Currumbin Clinic

a member of the healthe care group

Pharmacotherapy of Alcohol use disorder

Dr Wole Akosile, MBBS, MPH, Cert Addiction Psych, FRANZCP FAChAM

Addiction Specialist,

Currumbin Clinic

Senior Lecturer Griffith University

Senior Lecturer University of Queensland

Alcohol Use Disorder (AUD)

Alcohol Use Disorder (AUD)

- Defined as alcohol abuse and alcohol dependence.
- AUD IS A chronic relapsing illness
- It is A genetic disorder (Genetic factors are believed to contribute 40% to 60% to the risk of aud)-multiple genes and epigenetic factors implicated.
- It is A medical disorder with significant social consequences

AUD=Alcohol abuse + alcohol dependence

- Alcohol abuse is defined as a recurring pattern of high-risk drinking that creates problems for

✓ the drinker,

✓ for others, or

✓ for society.

AUD=Alcohol abuse + alcohol dependence

- Alcohol dependence, also called alcoholism (alcohol addiction), is a complex disease characterized by

✓ persistent and intense alcohol-seeking,

✓ loss of control over drinking,

✓ a preoccupation with drinking,

✓ compulsion to drink or inability to stop, and

✓ the development of tolerance and dependence

AUD=Alcohol abuse + alcohol dependence

- The development of AUD involves repeated alcohol use
- Alcohol withdrawal syndrome (AWS),
- Physical and psychological dependence
- Loss of ability to control excessive drinking.
- Salience-Alcohol predominates-its “alpha and omega”

AUD=Alcohol abuse + alcohol dependence

- Without a pharmacological adjunct to psychosocial therapy, the clinical outcome is poor, with up to 70% of patients resuming drinking within 1 year (Becker et al).
- Alcohol affects brain function by interacting with multiple neurotransmitter systems.
- Alcohol can disrupt the delicate balance between Gaba-aminobutyric acid (GABA), the primary inhibitory neurotransmitter, and glutamate, the major excitatory neurotransmitter in the central nervous system.

Match the AUD quotes and name?

“It provokes the desire, but it takes away the performance. Therefore, much drink may be said to be an equivocator with lechery”

“I neither want it [brandy] nor need it, but I should think it pretty hazardous to interfere with the ineradicable habit of a lifetime.”

“My makeup wasn't smeared, I wasn't dishevelled, I behaved politely, and I never finished off a bottle, so how could I be alcoholic?”

AUD=Alcohol abuse + alcohol dependence

- Chronic relapsing nature of alcohol use disorder involves impulsivity and compulsivity that yield three stages:

✓ binge/intoxication’,

✓ 'withdrawal/negative affect', and

✓ 'preoccupation/anticipation' (craving)

AUD=Alcohol abuse + alcohol dependence

- Animal and human imaging studies have revealed discrete circuits that mediate the three stages of the addiction cycle with key roles of

✓ the ventral tegmental area (VTA),

✓ ventral striatum

✓ and amygdala

- The transition to addiction involves neuroplasticity in all of these structures
- This may begin with changes in the mesolimbic dopamine system and a cascade of neuroadaptations from the ventral to dorsal striatum

AUD=Alcohol abuse + alcohol dependence

- D2 receptors in the striatum are primarily localized in GABAergic neurons.
- There is likely GABAergic involvement in the dopaminergic abnormalities seen in clients with aud.
- GABAA mediate several important effects of alcohol.
- Considerable evidence indicates that GABAARs are the major target of EtOH in the CNS
- Human studies found that single nucleotide polymorphisms (SNPs) in the gene encoding the GABA α receptor subunit (GABRA2) are associated with complex behaviors considered to be part of AUD

Pharmacotherapy options (NALTREXONE)

- Naltrexone
- Naltrexone is an opioid receptor antagonist that is thought to;
- reduce the reward,
- excitement associated with drinking alcohol,
- AND THE related cues in the environment (anticipatory excitement).

HIGHLIGHTS

- First line treatment
- Efficacy demonstrated in the combined study by anton 2006
- Naltrexone is listed on the PBS as an authority item for alcohol dependence
- NALTREXONE IS CONTRAINDICATED IN INDIVIdUALS WITH LIVER TOXICITY.

