MEDICAL TREATMENT OF ALCOHOL DEPENDENCE

Ganesh Suryakant Kanchan¹, Abdul Hannan², Momin. Mohd Abdul Mujeeb³, Sadiq Patel⁴, Rohan Sequeira⁵

¹Resident, Department of Pharmacology, Grant Govt. Medical College, Mumbai.
²Assistant Professor, Department of Pharmacology, Grant Govt. Medical College, Mumbai.
³Associate Professor, Department of Pharmacology, Grant Govt. Medical College, Mumbai.
⁴Professor and HOD, Department of Pharmacology, Grant Govt. Medical College, Mumbai.
⁵Associate Professor, Department of General Medicine, Grant Govt. Medical College, Mumbai.

ABSTRACT

Alcohol dependence is a complex psychological and neurobiological disorder. It is important to recognize that as an individual moves from initial alcohol use to the other end of the spectrum (Dependence), parallel dynamic changes are occurring throughout the nervous system. Considerable evidence has emerged suggesting that the dopamine system plays a central role in the biology of alcoholism. Mesolimbic dopamine A10 neurons are activated by alcohol, resulting in a release of the neurotransmitter in the nucleus accumbens and mediating positive reinforcement and reward. As for the major mechanism of alcohol-induced neurodegeneration, early research has highlighted that chronic alcohol consumption causes excitotoxicity, thus activating glutamatergic transmission and ultimately resulting in neuronal damage via intracellular signal pathways.

KEYWORDS

Alcohol Dependence, Dopamine.


INTRODUCTION

Alcoholism remain a serious cause of morbidity and mortality, despite progress through neurobiological research in identifying new pharmacological strategies for its treatment. Alcohol is a psychoactive substance with properties known to cause dependence. An estimated 3.8% of all deaths and 4.6% of disability-adjusted life-years globally are attributable to pathological alcohol use.¹ Such alcohol-attributable costs exceed 1% of the gross national product of high-and middle-income countries, making pathological alcohol use one of the largest avoidable risk factors for the worldwide burden of disease. Alcohol use disorders are present across medical specialties, with alcohol-related deaths particularly prevalent in the categories of injury, cancer, cardiovascular disease, and liver cirrhosis.

Nonetheless, implementation of alcohol-specific medications remains limited across most medical specialties. Alcohol dependence, also referred to as alcohol use disorder, is a chronic, relapsing disorder marked by compulsive alcohol use, an inability to stop drinking despite harmful consequences, and the emergence of a withdrawal syndrome upon cessation of use. Early abstinence is associated with activation of brain stress systems in the extended amygdala. Clinically, protracted abstinence involves symptoms of craving, mood and sleep disturbance, all of which have been identified as risk factors for relapse. New pharmacological treatments target modulation of the cortico-mesolimbic dopamine system, a network that governs alcohol’s reinforcing effects, which are associated with its abuse liability.² Alcohol dependence is a complex psychological and neurobiological disorder.

It is important to recognize that as an individual moves from initial alcohol use to the other end of the spectrum (Dependence), parallel dynamic changes are occurring throughout the nervous system (i.e., these systems are constantly moving targets). These perturbations and disruptions result in neuroadaptations that contribute to overall dysregulations in normal daily behaviours (e.g., work, social interactions) as well as the development of alcohol dependence. Several key receptors mediate the response to acute and chronic alcohol intake.³

What is Already Known about this Topic

- Alcoholism remain a serious cause of morbidity and mortality.

What this Study Adds

- Early alcohol abstinence is associated with activation of brain stress systems in the extended amygdala.
- Neurotransmitters which plays important role in alcohol dependence with notable sensitivity include dopamine, serotonin, gamma-aminobutyric-acid (GABA), glutamic acid, adenosine, neuropeptide Y, norepinephrine, cannabinoid receptors, and opioid peptides.

