Long Term Pharmacotherapy for Alcohol Use Disorder

Dr. Indranil Saha¹, Dr. Supartha Barua², Dr. Arijit Mondal³

¹Associate Professor, ²Assistant Professor, ³Senior Resident, Institute of Psychiatry – A Centre of Excellence, IPGMER & SSKM Hospital, Kolkata.

Corresponding Author : Dr. Arijit Mondal, Senior Resident, Institute of Psychiatry, 7 D L Khan Road, Kolkata – 700 025. Mobile : +91 8820255962. Email : drarijitmondal2010@gmail.com

Abstract : The psychopharmacology of alcohol dependence is today poised at interesting crossroads. Three major drugs Naltrexone, Disulfiram and Acamprosate have been tried and tested in various trials and have many meta-analyses each to support them. While Naltrexone may reduce craving, Acamprosate scores on cost effectiveness worldwide with Disulfiram being an alcohol deterrent drug. Studies support, refute and criticize the use of each of these drugs. Combining one or more of them is also a trend seen. The most important factor in efficacy has been the combination of psychosocial treatment with medication. In this article, we are going to discuss about long term pharmacological management of chronic alcoholism.

Introduction :

Substance use disorder is a serious public health issue globally with its detrimental impact not only on personal, family and social spheres, but also has economic and medical consequences. Substance use disorder is chronic disorder with relapsing and remitting course like other chronic illnesses. Behavior therapy is well accepted intervention globally for relapse prevention. Currently, pharmacological approach is considered central to intervention for relapse prevention. Here, we will discuss about the long term pharmacological management for chronic alcoholism.

Addiction is characterised by (1) compulsion to seek and take a given drug (2) loss of control of limiting the intake (3) emergence of a negative emotional state (dysphoria, anxiety, irritability) when the drug is unavailable or access to it is prevented. Drug addiction has aspects of both impulse control and compulsive disorders. Impulse control disorders are characterized by three factors : (1) an increasing sense of tension or arousal before committing an impulsive act (2) pleasure, gratification or relief at the time of committing the act (3) regret, self reproach or guilt following the act. In contrast compulsive disorders are characterized by two factors : (1) anxiety and stress before committing a compulsive repetitive behaviour (2) relief from the stress by performing the compulsive behaviour. Drug addiction can be conceptualized as a disorder that progress from impulsivity to compulsivity in a cycle that comprises of three stages : (a) preoccupation / anticipation (b) binge / intoxication and (c) withdrawal / negative affect¹.

The word 'craving' commonly means 'a strong desire or intense longing' and refers to intense desires for something. A 'craving' can be a strong, sudden, situation- specific, sometimes unexpected and culturally inappropriate, urge specifically to engage in the drug-taking behavior. Craving for substance is generally thought to arise either from the desire to experience substance's positive effects or from the desire to avoid the negative effects of withholding substance, such as withdrawal symptoms. Incorporating craving measurements into routine clinical practice can produce several potential benefits. Its assessment can increase the patient's capacity to recognize and monitor his internal states that are related to drinking and this can be used in recommending appropriate treatment and in decisions regarding treatment intensity and duration².
The Neurobiology of Alcohol Dependence:

Alcohol acts by enhancing membrane fluidity, changing the function of macro-molecules in the cell membrane. Recent evidence, however, indicates that alcohol binds to hydrophobic proteins, modulating their function by altering 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.

Mesolimbic dopamine pathway are activated by alcohol, resulting in 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 behavioral 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.

The facilitation of inhibitory GABAergic and the inhibition of excitatory glutamatergic neurotransmission are important targets for the acute effects of alcohol. Potentiation of GABAergic inhibition is widely accepted as the underlying cause of the acute sedative effects of alcohol. Long-term adaptive changes to the sedative effects of alcohol in these two neurotransmitter systems are thought to underlie the development of alcohol dependence. After chronic exposure to alcohol, there is a compensatory up-regulation of the glutamatergic system (and down-regulation of the GABA system) in an attempt to balance alcohol's inhibitory action. The result is an increased tolerance for alcohol. When alcohol is abruptly withdrawn, however, a state of hyper-excitability emerges. This is perceived by the patient as a disagreeable state of arousal, anxiety and sleeplessness and is the core of the negative affective state which the alcoholic patient will drink to relieve. These plastic changes in the brain, brought about by change in protein synthesis, are only slowly reversible. This may explain the persistence of negative craving during alcohol withdrawal and why stable abstinence after acute detoxification is so difficult to achieve. Antiglutamamatergic agents, such as NMDA antagonists and anticonvulsant agents, have been proposed to reduce the motivation for drinking by suppressing symptoms of alcohol withdrawal. Recent data suggest that NMDA antagonists may have other beneficial effects in alcohol dependent patients, such as substituting for deficits in negative feedback signals or reducing the development of tolerance/sensitization to alcohol.