NALTREXONE

- Patients are often started on a half tablet (25 mg) daily for the first 3–5 days to minimise adverse effects.
- There are no specific ill effects from alcohol consumption during treatment and patients do not need to be advised to stop therapy if they relapse.
- It has a slightly larger effect size than Acamprosate, but has more adverse effects including

✓ headache,

✓ nausea,

✓ lethargy

✓ dysphoria.

- These effects are usually transient and rarely lead to cessation of therapy.
- USUALLY NOT PRESCRIBED IN CLIENTS WITH CHRONIC PAIN DISORDER.

Combined study

- Largest alcohol pharmacotherapy study
- Done in the usa
- Eight groups of patients received medical management with 16 weeks of naltrexone (100 mg/d) or acamprosate (3 g/d), both, and/or both placebos, with or without a combined behavioral intervention (CBI). A ninth group received CBI only (no pills). Patients were also evaluated for up to 1 year after treatment.

Combined study

CONCLUSION

- Patients receiving medical management with naltrexone, CBI, or both fared better on drinking outcomes.
- whereas acamprosate showed no evidence of efficacy, with or without CBI.
- No combination produced better efficacy than naltrexone or CBI alone in the presence of medical management.
- Placebo pills and meeting with a health care professional had a positive effect above that of CBI during treatment.
- Naltrexone with medical management could be delivered in health care settings, thus serving alcohol-dependent patients who might otherwise not receive treatment.

ACAMPROSATE (DEVIL'S TABLET)

- Acamprosate is a structural analogue of gammaaminobutyric acid (GABA).
- It is thought to work by affecting calcium channels and modifying transmission along GABA and glutamine pathways in the brain.
- This may result in decreased positive reinforcement of alcohol intake and withdrawal cravings.
- SOME EVIDENCE OF NEURO-PROTEction.
- Five previous meta-analyses concluded that abstinence was significantly higher with Acamprosate.
- CONSIDERED FIRST LINE IN AUSTRALIA
- The recommended dose is two 333 mg tablets, three times a day for people over 60 kg.
- VERY WELL TOLERATED.
- The most common adverse event is transient diarrhoea and flatulence.
- It has LIMITED ABUSE potential and does not interact with alcohol or drugs commonly prescribed in people with AUD such as antidepressants, anxiolytics, disulfiram, naltrexone and neuroleptics.
- It can be given to patients with liver dysfunction.

ACAMPROSATE (DEVIL'S TABLET)

- DOES IT WORK?
- Two large US trials failed to confirm the efficacy of acamprosate, although secondary analyses in one of the studies suggested possible efficacy in patients who had a baseline goal of abstinence

- Recent studies have shown that acamprosate had a significantly larger effect size than naltrexone on the maintenance of abstinence.
- naltrexone had a larger effect size than acamprosate on the reduction of heavy drinking and cravings,.
- in treatment for alcohol use disorders, acamprosate is slightly more efficacious in promoting abstinence.
- naltrexone is slightly more efficacious in reducing heavy drinking and cravings

Disulfiram-Aversive therapy

- Disulfiram (Antabuse) interferes with the degradation of alcohol.
- resulting in the accumulation of acetaldehyde.
- alcohol is broken down in the liver by the enzyme alcohol dehydrogenase to acetaldehyde.
- the enzyme acetaldehyde dehydrogenase converts acetaldehyde to the harmless acetic acid
- Disulfiram blocks the enzyme acetaldehyde dehydrogenase.
- After alcohol intake under the influence of disulfiram, the concentration of acetaldehyde in the blood may be 5 to 10 times higher than that found during metabolism of the same quantity of alcohol alone.
- acetaldehyde is one of the major causes of the symptoms of "hangover",
- this produces a severe negative reaction to alcohol intake. Symptoms include flushing of the skin, accelerated heart rate, shortness of breath

Disulfiram-Aversive therapy

- The utility and effectiveness of disulfiram are considered limited because;
- ✓ compliance is generally poor.
- ✓ Not for emotionally unstable clients.
- ✓ Not for clients who are "tunnel visioned" during crisis.
- ✓ Prescription must be done under expert guidance.

- disulfiram may cause a peripheral neuropathy
- May be useful in;
- ➢ Professionals-doctors, nurses, judges
- ➢ Under supervised dispensing until intrinsic motivation is bolstered.
- ➢ It certainly has a place in management of AUD!!!!!!

