

Anti-Craving Medications in the Treatment of Alcoholism

Atul Ambekar, Shivanand Kattimani***

Introduction

Alcohol use disorders constitute one of the most serious public health problems globally, not only because of their high prevalence and impact on the personal, family, occupational and social spheres, but also because of their economic and medical consequences. Alcohol dependence is a chronic disorder, with a relapsing and remitting course like other chronic diseases, such as diabetes and hypertension. The protocol for detoxification of alcohol-dependent patients (i.e. management of acute withdrawal symptoms of alcohol cessation) is well established, time-limited, and easy to understand. However, the major challenge in the treatment of alcoholism is the prevention of relapse to heavy drinking. Although behavioral approaches were universally available in drug abuse treatment programs by the late 1980s, currently, pharmacotherapy is considered central to interventional programs aiming for prevention of relapse. Many pharmacological agents can be used to prevent alcoholic relapse. Whereas deterrent drugs (such as Disulfiram) make the ingestion of alcohol unpleasant, there are others, which, appear to reduce alcohol intake by reducing the reinforcing effects of alcohol or by reducing the urge or craving to ingest alcohol. Use of Disulfiram has its own limitations and problems. In fact, some authors recommend that because of the problems with adverse effects and compliance, disulfiram should not be used in the primary care settings.

There is always a subgroup of patients who are not suitable candidates for disulfiram. Moreover, many patients also report 'craving' as an important factor posing risk for relapse. In the recent years, anticraving medications are taking prominence for treatment of alcoholism.

This chapter will focus upon pharmacotherapy for the long-term treatment of alcoholism other than deterrence-based approaches. Briefly, we will address issues related to craving in alcohol dependence. This will be followed with discussion about certain medications, which could be labeled as 'anti-craving' agents.

Rationale for Using Anti-Craving Medications: Craving in Alcoholism Concept and Measurement

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. Studies suggest that occasional drinkers report low alcohol craving, while heavy drinkers show a significantly higher craving especially in presence of increased levels of stress and when there is associated higher expectancies for reward and relief as a result of alcohol consumption.

* Assistant Professor, National Drug Dependence Treatment Centre, All India Institute of Medical Sciences

**Senior Resident, National Drug Dependence Treatment Centre, All India Institute of Medical Sciences

Direct relationship between craving and relapse, though not well established, appears to occur through intermediate factors.

Craving for alcohol is generally thought to arise either from the desire to experience alcohol's positive effects or from the desire to avoid the negative effects of withholding alcohol, such as withdrawal symptoms. Other models have suggested other important dimensions of craving, such as the desire and intention to consume alcohol, lack of control over alcohol use, and preoccupation with drinking-related thoughts and behavior. Irrespective of the model used for understanding 'craving', it is suggested that the term should be used only to convey a 'strong desire' to take drug.

Craving measures fall into two main categories with respect to their timeframe: (1) state measures, of current craving status, and (2) global measures, which ask the patient to describe his or her general experience of craving over the course of 1 day, 1 week, 1 month, or an even longer time period.

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 duration. Studies have suggested that alcoholics who report higher levels of craving benefit the most from the anti-craving medication like naltrexone.

After this brief discussion on craving we now discuss the pharmacology and evidence-base for some of the important anti-craving agents.

Anti-Craving Medications for Alcoholism

I. 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

Studies conducted involving more than 4000 patients with alcohol dependence who had completed detoxification, provide consistent evidence of the efficacy of acamprosate in alcoholism rehabilitation; Most studies were randomized controlled trials comparing acamprosate with placebo or other anticraving agent such as Naltrexone. These outcomes have shown to be substantially homogeneous. Overall it was found that with acamprosate there is an increase in the cumulative abstinence period, decrease in the likelihood of return

to drinking, and better compliance compared to other approved anticraving agent, naltrexone. It has also been found that the effect is better with higher doses and that the effect is synergistic when acamprosate is combined with disulfiram. Cost-effectiveness of using acamprosate has also been studied and reported that use of acamprosate for 24 month period led to a net savings of 528 euros (equivalent to approximately US \$880) per patient compared with no pharmacological treatment.