Etiological Subtypes of Alcoholism:

Another approach to understanding the etiology of alcoholism is to identify distinct subtypes of alcoholics. These include unidimensional approaches based on drinking history, drinking pattern, severity of alcohol dependence, family history of alcoholism, gender, personality style, comorbid psychopathology, cognitive impairment, and sociopathy, as well as multidimensional approaches that combine these characteristics into meaningful clusters. The best known of these typologies is the Type1/Type2 distinction developed by Cloninger and colleagues (1981) from studies of adopted sons of Swedish alcoholics.
Cloninger classification of ADS – Type I and Type II

| Type          | Description                                                                 |
|---------------|-----------------------------------------------------------------------------|
| Type I        | Also called milieu limited, affect both sexes, no family history, age of onset < 25 years, environmental causation, may or may not have personality disorder, social drinking pattern, and favourable prognosis. |
| Type II       | Also called male limited, usually affects male, positive family history, age of onset > 25 years, genetic causation, dissocial personality common, solitary drinking pattern and poor prognosis. |

There are currently three US FDA approved medications for the relapse prevention of alcohol dependence. These are Disulfiram (1951), Naltrexone (oral in 1994 and long acting depot injection in 2006) and Acamprosate (2004).

**Aversive Agent : Disulfiram**

The first agent to be approved for treatment of alcohol dependence was disulfiram. This substance was serendipitously discovered to be an agent causing alcohol aversion in Ohio rubber workers in 1939.\(^{11}\)

**Mechanism of Action :** The major metabolic pathway for alcohol metabolism is a two-step enzymatic process (ethanol \(\rightarrow\) acetaldehyde \(\rightarrow\) acetic acid). Disulfiram is an irreversible inhibitor that blocks the second stage of alcohol metabolism, causing an accumulation of toxic intermediate acetaldehyde, which results in hypotension, flushing, nausea, and vomiting. The objective of disulfiram treatment is thus to create an aversion to alcohol, rather than to modulate its neurochemical effects.\(^{11}\)

**Evidence base :** The largest disulfiram treatment study\(^1^{2}\), a cohort of 605 males with alcoholism – 202 participants received disulfiram 250 mg daily, 204 participants were administered disulfiram 1 mg QD, 200 participants were prescribed riboflavin. After one year of treatment, there was no difference in the percentage of patients from the three groups in total abstinence, time to first drink, employment, or social stability.

The first systematic meta-analysis\(^1^{3}\), which included 11 RCTs with a total 1527 patients from India, Denmark, USA, Austria, Finland and Italy, concluded that disulfiram had some short term clinical benefits including short term abstinence, number of drinking days, and days until relapse.

The evidence for disulfiram is weaker than for acamprosate and naltrexone. NICE recommends its use ‘as a second-line option for moderate-to-severe alcohol dependence for patients who are not suitable for acamprosate or naltrexone or have a specified preference for disulfiram and who aim to stay abstinent from alcohol’.\(^{14}\)
disease or coronary occlusion, psychoses, and hypersensitivity to disulfiram (c) inability to understand implications of therapy [The patient must be fully informed of the disulfiram-alcohol reaction] (d) pregnancy (1st trimester) is only absolute contraindication. 

**Where it will work ? :**

1. motivated client
2. commitment to abstinence
3. supervised dose
4. external factor as the reason for relapse
5. no positive expectation from alcohol. 

**Pre disulfiram checklist :**

(i) informed consent
(ii) last alcohol intake > 2 weeks before
(iii) near normal liver profile
(iv) absence of neuropathy, psychosis
(v) BP monitoring

**Anticraving Agent : Naltrexone**

**Mechanism of Action :** Naltrexone, a potent opioid-receptor antagonist, blocks the effects of endogenous opioids, which increase after alcohol consumption. It is believed that naltrexone works through its blockage of mu-opioid receptors, which reduces the reinforcing effects of alcohol leading to decreased feelings of intoxication and fewer cravings. It is approved for use in the treatment of alcohol dependence in conjunction with psychosocial interventions. 

Naltrexone appears to break the vicious, self-destructive cycle in alcoholics whereby one drink leads to another. It decreases alcohol craving, rate of relapse, and length of drinking episodes. 

