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Pharmacotherapy of Alcohol Dependence

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Abstract

Alcohol is a commonly used psychoactive substance all over the world and responsible for a significant proportion of mortality and morbidity. The treatment of alcohol dependence consists of two phases, detoxification and rehabilitation. Pharmacotherapy is being investigated to enhance abstinence and prevent relapse and complement interventions at a psychosocial level.

Alcohol activates dopamine in the nucleus accumbens and mediates positive reinforcement and reward. The US Food and Drug Administration (FDA) have approved three medications, disulfiram, naltrexone and acamprosate for the treatment of alcohol dependence. The selective serotonin reuptake inhibitors (SSRIs) particularly fluoxetine and citalopram have been evaluated. Bupropion and Ondansetron have also been tried for alcohol dependence.

Combination of naltrexone and acamprosate has shown promising results. It is essential to develop clinically useful pharmacological treatments, which can be evaluated using large-scale clinical trials. Clinical trial methodologies to evaluate combination treatments and using medications along with psychosocial treatments are required.

Key Words

Alcohol; Dependence; Detoxification; Pharmacotherapy; Rehabilitation

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Alcohol is a commonly used psychoactive substance all over the world. In Nepal, alcohol has been consumed since a long time. The substance

has deep-rooted religious, cultural and traditional dimensions and social implications [1]. Alcohol use is common among both genders and around 25% of respondents were found to be dependent on alcohol in a survey in a town of Eastern Nepal [2].

Brief epidemiology:

Up to 25% of accidents in the workplace and around 60% of total accidents at work may be associated with alcohol [3]. Almost one third of Americans consume enough alcohol to be considered at risk for alcohol dependence and there are more than 100,000 deaths each year from alcohol related diseases and injuries [4]. In Australia, alcohol accounted for an estimated 3668 deaths and 95917 hospital admissions in the financial year 1996-97 [5]. In Korea, a recent study had established that 10.2% of the adult population had a lifetime prevalence of alcohol dependence and this makes the

condition, the second most common psychiatric disorder in Korea [6]. In India, about 15-20% of people consume alcohol and the number of drinkers has increased to about one in twenty and about five million people are addicted to alcohol [7].

Alcohol dependence:

The criteria for alcohol dependence have been defined by the fourth edition of the Diagnostic and Statistical Manual of Mental disorders [8]. Among the criteria are tolerance, characteristic withdrawal symptoms on stopping use, abandonment of important social, occupational or recreational activities because of alcohol ingestion and continued use of alcohol despite problems. Alcohol dependence is a chronic disorder, which results from a variety of genetic, psychosocial and environmental factors [9].

Management of alcohol dependence:

The treatment of alcohol dependence consists of two phases, detoxification and rehabilitation. The initial detoxification phase deals with the acute withdrawal symptoms while rehabilitation attempts to prevent relapse and develop long-term abstinence [10]. Psychosocial treatments have been shown to be effective in reducing alcohol consumption and maintaining abstinence. However, 40 to 70% of patients relapse and start drinking within a year following treatment [11].

Pharmacotherapy is being investigated to enhance abstinence and prevent relapse and complement interventions at a psychosocial level. Recent advances in neurobiology have identified the effects of alcohol on various neurotransmitter systems and these can be targets for drugs [10]. Alcohol dependence is a heterogeneous condition.

Neurobiology of alcohol dependence:

Alcohol changes the 3-dimensional structure of proteins. The ion channels, neurotransmitter receptors and enzymes involved in signal transduction are particularly sensitive [12]. Dopamine, serotonin, gamma amino butyric acid (GABA), glutamic acid, adenosine, neuropeptide Y, nor-epinephrine, cannabinoid receptors and opioid peptides are affected [13].

The dopamine system plays a central role in the biology of alcoholism. Alcohol activates releases dopamine in the nucleus accumbens and mediates positive reinforcement and reward [14]. Alcohol use increases release of endorphins and indirectly

activates the dopaminergic reinforcement and reward system [15].