THE NEUROBIOLOGY OF ALCOHOL DEPENDENCE

For many years, it has been suggested that alcohol exerts its neurobiological effects mainly by increasing membrane fluidity, altering the function of macro-molecules in the cell membrane. New evidence, however, indicates that alcohol binds to hydrophobic pockets of proteins, modulating their function by changing their 3-dimensional structure. Proteins that are particularly sensitive to this effect include ion-channels, neurotransmitter receptors, and enzymes involved in signal transduction. Neurotransmitters with notable sensitivity to this effect include dopamine, serotonin, gamma-aminobutyric-acid (GABA), glutamic acid, adenosine, neuropeptide Y, norepinephrine, cannabinoid receptors, and opioid peptides.⁴ These neurotransmitter systems are

Financial or Other, Competing Interest: None.
Corresponding Author:
Dr. Ganesh Suryakant Kanchan,
Room No. 533, 300, Resident Hostel,
JJ Hospital Campus, Grant Medical College,
Byculla, Mumbai-400008.
E-mail: mominmujeeb23@gmail.com
dr.gskanchan@gmail.com
involved in the different components of alcohol dependence and are therefore targets for pharmacotherapeutic interventions.

The Brain Reward System: Dopamine and Endogenous Opioid
Considerable evidence has emerged suggesting that the dopamine system plays a central role in the biology of alcoholism. Mesolimbic dopamine A10 neurons are activated by alcohol, resulting in a release of the neurotransmitter in the nucleus accumbens and mediating positive reinforcement and reward. It is postulated that repeated alcohol use sensitizes the system, so that behavioural stimuli associated with alcohol also cause the release of dopamine and facilitate additional alcohol use. This sensitization may account for the craving and preoccupation with alcohol that are the hallmarks of alcohol dependence.

The endogenous opioid system seems to play a modulatory role on the dopaminergic system, whereby activation of opiate receptors stimulates the release of dopamine in the brain. Alcohol consumption increases the release of endorphins (which are endogenous opioid peptides) in the brain, thus indirectly activating the dopaminergic reinforcement/reward system. It has been postulated that individual differences in the sensitivity of endogenous opioid systems may underlie individual differences in the intensity of alcohol craving and the risk of becoming alcohol dependent.

The Alcohol Withdrawal Syndrome
Long-term alcohol consumption affects brain receptors, which undergo adaptive change in an attempt to maintain normal function. Some key changes involve decrease in both brain gamma-amino butyric acid (GABA) levels and GABA-receptor sensitivity and activation of glutamate systems, which leads to nervous system hyperactivity in the absence of alcohol. Alcohol potentiates GABA’s inhibitory effects on efferent neurons, thereby suppressing neuronal activity. With chronic alcohol exposure, GABA receptors become less responsive and higher alcohol concentrations are required to achieve the same level of suppression, which is termed ‘tolerance’. Alcohol also acts on N-methyl-D-aspartate (NMDA) receptor as an antagonist, thereby decreasing the CNS excitatory tone. Therefore, chronic use of alcohol leads to an up regulation of glutamate to maintain CNS homeostasis. Even when alcohol is no longer present in this adapted system, the GABA receptors remain less responsive; leading to an imbalance in favour of excitatory neurotransmission as the CNS excitation mediated by glutamate is left unopposed. This CNS excitation is clinically observed as symptoms of alcohol withdrawal in the form of autonomic over activity such as tachycardia, tremors, sweating and neuropsychiatric complications such as delirium and seizures.

Dopamine is another neurotransmitter that is involved in alcohol withdrawal states. During alcohol use and the increase in the dopamine levels in CNS contribute to the autonomic hyper arousal and hallucinations. Withdrawal seizures are also thought to result from a lowering of seizure threshold due to kindling.

Symptoms of Alcohol withdrawal reaction
Within 6 to 12 hours of cessation of alcohol minor withdrawal symptoms are seen like insomnia, tremors, anxiety, gastrointestinal upset, headache, diaphoresis, palpitations, anorexia, nausea, tachycardia, hypertension. Within 12 to 24 hours visual, auditory, or tactile hallucinations are seen. Within 24 to 48 hours generalized tonic-clonic seizures are seen. And at 48 to 72 hours Alcohol withdrawal delirium i.e. delirium tremens is seen characterized by hallucinations (Predominately visual), disorientation, agitation, diaphoresis.

TREATMENT OF ACUTE ALCOHOL WITHDRAWAL SYNDROME
Detoxification
Detoxification is the process of weaning a person from a psychoactive substance in a safe and effective manner by gradually tapering the dependence producing substance or by substituting it with a cross-tolerant pharmacological agent and tapering it. This process minimizes the withdrawal symptoms, prevents complications and hastens the process of abstinence from the substance in a more humane way.