**Evidence Base :** The USA FDA's approval of naltrexone for the treatment of alcohol dependence was based mainly on two small, double-blind, placebo-controlled trials demonstrating a reduced rate of relapse to heavy drinking, reduced craving, and less frequent drinking in naltrexone-treated patients. During the following years, several more trials have followed and three meta-analyses have concluded that naltrexone is efficacious in the treatment of alcohol dependence. To summarise, naltrexone appears to produce a modest effect on drinking behavior among alcoholics. It can be administered to those who are actively drinking, so that their consumption can be decreased.

**Side-Effects :** Nausea , headache , anxiety , sedation , insensitivity to opioid analgesia, hepatotoxicity (LFT should be monitored)

**Drug interaction :** Naltrexone blocks the action of opioid analgesics, which can be problematic in clinical practice for those patients who are receiving opioids concurrently. Hence, Naltrexone should be avoided in patients receiving long-term opioid therapy for chronic pain or heroin dependence.

**Contraindications :** Contraindicated in patients with hepatitis or liver failure, and all patients should have hepatic transaminase levels checked monthly for the first three months and every three months thereafter.
Where it will work?

(1) early onset alcohol dependence syndrome
(2) excessive craving
(3) family history of addiction
(4) impulsivity
(5) wants to be a social drinker

Naltrexone Checklist: (a) Liver function test (b) no opioid use (c) any pain syndrome (d) h/o depression or anxiety disorder

Acamprosate

Mechanism of Action: Acamprosate (calcium acetylhomotaurinate) is a simple derivative of the essential taurine amino acid and displays a structural resemblance to gamma-amino butyric acid (GABA). Acamprosate enhances the GABAergic neurotransmitter system, which is reduced in persons with chronic exposure to alcohol, and interferes with glutamate action in different pathways, such as the N-methyl-D-aspartate (NMDA) receptors. Acamprosate also acts on the calcium channels and reduces central nervous system hyperexcitability caused by cessation of alcohol intake. Acamprosate is thought to work by decreasing craving related to conditioned withdrawal.

Evidence Base: The US FDA approval of acamprosate was based on three trials that showed acamprosate’s efficacy in reducing relapse and maintaining abstinence in patients with alcohol dependence. A number of reviews and meta-analyses have demonstrated moderate efficacy of acamprosate in the management of patients with alcohol dependence. The clinical efficacy of acamprosate was evaluated in a systematic review of published clinical trials up to 1997 with a consistent finding being 30-50% increase in non drinking days. A relatively recent meta analysis of 22 studies also reported the same effect. In summary, there is good evidence to support increased abstinence and decreased drinking days with acamprosate compared to placebo in the treatment of alcohol-dependent patients. The strongest effect of acamprosate is seen in recently detoxified alcohol dependents with very good data supporting its efficacy in long term studies.

Pharmacokinetics: Only 10% of acamprosate is absorbed, of which 90% is excreted unchanged into urine. Since it is not metabolized in the liver, it can also be used in patients of alcohol dependence with mild to moderate liver dysfunction.

Dose and administration: Acamprosate is available as 333 mg tablets. The recommended daily dose for adults weighing over 60 kg is six tablets (1998 mg) orally in three divided doses (i.e. 2 t.d.s.), with meals. Adults weighing less than 60 kg should take four tablets (1332mg) per day. Usual practice is to start at half these doses and increase by one tablet a week.

Special tests prior to induction: Kidney function tests (KFT) and Liver function tests (LFT).

Adverse effects: Acamprosate is well tolerated with limited side effects. Most commonly encountered side effect is transient diarrhea (occurring in approximately 10 percent of patients). Occasionally, headaches, dizziness and pruritus have been described. Rash or isolated pruritus, paraesthesiae, decreased libido and confusion have all been reported at low frequencies.
Where it will work?
(1) late onset alcohol dependence syndrome [ADS]
(2) protracted withdrawal
(3) ADS with significant hepatic damage
(4) multiple medical issues
(5) can be started along with detoxification
(6) can be taken along with alcohol

Comparison between Acamprosate and Naltrexone
Naltrexone and acamprosate are at the forefront of currently available pharmacological options and they share many important features. The important difference between naltrexone and acamprosate are mainly attributed to their mechanisms of action.

| Attribute                                      | Acamprosate | Naltrexone |
|------------------------------------------------|-------------|------------|
| Increases abstinence                           | Yes         | May be     |
| Decreases heavy drinking                      | May be      | Yes        |
| Long term efficacy (>1yr)                     | Yes         | No         |
| Compliance                                    | Good        | Variable   |
| Contingent on psychosocial intervention        | Independent | Variable   |
| Hepatic dysfunction                           | No          | Yes        |
| Use in opioid users including those on methadone | Suitable    | Unsuitable |
| Overall safety profile                        | Good        | Good       |

Topiramate:

Mechanism of Action: Topiramate is an anticonvulsant that inhibits dopamine release through antagonism of glutamate activity and facilitation of gamma-aminobutyric acid (GABA) transmitter in areas of the brain that may be associated with reward effects of alcohol. It inhibits mesocorticolicmbic dopamine release, which is believed to be associated with craving for alcohol.