Alcohol is a depressant of the central nervous system (CNS) and potentiates GABAergic inhibition. On chronic exposure, there is a compensatory up regulation of glutamatergic and down regulation of the GABA system, which can result in an increased tolerance for alcohol [16].

Medications for treating alcohol dependence:

The US Food and Drug Administration (FDA) have approved three medications, disulfiram, naltrexone and acamprosate for the treatment of alcohol dependence [4]. Table 1 shows pharmacokinetics of selected drugs used in management of alcohol dependence while table 2 shows dosage, adverse effects, contraindications and precautions regarding use of selected drugs for management of alcohol dependence

Aversive agents: Disulfiram

Disulfiram inhibits the enzyme aldehyde dehydrogenase (ALDH) which catalyses oxidation of acetaldehyde to acetic acid. Blood levels of acetaldehyde increases and a characteristic disulfiram-ethanol reaction (DER) is produced [17]. A number of studies have been performed with disulfiram; however controlled clinical trials have failed to establish clearly the benefit of disulfiram in enhancing abstinence [18].

The usual dose is 250 mg per day and the maximum dose is 500 mg per day. On consuming alcohol while on disulfiram adverse reaction like palpitations, flushing, nausea, vomiting and headache may develop [4]. Myocardial infarction, congestive cardiac failure, respiratory depression and even death can occur. The drug is contraindicated in patients on metronidazole, with psychosis or cardiovascular disease. It is also not recommended in patients with severe pulmonary disease, chronic renal failure, diabetes, peripheral neuropathy, seizure, liver cirrhosis or more than 60 years of age. Disulfiram is converted to 5-ethyl N, N-diethylthiocarbamate sulphoxide (DETC-MeSO) and this metabolite is responsible for

inactivating ALDH [19]. A number of factors can influence the metabolism of disulfiram and other medications metabolised by the same cytochrome P-450 enzymes can inhibit disulfiram metabolism [20]. DETC-MeSO is potent and its pharmaceutical characteristics may make a transdermal or a sustained release formulation feasible [17]. The variability in metabolism can also be reduced. Further development of this metabolite as a drug can be considered. Disulfiram implants can improve compliance. However, the bioavailability of disulfiram following implantation is variable [18].

Serotonergic agents:

The selective serotonin reuptake inhibitors (SSRIs) particularly fluoxetine and citalopram have been most extensively evaluated [17]. Naranjo and coworkers in 1990 first reported on the effects of fluoxetine on alcohol consumption in heavy drinkers [21]. Fluoxetine 60 mg/day decreased average daily alcohol consumption by around 17% compared to base line. Further studies have shown conflicting results [17].

In 1987, Naranjo et al reported that citalopram 40 mg daily reduced number of drinks and increased number of abstinent days in non-depressed, early stage problem drinkers. However further studies have shown diverse results [17]. The diversity of subject samples may be partly responsible for the variable effects of SSRIs.

Fluoxetine is usually started at a dose of 20 mg per day and may be increased to 60mg daily as needed. Nausea, headache and sexual dysfunction may be among the adverse effects.

Other agents acting on serotonergic receptors:

Buspirone and ondansetron have also been tried for alcohol dependence [18]. Ondansetron is usually given in a dose of 4 µg per kg body weight twice daily and malaise, fatigue, headache, dizziness and anxiety are the major side effects. The therapy is however more expensive compared to other agents.

Drugs acting on the opioid receptors:

Naltrexone is an opioid receptor antagonist and has been approved for the treatment of alcohol dependence by the US FDA [10, 18]. Two small, double-blind, placebo-controlled trials had shown a reduced rate of drinking relapse, reduced craving and less frequent drinking in patients treated with naltrexone [22, 23]. A systematic review of 11

trials found that naltrexone reduced short term relapse rates in alcohol dependent patients when combined with psychosocial treatments [24]. However, more recent RCTs working at longer term outcomes have reported mixed results [4].