General Supportive Care
Patients in alcohol withdrawal should preferably be treated in a quiet room with low lighting and minimal stimulation. All patients with seizures or DT should have immediate intravenous access for administration of drugs and fluids. Intramuscular lorazepam may be given to calm the patient as early as possible and physical restraints may be used as required in order to prevent injuries due to agitation. Fluid and electrolyte imbalances must be promptly corrected. Adequate nutrition must be ensured with care to prevent aspiration in over-sedated patients. Vitamin B supplementation helps to prevent Wernicke’s encephalopathy (WE).

Drugs Used for Detoxification
Benzodiazepines
Benzodiazepines are a class of psychoactive drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring. Benzodiazepines (BDZs) bind to the gamma sub-unit of the GABA-A receptor. Their binding causes an allosteric (Structural) modification of the receptor that results in an increase in GABA A receptor activity. BDZs do not substitute for GABA, which bind at the alpha sub-unit, but increase the frequency of channel opening events which leads to an increase in chloride ion conductance and inhibition of the action potential, resulting in sedative, hypnotic, anxiolytic (Anti-anxiety), anticonvulsant, and muscle relaxant properties. These properties make benzodiazepines useful in treating alcohol withdrawal. Dopamine is another neurotransmitter involved in alcohol withdrawal states.

During alcohol use and withdrawal, the increase in CNS dopamine levels contribute to the clinical manifestations of autonomic hyper arousal and hallucinations. Repeated episodes of withdrawal and neuroexcitation results in a lowered seizure threshold as a result of kindling predisposing to withdrawal seizures. In 1969, a landmark study by Kaimet al., proved beyond doubt that Chlordiazepoxide (A
benzodiazepine) was far better in preventing seizures and DT in patients with alcohol withdrawal compared to chlorpromazine, hydroxyzine, thiamine or placebo. Evidence is strongly in favour of the use of benzodiazepines to treat alcohol withdrawal states. The dose of benzodiazepine required per day is calculated according to the average daily alcohol intake. An estimate of the amount of alcohol consumption is given by the following formula.

\[
\text{Alcohol (in g)} = \text{Volume of liquor (ml)} \times 0.008 \times (\%) \text{ ethanol content in the liquor (w/v)}. \]

**Fixed Dose Regimen**

A daily divided daily dose of benzodiazepines is administered in four divided doses. The daily dose is calculated by using the aforementioned formula. Approximately 5 mg of diazepam equivalents is prescribed for every standard drink consumed. However, it needs to be based upon the severity of withdrawals and time since last drink. For example, a person presenting after 5 days of abstinence, whose peak of withdrawal symptoms has passed, may need a lower dose of benzodiazepines than a patient who has come on the second day of his withdrawal syndrome. Chlordiazepoxide and diazepam remain the agents of choice. However, in the presence of co-morbidities shorter acting drugs such as oxazepam and lorazepam are used. A ceiling dose of 60 mg of diazepam or 125 mg of Chlordiazepoxide is advised per day.

**Symptom-Triggered Treatment (STT)**

The STT was proposed by Saitz et al. in 1994 where in Chlordiazepoxide was given when CIWA-Ar ratings were eight or more. The STT requires dose monitoring as inpatient. Patients who are non-verbal (e.g., stupor due to head injury) may not be suited for this regimen as they may not be able to inform the nursing personnel if they were to experience any withdrawal symptoms. This protocol is not safe in patients with a past history of withdrawal seizures because they can occur even in a patient without overt autonomic arousal or symptoms of alcohol withdrawal. STT decreases the duration of detoxification and dose of benzodiazepine required compared with fixed dose regimen and may be useful in patients who have never had complicated withdrawals.

**Symptom-Monitored Loading Dose (SML)**

We recommend that clinicians take into account the past history of seizures or DT as well as the current clinical status while deciding upon medications for a patient. In the presence of an acute medical illness at present or a past history of severe withdrawals, a single loading dose of 20 mg diazepam should preferably be given immediately and the patient be monitored for further signs of alcohol withdrawal. Further doses of diazepam (20 mg) should be given orally every 2 h until CIWA-Ar scores are less than ten. Up to three doses are required in most patients, which helps in reliably preventing the occurrence of withdrawal seizures. This strategy, which could aptly be called SML combines the principles and advantages of a STT, whereas at the same time takes into account a past history of severe withdrawals and gives a loading dose regardless of the appearance of symptoms.

