Pharmacologic Management for Alcohol Use Disorder

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Addiction Medicine

Family Medicine

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ADDICTION (Alcohol use disorder) is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences.

Despite availability of effective pharmacologic and psychosocial options, fewer than 10% of individual with AUD received treatment

Alcohol Use disorder Effects

Dopamine

-Dopamine enhancement (ventral Tegmental Area) involved in pleasurable effect of ACUTE alcohol use. CHRONIC use creates dysregulation of Dopamine.

Serotonin

-Release increase by acute alcohol use

-CHRONIC use depletes serotonin stores (via Dorsal Raphe Nucleus)

Gamma-Aminobutyric acid (GABA)

-inhibition by ACUTE alcohol use

-compensatory upregulation of Glutamate

Alcohol Use disorder Effects

N-Methyl-D-Aspartate (NMDA)

- NMDA receptor is inhibited by alcohol. Chronic use produces enhance sensitivity of NMDA Receptors (to glutamate).

Endogenous Opiate-like compound (Beta endorphins)

- Alcohol stimulates beta endorphins, produce pleasurable effect via disinhibition of dopamine neuron in ventral tegmental area - nucleus accumens.

Pharmacologic Management for Alcohol use disorder

FDA Approved

- Naltrexone
- Acamprosate
- Disulfiram

Off Label Use

- Gabapentin
- Baclofen
- Topiramate

Naltrexone

- Semi synthetic mu-opioid antagonist

Mechanism of Action:

- Blockade of the mu (& kappa?)- opioid receptor
- Reduces the dopamine release in the mesolimbic reward pathway
- Reduce the reinforcing effect of Alcohol

Naltrexone

Dose: 50-100mg po daily

: Targeted dosing

Long-acting injectable form (Vivitrol – 380mg IM monthly)

Metabolized by Liver

Side effects: nausea (33%), Headache (25%), dizziness (12%), dysphoria (10%)

Naltrexone

Clinical Effects

Reduces:

- Subjective effect
- Dopamine release
- Euphoric effect
- Heavy drinking

Naltrexone

- Appropriate for patient who wants to cut down or maintain their abstinence
- Overall benefit seems to be better in patient can maintain abstinence at least 4 days
- To cut back in drinking is a reasonable goal, but it may not be appropriate in longer term (moderate – severe alcohol use disorder)

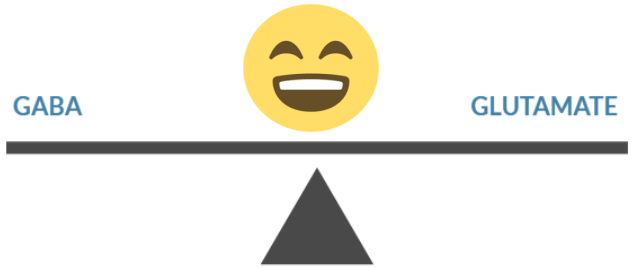
Acamprosate

- Glutamatergic antagonist/ Gaba agonist

Mechanism of Action

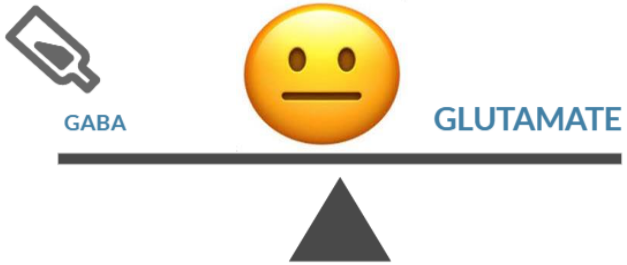
- Enhances GABA reception & transmission which are reduced by chronic alcohol exposure