Baclofen

- Baclofen, a selective GABA-aminobutyric acid B (GABAB) receptor agonist, has been extensively used as an anti-spasticity agent for several decades
- baclofen has been utilised as an anti-craving agent in the treatment of alcohol use disorders
- Development and progression of AUD has been associated with modulation of dopaminergic neurotransmission
- and amino acid stimulation of GABAB receptors in the mesolimbic reward system of the brain
- Therefore, as a GABAB receptor agonist, baclofen is a biologically plausible therapeutic in the prevention of progression of AUDs.
- baclofen can be used in patients with established liver disease because it is predominantly excreted via the kidneys.
- Different meta-analysis and RCTS have shown mixed reviews (Addolorato ET AL)
- However dose dependent effectiveness is consistent.

Baclofen

- It is primarily aimed at drinkers seeking to maintain abstinence but is not approved for this indication in Australia.
- highly toxic in overdose
- BACLOFEN USE DISORDER HAS BEEN REPORTED IN the LITERATURE (AKOSILE ET AL)
- Abrupt cessation may result in seizures or confusion.
- Baclofen dose needs careful titration over weeks
- Beginning with 5 mg three times a day.
- The optimum dose generally ranges between 30 mg and 75 mg.
- Adverse effects include sedation and impairment of ability to drive or use machinery.
- These are exacerbated by concurrent alcohol use.
- Baclofen may also cause nausea, visual disturbance and urinary disturbance.

Topiramate

- A sulfamate-substituted monosaccharide related to fructose.
- An antiepileptic with neuroprotective properties.
- It reduces the rewarding effects of acute alcohol use by suppressing dopamine release, and normalises dopamine activity in chronic alcohol use.
- This reduces cravings for alcohol and withdrawal symptoms.
- Topiramate IS A MOOD STABILISER.
- may be USEFUL in clients with co-morbidity e.g. bipolar disorder, borderline personality disorder and post-traumatic stress disorder (most aud clients have co-morbidity).
- topiramate may be viewed as a way to address multiple disorders with one drug.

Topiramate

- Adverse effects are;

✓ Dizziness

✓ paraesthesia,

✓ psychomotor slowing

✓ memory or concentration impairment.

✓ weight loss.

✓ A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has occasionally been reported.

✓ If there are sudden vision changes, eye pain or redness then topiramate should be ceased and medical review arranged.

- Topiramate can be commenced before cessation of alcohol. Dosing requires slow titration from 25 mg daily to a maximum of 150 mg twice daily

Summary

- Naltrexone

- PBS listed
- First line
- Patients who wish to cut down
- No liver disease
- No chronic pain issues

Summary

- Acamprosate

- PBS listed
- First line
- Abstinence is the goal
- No co-morbidity
- Obsessed with taking medications…three times a day

Summary

- Baclofen

- Not Pbs Listed
- Specialist Advice Needed
- Liver Toxic Client
- Good In Anxious Clients
- Good In Chronic Pain Clients

Summary

- Disulfiram

- Not PBS listed, 90 dollars a month.
- Motivated.
- Supervised.
- Professional-a lot at stake.
- Able to follow recovery plan in crisis.
- Must still engage in an abstinence based program.
- Specialist advice required

Summary

- Topiramate

- Not PBS listed
- Co-morbidity
- Mood lability
- Has some serious side effects

Summary

FUTURE DIRECTION

Ivermectin-ANTIPARASTIC IN MICE MODELS SHOWING EFFICACY IN REDUCING CRAVING

The plant Hovenia has been used in traditional herbal medicine as a treatment for alcohol hangovers for hundreds of years

dihydromyricetin (DHM), a flavonoid compound isolated from Hovenia and teas, blocked acute alcohol intoxication and alcohol tolerance and prevented signs of withdrawal when co-administered with ethanol.

DHM also greatly reduced voluntary alcohol drinking in rats.

Kudzu (Pueraria lobatA) IS A root-based herb with MIXED RESULTS IN ANIMAL AND HUMAN TRIALS.


Thank You

file:///C:/Users/akosi/Downloads/NPS%20Alcohol-dependence.pdf

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4125717/