Evidence-base: It is an anticonvulsant indicated as adjunctive drug for treatment of refractory seizures. Topiramate at the dose of 25-300 mg/day is the best-studied anticonvulsant for treatment of alcohol dependence. In a 12-week double-blind study of actively drinking patients with alcohol dependence, topiramate was found to be more effective than placebo in initiating abstinence and in reducing self-reported drinks per day, drinking day, and heavy drinking days. In an open label small study of 12 weeks duration, alcohol dependent subjects received topiramate upto 300mg/day. Study subjects reported improvement in self-reported drinking outcomes and craving.

Side Effects: (a) psychomotor slowing, memory problems, fatigue, confusion, and somnolence (b) paresthesias (c) weight loss (d) kidney stone and glaucoma – rare but serious
Special test prior to induction: Renal function test

Dose: initially 12.5 - 25 mg once or twice a day and the total daily dose is increased by 12.5 - 25 mg every week up to 150 mg BD

Where it will work?

1. Both early and late onset alcoholism
2. Cheaper anticraving agent
3. Comorbid seizure disorder/ migraine/ obesity
4. Binge pattern of drinking

Baclofen

Mechanism of Action: Baclofen a stereo selective gamma aminobutyric acid B receptor (GABA) agonist which is used in management of central muscle spasms for several decades. Baclofen has been found to inhibit the release of several neurotransmitters, including dopamine, noradrenaline, glutamate and serotonin.

Evidence Base: A recent systematic review of three prospective RCT concluded that compared with placebo, those who were on Baclofen had higher rates of abstinence and low anxiety scores.

Dosage: It is well tolerated and can be given to alcohol dependent patients with liver cirrhosis. Studies have used a 10 mg tds dose, but a 20 mg tds dose may have superior outcomes.

Where it works?

1. Significant liver dysfunction
2. Strong craving
3. High positive expectation from alcohol
4. Those who prefer harm reduction strategy

Selective Serotonin Reuptake Inhibitors (SSRI)

Data on the effects of serotonergic medications on alcoholism are limited. Studies which have used SSRIs in trials have been less consistent in non depressed patients. At present use of SSRIs could only be recommended only for those alcoholics for whom SSRIs are otherwise indicated (e.g. as antidepressants) and dose required is higher than antidepressant dose.

Ondansetron

Ondansetron, a selective 5-HT3-receptor antagonist, has been shown in one study to have a beneficial effect on early onset alcohol dependence, presumably by modulating dopamine release in mesocorticolimbic dopamine pathways. In a randomized control study, ondansetron 4 mcg per kg twice per day was shown to significantly reduce self-reported drinking, increase percentage of days of abstinence and increase total number of days abstinent per study week in patients with early onset alcoholism. However there is insufficient evidence to justify its routine use at present.
Combination Pharmacotherapy: Naltrexone plus Acamprosate

Combining naltrexone and acamprosate in the treatment of alcohol dependence is an attractive concept for several reasons. Since naltrexone and acamprosate have different mechanisms of action and different target neurotransmitter systems, presumably, they affect different aspects of alcohol use behavior. (Naltrexone decreases alcohol consumption and acamprosate stabilizes abstinence.) Pharmacokinetic and behavioral assessments of combining naltrexone and acamprosate have found the combination to be safe.\(^\text{11}\)

Combination of acamprosate or naltrexone with disulfiram: Some researchers have reported increased benefit of disulfiram when used either with acamprosate or naltrexone.

Composite combination of pharmacological and non-pharmacological intervention: One of the largest, multi-site clinical trial of pharmacologic and behavioral treatments for alcohol dependence (COMBINE trial)\(^\text{35}\), recruited recently abstinent alcohol dependent patients (n=1383) in outpatient setting to one of nine treatment groups. Eight groups of patients received medical management with 16 weeks of Naltrexone (100mg/day) or Acamprosate (3g/d), both, and/ or both placebos, with or without a Combined Behavioural Intervention (CBI). A ninth group received CBI only (no pills). Patients were also evaluated for up to 1 year after treatment. Two primary drinking outcome were percent days abstinent (PDA) and time to first heavy drinking day. All groups showed substantial reduction in drinking. Patients receiving medical management with naltrexone, CBI, or both fared better on drinking outcomes. Acamprosate showed no significant effect on drinking vs placebo, either by itself or with any combination of naltrexone, CBI, or both.