Effects of Alcohol GABA/Glutamate

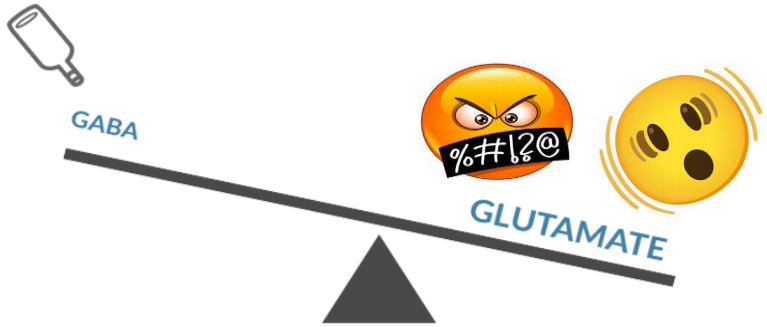


Consciousness

Alcohol Use



Long-term Compensation



Withdrawal

Acamprosate

Dose: 666mg (2 pills) three times daily

333mg TID for CrCL: 30-50ml/min

Metabolized by Renal

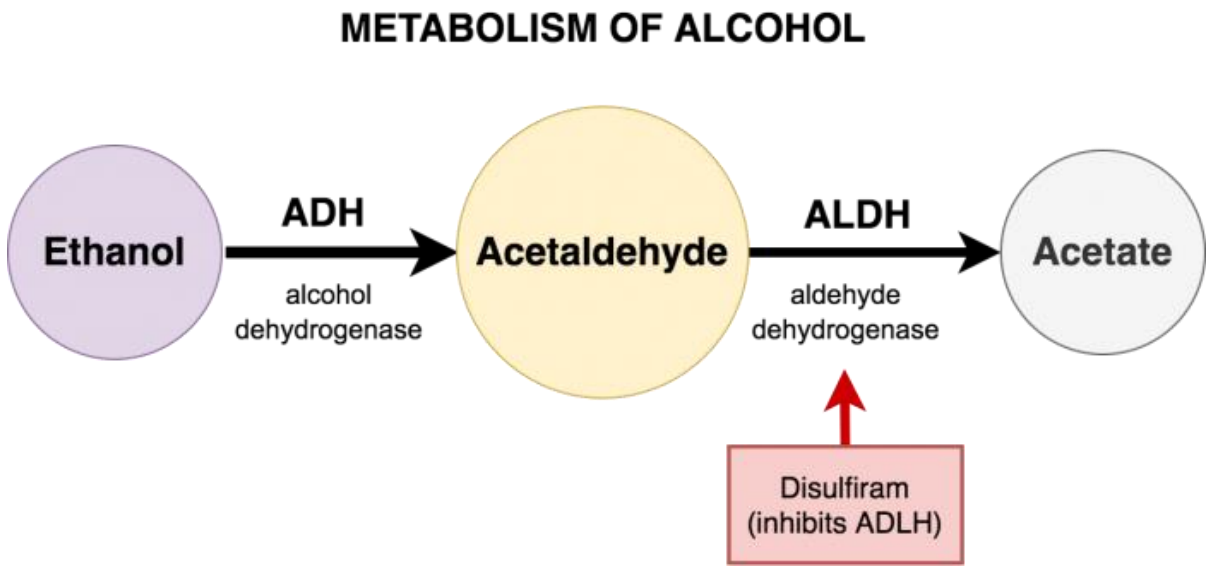
*Dose reduction required for renal impairment

Acamprosate

- Effective in maintaining abstinence in individuals with alcohol use disorder who were recently detoxified from alcohol use.
- Associated decrease return to any drinking
- Well tolerated
- No drug –drug interaction

Disulfiram

- Inhibits acetaldehyde dehydrogenase



Disulfiram

-Accumulation of Acetaldehyde causes unpleasant reaction: flushing, nausea, headache, palpitation, diaphoresis, hypotension

- Not an anti-craving drug and does not modulate the neurobiological mechanism of addiction

- Aversion treatment

Disulfiram

Dose: 250mg to 500mg daily

Metabolized by Liver

Contraindication: severe myocardial disease, history of psychosis

Caution: patient taking metronidazole, alcohol-containing preparation OR history of heart disease, over age 60, hypertension.

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Baclofen

- GABA B receptor agonist approved by FDA to reduce spasticity

Mechanism of Action (2 Pathways)

- Impacts regulation of emotional behavior through activation of GABA-B receptor in limbic system which lead to improved control over anxiety. Down regulates the neuronal stress circuitry.
- Local suppression of dopaminergic neuron, reduce the positive reinforcement of alcohol.

Baclofen

- Meta-Analysis data from 13 RCTs (N=1492) indicate that Baclofen was effective in:
- increasing the time between first drinking lapses
- Increase likelihood of abstinence during treatment
- Greater chance of abstinence during treatment

Baclofen

Dosed 30 to 80mg by mouth daily

Renally metabolized

Baclofen

Adverse Effect:	Primary sedation
	Dizziness
	Headache
	Excessive perspiration
	Slurred speech
	itching

Gabapentin

- FDA approved for post-herpetic neuralgia and adjunct therapy in treatment for partial seizure.
- Structurally similar to GABA, it has no activity at GABA receptor
- GABA analog that reduces excitatory neurotransmission and affects the downstream mediation of neurologic changes associated with withdrawal and abstinence in heavy drinker

Gabapentin

Off-label, three placebo-controlled trials (n=231) have shown

- Aid in symptoms of alcohol withdrawal
- Increase abstinence rate
- Decrease heavy drinking days
- Decrease alcohol cravings
- Decrease anxiety
- Helps with insomnia

Gabapentin

Dose 300mg to 600mg by mouth three times a day

Side effects:

- Dizziness
- Somnolence
- Ataxia
- Peripheral edema

**addictive potential & misuse

Topiramate

- FDA indicated for treatment for seizure, migraine prophylaxis , weight loss & chronic weight management (combination with phentermine)
- Known to modulate the brain’s dopamine reward pathways as an antagonist of excitatory glutamate receptor and inhibiting dopamine release within mesolimbic system while enhancing inhibitory GABA -> reduces dopamine, decrease alcohol induced reinforcement and the propensity to drink.

Topiramate

Clinical Outcomes:

- Higher rates of abstinence
- Fewer drinks/drinking days
- Less heavy drinking

Topiramate

Dosed 25mg to 150mg by mouth two times per day

* Start at 25 to 50mg daily with dose increases no more frequent than weekly

Topiramate

Adverse Effect

- Mental fogginess
- Weight loss
- Altered taste
- Headache
- fatigue

In Summary

- Alcohol use disorder is a preventable and treatable condition, similar to other chronic disease condition.
- AUD can be effectively treated with recurrence rates no higher than those for other chronic illness.
- FDA has 3 approved medications: Naltrexone, Acamprosate & Disulfiram.
- Off Label medication show modest efficacy with treating alcohol use disorder
- Pharmacologic treatment should be based on guidelines with individualization according to comorbidities and patient's goals for treatment.

ADDICTION (Alcohol use disorder) is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences.

Treating a Biobehavioral Disorder Must Go Beyond Just Fixing the Chemistry
We Need to Treat the Whole Person!
Pharmacological (medications)
Behavioral Therapies
Medical and
Social Services
In Social Context