**Anticonvulsant Drugs**

BZD’s are the drugs of choice for AWS in most of the treatment settings; however, anti-convulsant drugs may represent suitable alternatives. There are several potential advantages to using anti-convulsant drugs. Use of an anti-convulsant drug decreases the probability of a patient experiencing a withdrawal seizure, thereby reducing the complications. Anti-convulsant drugs also reduce craving. Anti-convulsant drugs have been shown to block kindling in brain cells. Anti-convulsant drugs do not appear to have abuse potential. Anti-convulsant drugs have been effectively used to treat mood disorders, which share some symptoms with AWS, including depression, irritability, and anxiety. The propensity of anti-convulsant drugs to cause sedation is much less as compared to BZD’s.

Carbamazepine was found superior to benzodiazepines in prevention of rebound withdrawal symptoms and reducing post-treatment alcohol consumption, especially in patients who had multiple repeated withdrawals. Carbamazepine use, however, has been limited due to its interaction with multiple medications that undergo hepatic oxidative metabolism, making it less useful in older patients and patients with medical co-morbidities. Gabapentin, which has structural similarity to GABA, is shown to be effective in the treatment of alcohol withdrawal. Its low toxicity makes it a promising agent. Gabapentin was as effective as lorazepam in a randomized, double blind controlled study on 46 in-patients with alcohol withdrawal in the treatment of acute mild to moderate AWS.

**Adrenergic Medications**

Adrenergic medicines (centrally acting alpha-2 agonists like clonidine; and antagonist like propranolol), which alter the function of adrenergic receptors, are thought to significantly improve symptoms of AWS, especially autonomic symptoms, by reducing elevated pulse and blood pressure. There is no evidence that these medications prevent or treat delirium or seizures. Adrenergic medications are of value largely as adjuncts to BZD’s in the management of AWS. These medications also may be useful in outpatient settings, where the abuse liability of BZD’s by patients is difficult to monitor or prevent and where AWS symptoms are generally less severe than among inpatient populations.

**Baclofen**

The advances in knowledge of neurobiology and neurochemistry have prompted the use of drugs in the treatment of alcohol withdrawal that act through "GABA pathways", such as the Baclofen, which are GABA-B agonist. In a preliminary RCT by the first author in 2002, Baclofen also reduced craving in alcohol-dependent patients. A study found that the efficacy of Baclofen in treatment of uncomplicated alcohol withdrawal was comparable to that of the “gold standard” diazepam, with significantly decreased CIWA-Ar scores.

**Other Drugs used in Alcohol Dependence**

**Naltrexone**

The reinforcing effects of alcohol associated with its abuse liability are mediated by dopaminergic pathways that originate in the ventral tegmental area, rely to the nucleus
acumbens with neuronal inputs from other limbic regions, and progress to the cortex. Naltrexone, a mu-opioid receptor antagonist, decreases alcohol reinforcement via two mechanisms: (1) suppression of alcohol-mediated beta-endorphin stimulation of dopamine neurons directly in the nucleus accumbens, and (2) reduction of beta-endorphin disinhibition of the tonic inhibition of dopamine cells by gamma-aminobutyric acid neurons in the ventral tegmental area. Oral naltrexone, FDA-approved for alcohol dependence in 1994, and extended-release injectable naltrexone, approved in 2006, block opioid receptors, inhibiting rewarding effects of alcohol and reducing craving. By far, naltrexone is the most researched medical treatment for alcohol dependence. Naltrexone is known to reduce craving for alcohol in both alcohol dependent patients and social drinkers.