Naltrexone may act by blocking the µ opioid receptors, which reduces alcohol's reinforcing effects. The recommended dose is 50 mg daily in a single dose [4]. The drug undergoes extensive hepatic first pass metabolism to Q-naltrexol, which is a weaker antagonist but has a longer half life [25]. The drug is generally well tolerated. Non-specific symptoms like headache, flu-like symptoms, nausea and anorexia have been reported [25]. Naltrexone blocks the action of opioid analgesics and is contraindicated in patients on long-term opioid therapy for chronic pain or heroin dependence.

Compliance may be a limiting factor in naltrexone treatment [26]. Sinclair had suggested that naltrexone is useful to prevent relapse rather than to maintain absolute abstinence [27]. The most common side effects are nausea, headache, anxiety and sedation [28]. Dose dependent hepatotoxicity may be a problem and the drug is contraindicated in patients with hepatitis or liver failure [10]. In April 2006, the US FDA approved an extended-release (30 day) injectable suspension of naltrexone [29].

It has been suggested that patients with high level of alcohol craving are more likely to benefit from naltrexone treatment [30]. Naltrexone not only blocks the opioid receptors but also indirectly increases the hypothalamo pituitary adrenal (HPA) activity and results in higher level of ACTH and cortisol [31].

Nalmefene

Nalmefene has similar properties and a similar mechanism of action to naltrexone [32]. A RCT had used nalmefene in dosage of 20 or 30 mg orally daily and observed that the drug significantly reduced relapse in heavy drinking [32]. Out side of research studies, the drug is available only in an injectable form.

NMDA/GABA receptor modulator:

Acamprosate

Acamprosate (calcium acetyl homotaurinate) blocks the glutaminergic NMDA receptors and activates GABA_A receptors and is approved by the FDA for treating alcohol dependence [4]. Acamprosate has a structure similar to GABA and enhances GABA transmission by increasing the number of sites for GABA uptake [25]. The drug also affects the calcium channels which increase in number as alcohol dependence develops [33].

The drug is available in 333 mg enteric-coated tablets and dosing is by weight. For an adult weighing above 60 kg the dose is six tablets orally in three divided doses along with meals [25]. For adults under 60 kg the dose is four tablets daily. Only 10% of acamprosate is absorbed and 90% is excreted unchanged in urine.

The side effects are mainly confined to the gastrointestinal system and can be minimized by gradually increasing the dose. Low frequencies of rash, pruritus, paresthesiae, decreased libido and confusion have been reported [25]. Transient diarrhea is the most common adverse effect and occurs in about 10% of patients.

The calcium component may inactivate tetracyclines during concurrent use. The safety of the drug in pregnancy or lactation has not been established [25]. Like naltrexone and disulfiram the FDA pregnancy category is C. The drug is contraindicated in patients with renal insufficiency or advanced cirrhosis but may be safely taken by patients with liver dysfunction.

Acamprosate has been studied in over 3000 patients and evidence of the efficacy in rehabilitation of alcoholics is generally consistent [17]. The drug has a prominent role to play in treating alcohol dependence. Chick and coworkers have raised the possibility that certain subgroups of alcoholics may be more responsive to treatment with acamprosate [34].

Chronic exposure to alcohol causes compensatory up regulation of the glutamatergic and down regulation of the GABA system and causes increased tolerance. Abrupt alcohol withdrawal causes a hyper excitable state. This is perceived as disagreeable by the patients. Acamprosate is an antiglutamatergic agent and reduces motivation to drink by suppressing alcohol withdrawal symptoms [10]. Acamprosate may have

other beneficial effects such as substituting for deficits in negative feedback signals and reducing the development of tolerance and sensitization to alcohol [35].

Lithium:

The exact mechanism of action is not known but it affects phosphoinositide signaling and enhances serotonin action in the brain [18]. Garbutt and coworkers concluded that lithium lacks efficacy in treating primary alcohol dependence.

Combination of naltrexone and acamprosate:

Combining these two drugs is attractive for several reasons. The drugs have different mechanisms of action [36]. Combination of two drugs would act simultaneously on two different aspects of craving and have a synergistic effect. Naltrexone reduces the quantity of ingested alcohol by decreasing the priming effect of initial intake or alcohol associated cues while acamprosate increases the probability that currently abstinent subjects remain abstinent [36].