Pharmacokinetics (Absorption and Metabolism)

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.

Indian Brands: T. Acamprol 333 mg Cost: Rs 6 per 333mg tablet

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.

Drug interactions

Tetracyclines may be inactivated by the calcium component in acamprosate during concurrent administration. There are no interactions with concomitant use of alcohol, diazepam, disulfiram, or imipramine. Thus, **patients with alcohol dependence can continue to use acamprosate during a relapse.**

Contraindications

Acamprosate is contraindicated in patients with known hypersensitivity to the drug, renal insufficiency or cirrhosis with severe hepatic decompensation, but patients with liver dysfunction of mild to moderate degrees may take it safely. The safety of acamprosate in pregnancy or lactation has not been established.

II. 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 μ -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.

Evidence-base

In a systematic review of 11 double blind, placebo-controlled trials, researchers found that naltrexone reduces short-term relapse rates in patients with alcohol dependence when combined with psychosocial treatments. Although there is good evidence supporting short-term benefit with naltrexone, the evidence for longer-term use is less compelling. A meta-analysis concluded that in the seven studies of naltrexone versus placebo, involving 804 patients, carried for 3 months duration, naltrexone produced a modest benefit in reducing relapse rate and in improving abstinence rates. Authors reported that benefits were lost six months after completion of treatment and adverse effects were significantly more common in patients treated with naltrexone. In general, the number of patients treated in double-blind studies of the drug has been comparatively few, and longer-term outcome studies are lacking. 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.

Pharmacokinetics (Metabolism)

Naltrexone undergoes extensive first-pass metabolism in the liver to β -naltrexol. Although a much weaker antagonist than naltrexone, the half-life of β -naltrexol is longer, and plasma concentrations of the metabolite are always higher than those of the parent drug. The mean elimination half-life values for naltrexone and β -naltrexol are four hours and 13 hours, respectively.

Indian Brands : T. Naltima 50 mg/T. Nodict 50 mg

Cost: Rs. 35-50 per 50 mg tablet

Dose and administration: Naltrexone is administered orally at 25 mg for 12 days, and then increased to the standard dose of 50 mg daily.

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

Adverse effects

Naltrexone has a dose-related hepatotoxicity, occurring at higher doses than those prescribed for alcohol dependence. Naltrexone generally is well tolerated; nausea is the most common adverse effect (reported by 10 percent of patients), followed by headache, anxiety, and sedation. Naltrexone is FDA pregnancy category C drug, meaning that no studies have been conducted to observe its adverse effects on pregnancy and on its outcome in animals and there are no adequate and well-controlled studies existing in pregnant women.

Drug interactions

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.

Comparison between acamprosate and naltrexone : Both of these drugs have been compared in very few studies. A meta-analysis found that both drugs exerted significant, but modest, effects on drinking outcomes, with sizeable variability in results between studies (Kranzler *et al*, 2001). More recent rigorous studies of naltrexone have found less favorable outcomes than the earlier ones. Overall, evidence appears to be more in favour of acamprosate, because more number of studies have been conducted with it, with longer duration, and better acceptability in patient groups due to lesser adverse effects as compared to naltrexone.

One potential advantage of naltrexone (though not studied well) is its convenience of administration. Taking two tablets of acamprosate thrice a day may be cumbersome for some patients and may affect compliance as compared to the relatively simpler regimen of naltrexone one tablet per day. While there is limited evidence for a depot preparation of naltrexone, a depot preparation of acamprosate has not been attempted yet.

Table 1: Comparison between acamprosate and naltrexone

Attribute	Acamprosate	Naltrexone
Increases abstinence	Yes	May be
Decreases heavy drinking	May be	Yes
Longer-term efficacy (>1 yr)	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

Source: Mason (2003)

III. 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 mesocorticolimbic 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, drinks per 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.