There are also a number of reviews and meta-analyses that support naltrexone as a treatment for alcohol dependence, along with 29 published randomized placebo controlled trials, some supportive and some not. Two pivotal early trials were the first to illustrate the efficacy of naltrexone in the management of alcohol dependence. A recent review has reported modest favorable effects of naltrexone on heavy drinkers. In a majority of the studies reviewed, Naltrexone reduces significantly the rates of drinking in heavy drinkers by 30-60%. It reduces craving significantly though abstinence is seen usually in 25-35% cases. Another meta-analysis, a Cochrane collaborative, found a decrease in the rate of relapse in alcohol dependence in case of short-term studies (<12 weeks), but the effect on increasing abstinence was small. Medium term trials (>12 weeks) are too limited in number (Eight studies) to show benefits for relapse prevention but do show increased time to the consumption of the first drink and decreased craving over time. The dosage used in most studies is 50-100 mg per day.

More often than not, naltrexone was used in combination with cognitive behavioral therapy, supportive individual or group psychotherapy and relapse prevention therapy. Naltrexone alone has been shown to reduce heavy drinking rates in a smoking cessation program. While it has also been shown to improve the cost effectiveness of cognitive behavioral therapy in alcohol dependence. Naltrexone also has a favorable safety profile. It does not reduce seizure threshold nor have any fatalities been reported with naltrexone overdose. It has not been associated with pleasurable effects, does not result in tolerance and has no abuse potential. The frequency of side effects with naltrexone is low, with nausea and vomiting being the most commonly reported, followed by headache, low energy, decreased alertness, depression and anxiety. These side effects resolve in one to two days after starting naltrexone, or after a few doses, or on reducing the daily dosage. Though naltrexone carries a black box warning of possible hepatotoxicity, there are no reports of hepatotoxicity with the recommended daily dosages. In fact, liver enzymes which are raised often reduce with naltrexone due to decreased alcohol consumption.

From the clinical perspective, it is essential to note that though naltrexone has been used widely in the management of alcohol dependence there are always potential barriers to naltrexone response. Among these, the most common are medication non-adherence and heterogeneity of the alcohol dependent patient population. There are also probably different endophenotypes of alcoholism whereby some patients would respond differentially to naltrexone. We are already aware of naltrexone responders associated with response to alcohol in the laboratory, family history of alcoholism and genotypes.

A long acting extended release injectable formulation of Naltrexone (Encapsulated naltrexone 380 mg in biodegradable microspheres) was approved by the European FDA in 1996 for the treatment of alcohol dependence. The preparation was shown to maintain therapeutic levels for a month after injection. It also had reduced side effects and less chance of hepatic toxicity as it eliminated first pass metabolism in the liver. Most studies with the preparation in keeping with oral naltrexone find reduction in the time to relapse in alcohol dependent patients.

**Acamprosate**

Relapse prevention is a major challenge in the treatment of alcoholism. About 50% of detoxified alcoholics relapse within 3 month. The observation that craving for alcohol and compulsion to drink are frequent causes of early relapse has led to the search for pharmacological treatments to reduce craving and to modulate alcohol-oriented behaviour in post-detoxification programmes. Acamprosate (Calcium acetylhomotaurinate) is an analogue of amino acid neurotransmitters such as taurine and homocysteic acid and is reported to exert anti-excitatory amino acid properties. Most placebo-controlled clinical trials with acamprosate in detoxified alcoholics demonstrated statistically significant decreases in relapse in patients treated with acamprosate. In three short-term studies (3 months) without follow-up, the number of relapses at the end of treatment was statistically significantly lower in patients treated with acamprosate.

Acamprosate, in combination with psychosocial support, was approved by the Food and Drug Administration (FDA) in July 2004 for the maintenance of abstinence from alcohol in detoxified alcohol-dependent patients. To date, its efficacy has been reported in 23 double-blind, placebo-controlled clinical trials conducted in 15 different countries. A recent survey found that acamprosate is now the most widely prescribed therapeutic agent for the treatment of alcoholism in the United States of America. Acamprosate, calcium acetylhomotaurinate, is a synthetic compound with a chemical structure similar to the amino acid neurotransmitter gamma-aminobutyric acid (GABA) and the amino acid neuromodulator taurine. Acamprosate has been shown to reduce ethanol consumption in rodents that have an extended history of ethanol exposure or are ethanol-dependent. Acamprosate has been shown to reduce the increased ethanol consumption associated with a period of enforced abstinence from ethanol (the alcohol deprivation effect) in rats. In addition to the direct effects on ethanol consumption, acamprosate has been reported to attenuate some of the behavioural and neurochemical events associated with ethanol withdrawal.