A study observed that co administration significantly increased the rate and extent of absorption of acamprosate [37]. A RCT observed that the combination was pharmacologically and behaviourally safe [38]. The COMBINE study had shown good initial results [39]. The study will answer important questions regarding the effectiveness of the drugs alone and in combination as well as that of psychosocial treatment. Combination treatment seems to be well tolerated and no serious adverse effects were reported. An increased incidence of diarrhoea and nausea has been seen perhaps due to a pharmacokinetic interaction.

Future perspectives:

It is essential to develop clinically useful pharmacological treatments, which can be evaluated using large-scale clinical trials. Clinical trial methodologies to evaluate combination treatments especially involving multiple medications and using medications along with psychosocial treatments are required [17]. Small scale, exploratory studies to

develop new candidate medications or formulations are however important. Combining medications with participations in self help groups may be a challenge [40]. Factors which may predict poor compliance with treatment and appropriate efforts to remedy these will be important. The optimal duration of treatment is not well defined. The role of pharmacotherapy in efforts at secondary prevention should also be defined. Alcoholics with co morbid drug use disorders and with other disorders are not included often in drug trials. This can form a population for future studies.

Conclusion:

Changes are taking place in the pharmacotherapy of alcoholism. Pharmacotherapy should be combined with concurrent counselling through professional or self-help programmes. Acamprosate and naltrexone are the best choices for relapse prevention. Disulfiram shows limited efficacy and may be used less frequently. SSRIs can be used in alcoholics with co morbid disorders. Topiramate and ondansetron show promise in treating alcohol dependence. The biology of addiction and dependence is being elucidated and this may lead to more effective drug treatments.

Table/Fig 1: Pharmacokinetics of selected drugs used in management of alcohol dependence

	Absorption from GIT	Average time to reach peak plasma concentration	Metabolism	Plasma protein binding	Excretion
Disulfiram	Variable	8 to 10 hours		Variable	Metabolites are excreted primarily in the urine; carbon disulfide is exhaled in the breath.
Fluoxetine	Readily absorbed	About 6 to 8 hours after oral doses	Extensively metabolised, by demethylation, in the liver to its primary active metabolite norfluoxetine	About 95%	Mainly via the urine
Buspirone	Rapidly absorbed	Within 40 to 90 minutes after an oral dose	Extensively in liver via the cytochrome P450 isoenzyme CYP3A4	About 95%	Mainly as metabolites in the urine, and also in the faeces
Ondansetron		About 1.5 hours after an oral dose of 8 mg, and about 6 hours after a rectal dose	In the liver through multiple enzymatic pathways; cytochrome P450 isoenzymes, primarily CYP3A4, but also CYP1A2 and CYP2D6	About 70 to 75%	Mainly in urine
Naltrexone	Well absorbed	About 1 hour	Extensively metabolised in the liver and the major metabolite, 6-β-naltrexol	About 20%	Excreted mainly in the urine
Nalmefene	Absorbed	-	Metabolized in the liver, mainly to the inactive glucuronide	-	-
Acamprosate	Slow but sustained		Does not appear to be metabolised	Not protein bound	Excreted unchanged in the urine
Topiramate	Readily absorbed	About 2 hours	Not extensively metabolised; however, up to 50% of a dose may undergo metabolism in the liver in patients also receiving enzyme-inducing drugs.	About 9 to 17%	Eliminated chiefly in urine
Gabapentin	Absorbed from the gastrointestinal tract by means of a saturable mechanism	Multiple dosing peak plasma concentrations are usually achieved within 2 hours of a dose	Not appreciably metabolised	Minimal	Most of a dose is excreted unchanged in the urine with the remainder appearing in the faeces

Table/Fig 2: Dosage, adverse effects, contraindications and precautions regarding use of selected drugs for management of alcohol dependence