Pharmacokinetics

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours. The pharmacokinetics of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). The mean plasma elimination half-life is 21 hours after single or multiple doses. Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose).

Indian Brands: T. Topex / T. Topirol / T. Topicon. Available in strengths of 25mg / 50mg / 100mg tablets
Cost: Rs 3 per 25mg tablet, Rs 6 per 50 mg tablet, Rs 12 per 100mg tablet

Dose and administration: 25 to 300 mg per day (Increase 25 mg every week). Abrupt withdrawal should always be avoided.

Special tests prior to induction: Renal function tests.

Adverse effects: dizziness and somnolence, ataxia, impaired concentration, confusion, fatigue, paresthesias, speech difficulties, diplopia, and nausea. Depression and cognitive impairment have been reported.

Drug Interactions: Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia. In most cases, symptoms and signs abated with discontinuation of either drug.

Contraindication: Hypersensitivity to the drug. Avoid in those with history of renal stones. Abrupt withdrawal should always be avoided.

IV. SEROTONERGIC DRUGS:

IVa. Selective Serotonin Reuptake Inhibitors (SSRI) : Data on the effects of serotonergic medications on alcoholism are limited, and the results are less consistent. The serotonergic medications that have been most extensively evaluated are the selective serotonin reuptake inhibitors (SSRIs), particularly fluoxetine and citalopram. Even among studies conducted with SSRIs, findings have been variable. Some studies suggest that SSRIs are efficacious only in heavy drinkers or in certain subgroups of alcoholics. Both acute and chronic administration of SSRI, has been shown to reduce ethanol consumption. It was reported that fluoxetine up to 60 mg per day had no significant effect on alcohol consumption in persons who were alcohol dependent without major depression. In a study, it was shown that patients with major depression and alcohol dependence showed beneficial effect when treated with 20 to 40 mg per day of fluoxetine over 12 weeks than those receiving placebo, in terms of decreasing frequency and quantity of drinks, and reducing heavy drinking days. Other SSRI like fluvoxamine has shown similar results. 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.

IVb. 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.

V. COMBINATION OF DRUGS

V a. Combination of naltrexone with acamprosate : Naltrexone increases rate and extent of absorption of acamprosate. Diarrhoea and nausea are the most significant side effects. A review shows that the combination is better than acamprosate alone and better than combination of acamprosate with placebo. However, their individual and combined roles need better delineation. Overall, acamprosate appears to be more useful at achieving abstinence, while naltrexone seems more indicated for controlling alcohol consumption. Many alcohol dependent patients, particularly those that respond insufficiently on monotherapy could benefit from this combination regimen.

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

V c. 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), recruited recently abstinent alcohol dependent patients (n=1383) in outpatient setting to one of nine treatment groups. Eight treatment groups received Medical management (MM)¹; four of these received

¹Medical management provided by health professional to all patients consisted of nine, brief, structured sessions following standard protocol.

naltrexone (100 mg/ day), acamprosate (3 gm/ day), both naltrexone and acamprosate, or placebo pills. The other four groups received in addition specialized alcohol counseling (up to 20 sessions of alcohol counseling by a behavioral specialist). The ninth group received only the specialized alcohol counseling, but no medications, and no more than four visits with a health professional for general medical advice. Contrary to the expectations, the researchers found no effect on drinking while on acamprosate and no additive benefit from combination of acamprosate and naltrexone. Highest chances of decreasing alcohol consumption were seen in patients who received medical management and naltrexone (but no alcohol counseling), at the end of four months. At the end of one year worst outcome was seen in patients who received medical management plus placebo and better outcomes in those who received medical management plus either naltrexone or specialized alcohol counseling. In other words, adding either naltrexone or specialized alcohol counseling to medical management enhanced the chances of decreasing heavy alcohol consumption, and reducing relapse.