**Disulfiram**

Disulfiram, FDA-approved to treat alcohol dependence in 1951, interferes with the metabolism of alcohol, by inhibiting...
aldehyde dehydrogenase, and produces flushing, nausea, palpitations, and other severe reactions if drinking occurs. A Disulfiram has been used in the treatment of alcohol dependence with consistently successful results in individuals with high compliance or when medication intake has been directly supervised. Its mechanism of action for maintaining alcohol abstinence is thought to be primarily psychological, and based on a highly disagreeable pharmacological effect if alcohol is consumed. Disulfiram blocks the enzyme aldehyde dehydrogenase (ALDH).

If alcohol is present, acetaldehyde accumulates usually resulting in an unpleasant reaction, the disulfiram-ethanol reaction (DER), consisting primarily of tachycardia, flushing, nausea, and vomiting. To prevent the first drink, however, the psychological or cognitive threat is thought to be dominant and active and thus dissuade use. The threat of a DER, indeed the expectancy of negative consequences if alcohol were to be absorbed and ensuing thoughts about avoiding pain and sickness account for the drug’s effectiveness. On the other hand, different pharmacodynamic rather than psychological mechanisms of action have been proposed to explain the success of disulfiram in cocaine addiction, and in one case report of pathological gambling. Several studies have proposed that cocaine use is reduced in subjects taking disulfiram because disulfiram inhibits dopamine beta-hydroxylase (DBH) and the consequent reduction of synaptic norepinephrine release alters the “high”. Despite its apparent success with compliant or supervised alcohol dependent patients, efficacy studies of disulfiram have been all but concordant, leading to confusion and debates that are largely based on poorly designed studies.

Disulfiram is available as 250mg tablets with the recommended dosage being 250-500mg per day. Disulfiram is often not recommended as the first line medication for newly diagnosed alcohol dependent patients but is reserved for treating patients who have previously failed one or more courses of treatment or those who are motivated to achieve complete abstinence. With the advent and emergence of Naltrexone and Acamprosate, there has been a decline in Disulfiram use with it slipping to a second line treatment in many centers for the treatment of alcohol dependence. Safety concerns may also be the reason for this as many alcoholic patients try to consume alcohol even when on Disulfiram and hence may cause themselves unnecessary harm. Several reviews support the efficacy of supervised use of Disulfiram in the management of alcohol dependence. This background alone ought to make everyone in the world of alcoholism treatment aware of disulfiram’s potential especially for the large and often demoralizing number of patients that do not respond to other treatments.

There is no doubt that supervised disulfiram therapy is an integral component of any alcohol treatment program. There are also a large number of limitations with respect to disulfiram research. In a review of studies published between 1948 and 1971 it was seen that among 42 studies only one had an adequate research design. The limitations still hold, with no randomized double blind trials being ever conducted on Disulfiram in this reviewer’s knowledge. Lack of double blinded controlled and randomized clinical trials with disulfiram is another hindrance. The reason for this is that awareness that the patient is on disulfiram is an essential for the action of disulfiram in order to enhance its efficacy and hence most studies are open ones. It has been noted that disulfiram is most effective when supervised and used in alcoholism with the help of a close family member.

Disulfiram is an old drug, long out of patent protection. It is thus cheap and marketed by manufacturers of the generic drug who do little advertising and research. There is also a ready availability of funding for naltrexone and acamprosate research which means that researchers with projects on these drugs are more likely to study acamprosate or naltrexone than disulfiram. Fears of disulfiram hepatotoxicity are often exaggerated. There is about one case in 25000 patient years. Death from disulfiram is also very rare. Disulfiram can be readily prescribed with Acamprosate and Naltrexone and is shown to improve the efficacy of Acamprosate. There have been cases where disulfiram has been continued safely for over 15 years. A long acting depot preparation of Disulfiram in the form of a Disulfiram implant is also available. It was introduced in the 1950s and is still used in some parts of the world.