Name of drug	Dosage	Adverse effects	Contraindications	Precautions
Disulfiram	800 mg, taken as a single dose, on the first day of treatment, reduced by 200 mg daily to a maintenance dose which is usually 100 to 200 mg daily	Drowsiness and fatigue, garlic-like or metallic aftertaste, gastrointestinal upsets, body odour, bad breath, headache, impotence, and allergic dermatitis. Peripheral and optic neuropathies, psychotic reactions, and hepatotoxicity	Cardiovascular disease or psychosis or severe personality disorders, and should not be given to patients known to be hypersensitive to it or to other thiuram compounds	Presence of diabetes mellitus, epilepsy, impaired hepatic or renal function, respiratory disorders, cerebral damage, or hypothyroidism, addicted to other drugs in addition to alcohol. pregnancy
Fluoxetine		Dry mouth and gastrointestinal disturbances such as nausea, vomiting, dyspepsia, constipation, anxiety, restlessness, nervousness, and insomnia, seizures, hallucinations, confusion, agitation, extrapyramidal effects, depersonalisation, mania, panic attacks, sexual dysfunction, and symptoms suggestive of a serotonin syndrome	Poorly controlled epilepsy	Caution in patients with epilepsy or a history of such disorders, patients receiving ECT, patients with angle-closure glaucoma
Bupirone	Initial doses of 5 mg two or three times daily, may be increased in increments of 5 mg at 2- to 3-day intervals if required.	Dizziness, nausea, headache, nervousness, light-headedness, excitement, paraesthesias, sleep disturbances, chest pain, tinnitus, sore throat, and nasal congestion tachycardia, palpitations, drowsiness, confusion, seizures, dry mouth, fatigue, and sweating	Patients with epilepsy or a history of such disorders, severe hepatic or renal impairment	Patients with renal or hepatic impairment, impair the patient's ability to drive or operate machinery
Ondansetron		Headache, a sensation of flushing or warmth, hiccups, and constipation, transient rise in liver enzymes, rare reports of immediate hypersensitivity reactions, including anaphylaxis	Hypersensitivity reaction to a member of this drug class	Patients with signs of subacute intestinal obstruction or ileus, moderate to severe hepatic impairment
Naltrexone	50 mg daily by mouth, modified-release intramuscular injection in a dose of 380 mg once every 4 weeks	Difficulty in sleeping, loss of energy, anxiety, dysphoria, abdominal pain, nausea, vomiting, reduction in appetite, joint and muscle pain, and headache, Dizziness, constipation, diarrhoea, skin rashes, and reduced potency and ejaculatory difficulties	Patients receiving opioids therapeutically, or in those misusing them, patients with acute hepatitis or hepatic failure	Patients with hepatic and/or renal impairment.
Nalmefene		Nausea, vomiting, tachycardia, hypertension, fever, and dizziness	Patients receiving opioids therapeutically, or in those misusing them, patients with acute	Patients with hepatic and/or renal impairment.

			hepatitis or hepatic failure	
Acamprosate	666 mg of acamprosate calcium given three times daily. Patients weighing less than 60 kg should be given a dose of 666 mg at breakfast followed by 333 mg at midday and 333 mg at night	Dosage-related diarrhoea; nausea, vomiting, and abdominal pain, pruritus, and occasionally a maculopapular rash; bullous skin reactions have occurred rarely. Depression and fluctuations in libido	Patients with severe hepatic impairment	
Topiramate		Ataxia, impaired concentration, confusion, dizziness, fatigue, paraesthesia or hypoesthesia, drowsiness, and difficulties with memory or cognition Agitation, anxiety, nervousness, emotional lability (with mood disorders), and depression, risk of developing renal calculi is increased, especially in predisposed patients		Patients with renal or hepatic impairment
Gabapentin		Most commonly reported adverse effects associated with gabapentin are somnolence, dizziness, ataxia, and fatigue. Nystagmus, tremor, diplopia, amblyopia, pharyngitis, dysarthria, weight gain, dyspepsia, amnesia, weakness, paraesthesia, arthralgia, purpura, leucopenia, anxiety, and urinary-tract infection may occur less frequently.		patients with a history of psychotic illness, caution in renal impairment

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