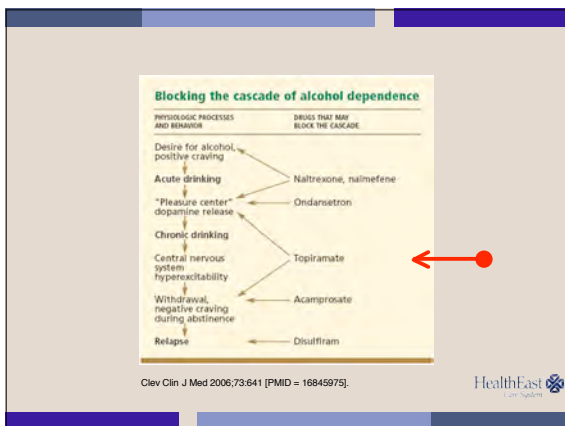
Clev Clin J Med 2006;73:641 [PMID = 16845975].



Ondansetron (Zofran)

- Serotonin receptors influence the dopamine reward pathways that are activated by alcohol
- Selective serotonin blockade reduces alcohol-mediated dopamine release, thereby attenuating its rewarding effects
- Most effective for early onset alcohol dependence (type II, type B, Dionysian)

Clev Clin J Med 2006;73:641 [PMID = 16845975].



Topiramate (Topamax)

- Alcohol alters the balance between gamma-aminobutyric acid (GABA) and glutamate
- Topiramate increases GABA and decreases glutamate function:
 - Attenuates dopamine release associated with alcohol consumption (positive cravings)
 - Attenuates symptoms of alcohol withdrawal (negative cravings)

Clev Clin J Med 2006;73:641 [PMID = 16845975].

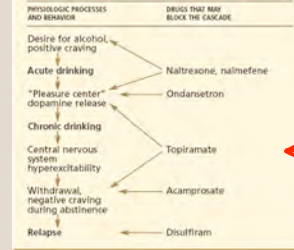
Topiramate (Topamax) [cont]

- Appears to reduce heavy drinking and alcohol-related harm
- Cognitive slowing (side effect) can limit its use

Clev Clin J Med 2006;73:641 [PMID = 16845975].



Blocking the cascade of alcohol dependence



Clev Clin J Med 2006;73:641 [PMID = 16845975].



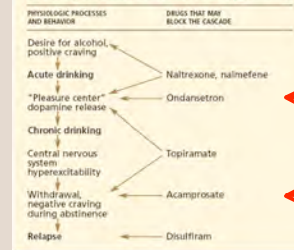
Baclofen (Lioresal)

- Alcohol alters the balance between gamma-aminobutyric acid (GABA) and glutamate
- Baclofen increases GABA function
- Reduces alcohol cravings and leads to a higher rate of abstinence

Lancet 2007;370:1915 [PMID = 18068515].



Blocking the cascade of alcohol dependence



Clev Clin J Med 2006;73:641 [PMID = 16845975].



Varenicline (Chantix)

- Alcohol activates reward pathways through a mechanism involving acetylcholine
- Varenicline blocks (antagonizes) the effects of alcohol at nicotinic acetylcholine receptors, thereby reducing its rewarding properties:
 - Reduces positive cravings

Proc Natl Acad Sci USA 2007;104:12518 [PMID = 17626178].

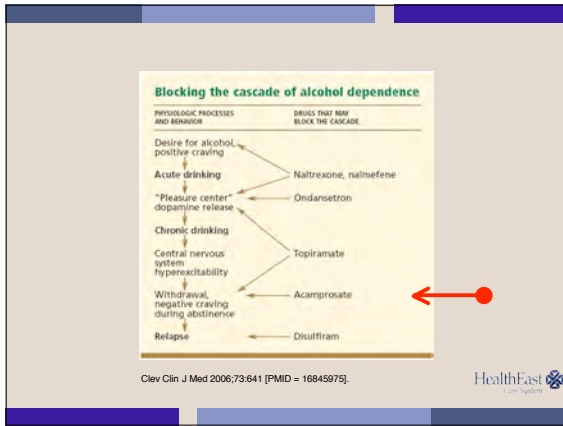


Varenicline (Chantix) [cont]

- Varenicline also activates (agonizes) nicotinic acetylcholine receptors, which reduces symptoms of withdrawal during abstinence:
 - Reduces negative cravings

Proc Natl Acad Sci USA 2007;104:12518 [PMID = 17626178].





Acamprosate (Campral)

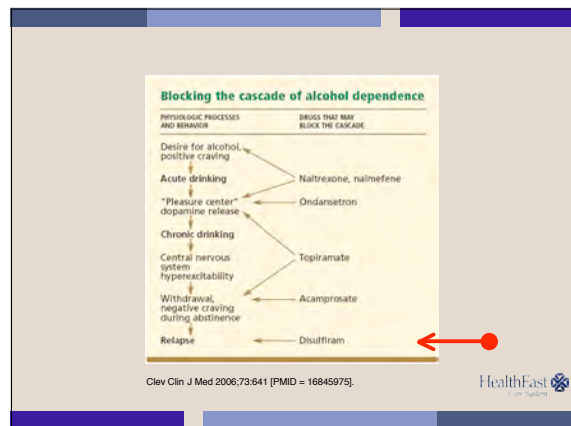
- Alcohol alters the balance between gamma-aminobutyric acid (GABA) and glutamate
- Acamprosate's exact mechanism of action is somewhat uncertain but likely affects the glutamate system:
 - Reduces negative cravings

Clev Clin J Med 2006;73:641 [PMID = 16845975].

Acamprosate (Campral)

- Is possibly more effective:
 - When started after abstinence is achieved ("lead in abstinence")
 - When abstinence is the patient's stated goal

Clev Clin J Med 2006;73:641 [PMID = 16845975].



Disulfiram (Antabuse)

- Irreversibly inhibits a key enzyme needed to metabolize alcohol
- Acetaldehyde accumulates when alcohol is consumed
 - Causes a noxious reaction involving nausea, vomiting, fast heart rate (tachycardia), low blood pressure (hypotension) and skin flushing

Clev Clin J Med 2006;73:641 [PMID = 16845975].

Disulfiram (Antabuse)

- In theory, should provide mental and physical disincentives to drink
- In reality, modestly decreases alcohol use but does not lead to a higher rate of abstinence
- Potentially dangerous for patients with poor underlying health

Clev Clin J Med 2006;73:641 [PMID = 16845975].



Benzodiazepine dependence

- Scope of the overall problem is probably smaller than you think but
- We (physicians) are a big part of the problem
- Iatrogenic:
 - Induced unintentionally by a physician through his diagnosis, manner or treatment

Compact Oxford English Dictionary, 2d ed, 1991, page 808 [ISBN = 0-19-861258-3].

Non-specific

- There are no non-specific diagnoses; there are only non-specific physicians
- Chest pain is a symptom:
 - Find the underlying cause and treat it
 - Don't give non-specific therapies (e.g., acetaminophen [Tylenol]) until the cause is known

Anxiety

- Is a symptom, not a diagnosis
- The underlying explanation for anxiety should be sought and treated:
 - Panic disorder
 - Social phobia
 - Generalized anxiety disorder
 - Et cetera

A general approach

- Medically supervised withdrawal:
 - Phenobarbital substitution + taper
- Diagnostic clarification:
 - Clarify the underlying anxiety disorder, if possible, and institute appropriate therapy
- Maintenance of abstinence:
 - Psychosocial supports



The end

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