Topiramate

Topiramate is a sulfamate-substituted analog of fructose-1,6-diphosphate. Topiramate is identified chemically as 2,3;4,5-Di-O-isopropylidene-beta-D-fructopyranose sulfamate and has structural similarity to acetazolamide, which has anticonvulsant effects. Topiramate is a potent anti-epileptic with strong neuroprotective properties. It is postulated to be effective in the management of alcohol dependence as it reduces dopamine release after alcohol consumption due to its ability to enhance GABA mediated inhibition through non-benzodiazepine receptors. The Food and Drug Administration (FDA) in the U.S. has approved topiramate for the adjunctive treatment of epilepsy, including partial-onset seizures, primary generalized tonic-clonic seizures, and Lennox-Gastaut syndrome. The FDA also has approved topiramate for the treatment of migraine.

Topiramate is being investigated as a potential treatment for a variety of other disorders, including: metabolic disorders such as diabetes mellitus and obesity; anxiety-related disorders such as post-traumatic stress disorder; and impulse dyscontrol-related disorders such as binge eating, pathological gambling, and substance abuse disorders. Johnson proposed a neuropharmacological model by which topiramate can decrease alcohol reinforcement and the propensity to drink. This model laid out a hypothesis by which topiramate would be expected to suppress both acute and chronic ethanol consumption. Notably, this model was developed prior to any focused animal experiments or clinical studies in alcohol- or drug-dependent individuals. Therefore, the clinical work that was done subsequent to this hypothesis represents a leap from a concept to a proof-of-concept demonstration of topiramate’s efficacy.

Serotonergic Agents and Ondansetron (5-HT3Antagonist)

During the last two decades, a number of drugs acting on serotonergic neurotransmission have been studied in alcohol dependence, since serotonin is widely implicated in a variety of consummatory behaviors and impulsivity. These agents are either selective serotonin reuptake inhibitors or receptor agonist/antagonists. Most of this work, however, has used...
small samples with relatively short treatment periods. Selective serotonin reuptake inhibitors, despite their effectiveness in animals, have shown inconsistent or disappointing results in humans and so the usefulness is still controversial. Meanwhile, no evidence of clinical efficacy in alcohol-dependent has been obtained with ritanserin (5-HT₂ antagonists). In addition, a meta-analysis of studies performed with bupropion (5-HT₃ partial agonist) concluded that any efficacy of bupropion was secondary to an anxiolytic effect, rather than on drinking per se. Of the numerous serotonergic drugs which have been suggested as pharmacotherapies for alcohol dependence treatment, ondansetron, a 5-HT₃ antagonist that is FDA-approved as an antiemetic, appears to be the most promising.

The 5-HT₃ receptor is involved in the expression of alcohol’s rewarding effects. Behavioral pharmacological studies show that many of the reward effects of alcohol are mediated by interactions between DA and the 5-HT₃ receptor in the mid-brain and cortex. 5-HT₃ receptors are densely distributed in the terminals of mesocorticolimbic DA-containing neurons where they regulate DA release in these brain regions. Following a previous clinical trial, Johnson et al. evaluated ondansetron as a treatment for alcohol dependence in a 12-week, double-blind, placebo-controlled trial of 321 patients. The early-onset, alcohol dependent group treated with ondansetron (Particularly 4 µg/kg b.i.d.) reported fewer drinks per day and fewer drinks per drinking days, while the late-onset group treated with ondansetron did not differ from those treated with placebo. It is interesting that while serotonin reuptake inhibitors have little effect on drinking among early-onset alcoholics, ondansetron, with functionally opposite effects in the serotonergic system, is effective for the early-onset subtype. Sufficient evidence exists that early-onset alcoholics are more prone to serotonergic dysfunction than late-onset alcoholics.

**Combined Naltrexone and Acamprosate Therapy**

Some authors have suggested a clinical rationale for combining Naltrexone and Acamprosate therapy in the management of alcohol dependence as they act on different neurotransmitter systems. Clinical trials have proved that the above combination is better than acamprosate alone, though not better than naltrexone alone, especially in terms of first relapse. These were also the first studies to suggest that combined therapy is better than monotherapy in the treatment of alcohol dependence. More recent researches may be underway but have not been published at this point of time in the author’s knowledge.