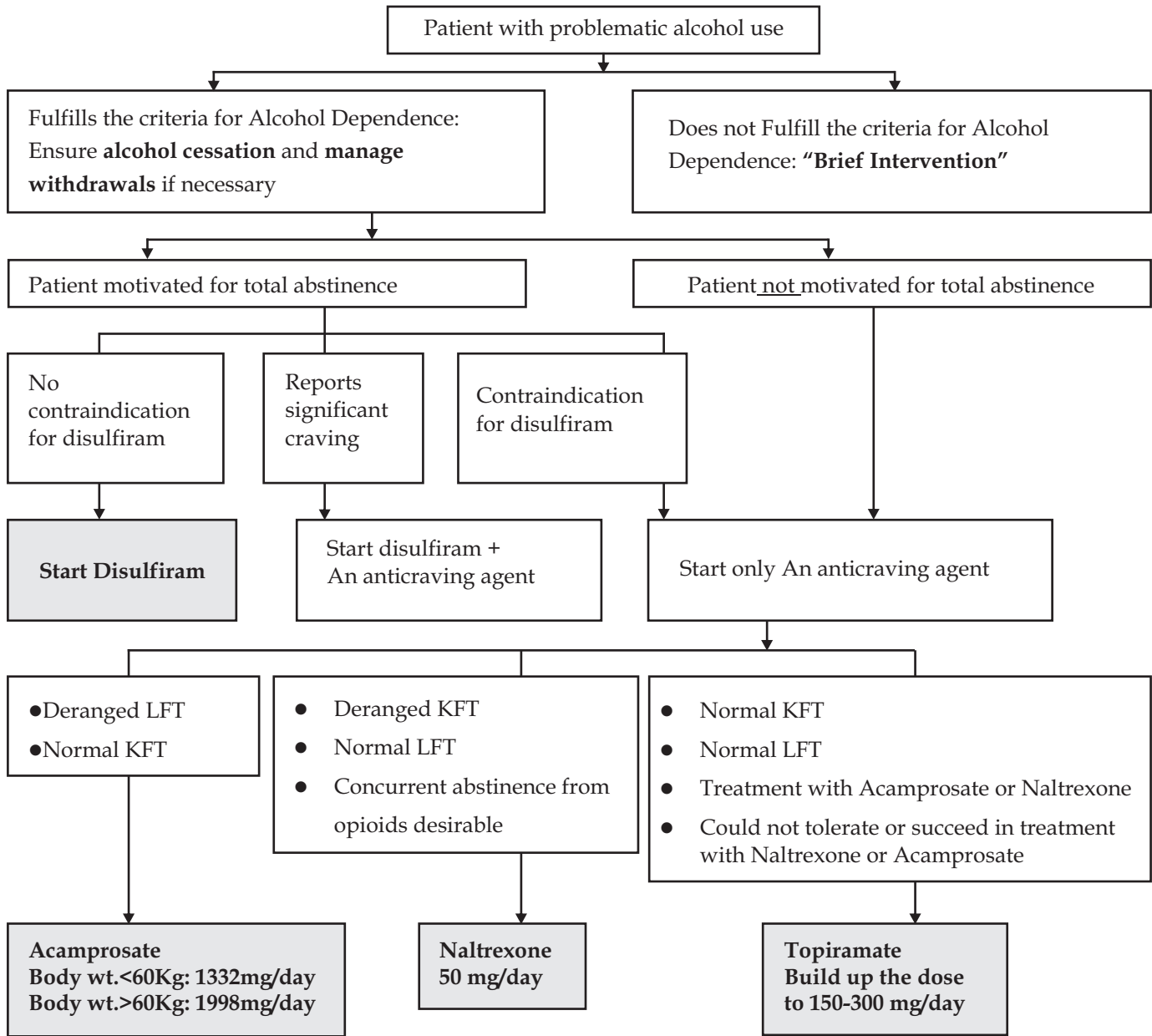
Conclusions

Thus, it can be seen that anti-craving agents could play a significant role in the long-term treatment of alcohol dependence. Many physicians are not aware that medications are effective in the treatment of addictive disorders and even if they are aware there is reluctance to use such medications. Despite many limitations, review of research confirms the safety and efficacy of acamprosate and naltrexone as treatments for alcohol dependence. There are insufficient data available to establish with any certainty the superiority of one drug over the other, at this moment. Acamprosate seems especially useful in a therapeutic approach targeted at achieving abstinence, whereas naltrexone seems more indicated for treatment goals oriented to controlled consumption. At present, acamprosate should probably be considered the first-line treatment for patients with moderate to severe alcohol dependence, because of the larger body of supporting evidence and the benefits extending after treatment. Naltrexone is indicated for alcohol-dependent patients in whom acamprosate has not proved effective or has not been well tolerated. There may be special indication for prescribing naltrexone to alcohol-dependent patients who are also dependent on opioids. The best choices for prevention of relapse are acamprosate and naltrexone with concurrent counseling through professional or self-help programs. Physicians may also consider the use of an SSRI in the presence of a comorbid mood or anxiety disorder. Topiramate and ondansetron show promise as treatments to increase abstinence.

Apart from these medications, non-pharmacological interventions like individual and group counselling and 12-step programmes are used in the rehabilitation of patients with alcohol dependence. Medications should be considered as adjuncts along with other nonpharmacotherapeutic interventions like alcohol counseling, family psychoeducation, motivation enhancement therapy and family therapy and other methods that are helpful in changing lifestyles patterns in healthier direction.

Thus, the development and successful clinical use of 'relapse preventing medications' opens up a completely new perspective in the treatment of alcohol-dependent patients. The ultimate goal is to develop therapies that optimize the combination of pharmacotherapy and psychosocial treatment in reducing the morbidity and mortality related with alcohol consumption.

Pharmacological treatment of alcoholism suggested algorithm