Special Population

Pregnancy and lactation: No conclusive evidence for relapse prevention medication.\(^\text{36}\) Psychological therapies which aim to maintain abstinence during pregnancy should be the first line of therapy. If they are not successful pharmacological therapies like disulfiram, Naltrexone, Acamprosate can be used. They should be used after completely explaining the pros and cons about the drugs, continuing pregnancy and effects on the foetal development.\(^\text{31}\)
**Children and Adolescents:** Most adolescents with alcohol use disorders also have one or more cooccurring psychiatric disorders, such as conduct disorder and/or major depression, ADHD, anxiety disorders, bipolar disorder, etc. The clinician who is treating them should assess for comorbidity and manage them accordingly. The evidence base for acamprosate, naltrexone and disulfiram in 16–19 year olds is evolving, but Naltrexone is best supported in this age group.

**Depression:** Relapse prevention medication should be considered in combination with antidepressants. Pettinati et al. have shown that the combination of sertraline (200 mg/day) with naltrexone (100 mg/day) had superior outcomes – improved drinking outcomes and better mood – than placebo and each drug alone.

**Bipolar Affective Disorder:** Bipolar patients tend to use alcohol to reduce symptoms of anxiety. Where there is comorbidity it is important to treat the different phases as recommended in guidelines for bipolar disorder. It may be worth adding sodium valproate to lithium as two trials have shown that the combination was associated with better drinking outcomes than with lithium alone. Lithium is best avoided completely in binge drinkers to avoid lithium toxicity from electrolyte imbalance.

Naltrexone should be offered, in the first instance, to help bipolar patients reduce their alcohol consumption. If naltrexone is not effective then acamprosate should be offered. In the event that both naltrexone and acamprosate fail to promote abstinence, then disulfiram should be considered, and the risks made known to the patient.

**Anxiety disorder:** Acamprosate and Baclofen have shown benefit in reducing anxiety of alcohol dependence subjects.

**Schizophrenia:** Antipsychotic medication should be optimized and clozapine may be considered. Naltrexone or Acamprosate is choice.

**Conclusions:**

The pharmacotherapy of alcohol dependence is keenly poised today. We have different drugs (Naltrexone, Disulfiram and Acamprosate) with varying mechanisms of action aimed at different populations which, when used judiciously, can bring about good results along with psychosocial interventions in the management of alcohol dependence.

It is important for clinicians treating alcohol dependence to note the following:

- Naltrexone and Acamprosate, though effective, only reduce craving and do not deter the patient from taking alcohol. He may still drink while on these drugs with no untoward effects.
- Disulfiram, though underused, is cheaper than the above two drugs but very effective as an alcohol deterrent as fear of a disulfiram ethanol reaction forces the patient to be off alcohol when on the drug.
- Combination therapy of disulfiram with any of the other drugs thereby acting on different neurobiological systems may be optimal for the effective management of alcohol dependence.
- The use of psycho-education about disulfiram and its actions is very essential to get the best effects out of the medication.
Conflict of interest: None declared

Patient fulfills the criteria for Alcohol Dependence: ensure alcohol cessation and management of withdrawals accordingly

Patient motivated for total abstinence

- No contraindication for disulfiram
  - Disulfiram

- Reports significant craving
  - Disulfiram + Anticraving agent

Patient not motivated for total abstinence

- Contraindication for disulfiram
  - Start only an anticraving agent
    - Normal KFT
      - Normal LFT
        - Treatment with Acamprosate or Naltrexone
          - Could not tolerate or succeed in treatment with Naltrexone or Acamprosate
            - Topiramate
    - Deranged KFT
      - Concurrent abstinence from opioids desirable
        - Naltrexone
    - Deranged LFT
      - Normal KFT
        - Acamprosate / Baclofen

Deranged KFT
- Normal LFT
- Concurrent abstinence from opioids desirable
- Naltrexone

Normal KFT
- Normal LFT
- Treatment with Acamprosate or Naltrexone
- Could not tolerate or succeed in treatment with Naltrexone or Acamprosate
- Topiramate

Normal LFT
- Treatment with Acamprosate or Naltrexone
- Could not tolerate or succeed in treatment with Naltrexone or Acamprosate
- Topiramate

Acamprosate / Baclofen
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