**Vitamin B and Magnesium**

Wernicke's Encephalopathy (WE) results from cell damage due to chronic thiamine deficiency. It rarely presents with the classic triad of confusion, ataxia and ophthalmoplegia and therefore goes undiagnosed in nearly 90% of the cases. It is difficult to diagnose in the presence of alcohol withdrawal symptoms. The presence of small mammillary bodies and thalami on magnetic resonance imaging brain may be helpful in diagnosis, but confirmation is by postmortem examination. WE has an associated mortality of 20%, with 75% developing a permanent severe amnestic syndrome (Korsakoff’s encephalopathy). This can be prevented by administering parenteral thiamine which achieves adequate blood thiamine level much earlier than the oral route. Allergic reactions are rare. All patients in alcohol withdrawal should receive at least 250 mg thiamine by the parenteral route once a day for the first 3-5 days, whereas for those with suspected WE, thiamine 500 mg/day for 3-5 days is advised.

If there is clinical improvement the supplementation is continued for total of 2 weeks. Concurrent administration of parenteral thiamine with glucose is advised traditionally. However, this is only to ensure that thiamine supplementation is not forgotten. Administration of glucose containing fluids before thiamine may not precipitate WE. Due to chronic malnutrition and gastric malabsorption that follows chronic alcohol abuse, many clinicians advise multivitamin supplements (B1 + B2 + B6 + nicotinamide + Vitamin C) in parenteral form for the initial 3-5 days. Chronic alcohol use is associated with abnormal magnesium metabolism. Those with neuropathy and presenting with severe withdrawal symptoms are more likely to show low serum magnesium level. Oral or parenteral magnesium supplementation may benefit such patients by reducing the severity and duration of alcohol withdrawal.

**Brain-Derived Neurotrophic Factor**

Alcohol, in particular, is an agent of diverse neuronal damages, including an increase in apoptosis, a decrease in the proliferation of nerve cells, and impairment of neural networks. As for the major mechanism of alcohol-induced neurodegeneration, early research has highlighted that chronic alcohol consumption causes excitotoxicity, thus activating glutamatergic transmission and ultimately resulting in neuronal damage via intracellular signal pathways. Neuronal damage has been shown to inhibit neurogenesis and to decrease dendritic networks of Purkinje neurons in the brain. Moreover, alcohol-induced modification of the cranial neural structure has been observed in quite a few parts of the brain (e.g., the corticolumbic area, hippocampus, and the entorhinal cortex).

Importantly, since the hippocampus is involved in memory or cognitive functioning in the brain, long-term alcohol consumption could damage the hippocampus, causing cognitive impairment. As polypeptide compounds, neurotrophins are mostly distributed in the nervous system, and are involved in neuronal activation, differentiation, and survival in the brain. As a representative neurotrophin, brain-derived neurotrophic factor (BDNF) is known to be involved in neuronal growth, differentiation, synaptic connection, modification, and survival. Activation of the GDNF pathway in the ventral tegmental area (VTA) has recently been highlighted as a promising approach to treat addiction to drugs of abuse, including alcohol.

**CONCLUSION**

Alcohol dependence is a heterogeneous chronic, relapsing brain disorder. All practitioners should be familiar with its early detection. Alcohol dependence is treatable, and the use of efficacious pharmacotherapies has opened up the potential of office-based treatment by non-specialists. Appropriate pharmacotherapy, along with a brief psychosocial intervention, constitutes optimal treatment. Choice of therapy can be guided by the patient’s history of alcoholism and the stage of life and, in the future, perhaps by
pharmacogenetics. Benzodiazepines are the mainstay of management of alcohol withdrawal states. Symptom-triggered treatment regimen reduces dose and duration of detoxification compared with traditional fixed dose regimen in mild to moderate alcohol withdrawal. For management of severe withdrawals, inpatient care and Symptom-monitored loading dose is advised. Thiamine supplementation should be routinely prescribed to prevent WE. Other drugs used in alcohol dependence like Naltrexone, Acamprosate, Disulfiram, Topiramate act by different mechanisms and have very promising role to play.

REFERENCES


37. Brewer C. Supervised disulfiram is more effective in alcoholism than naltrexone or acamprosate or even psychotherapy: how it works and why it matters. Addiction 2005;10(4):222-33.


40. Johnson BA. Recent advances in the development of treatments for alcohol and cocaine dependence: focus on topiramate and other modulators of GABA or glutamate function. CNS Drugs 2005;19(10):873-96.