Tips for follow-up:

- ⊙ Monitor LFT (Liver function tests) and KFT (Kidney function tests) at least once every three months even if normal. Increase frequency of tests if abnormal at any point in time
- ⊙ Look for side effects
- ⊙ Look for emergence of psychiatric symptoms and initiate appropriate treatment
- ⊙ Confirm reduction in alcohol consumed and frequency of consumption by family members
- ⊙ Enquire into reduction of craving
- ⊙ Non-pharmacological therapy is an integral part of the treatment (e.g., Motivational Enhancement Therapy, Relapse Prevention Sessions, Family Therapy and Occupational therapy)

Frequently asked questions

Q1. Can I prescribe these medications when patient wants to take medications but not ready to stop alcohol?

Ans. None of these medications require total abstinence from alcohol prior to starting these. If there is heavy dependence on alcohol, it is always better to treat withdrawal symptoms (detoxification) prior to starting these medications. Compliance is likely to be better if one stops drinking while on these medications. These medications do not cause adverse effects similar to that of disulfiram (a Disulfiram Ethanol Reaction) when alcohol is consumed while on these medications.

Q2. When do I say that the medication is not working?

Ans. Build-up the dose to the optimal levels, start non-pharmacological interventions and then wait at least for one month before declaring that the treatment is not effective. Assess in terms of decrease in craving, decrease in frequency of drinking, decrease in amount of drinking or decrease in episodes of heavy drinking compared to the baseline.

Q3. What is the frequency of visits and duration of treatment?

Ans. There are no fixed guidelines for this. In well motivated patients who have good social support and who show normal baseline investigations, a good follow-up schedule would be - monthly for the first six months then two monthly for the next six months. Encourage the patients to come with their family members. At the end of one year, decision to continue the treatment further may be taken in consultation with the patient.

Q4. Can family members give these medications to someone who does not want to come to clinic?

Ans. Though, these medications do not cause adverse effects when given clandestinely for someone who is unable to stop drinking, it is not an ethical practice. All patients must be seen to assess severity of problematic use of alcohol, comorbid other psychiatric or medical condition, and to assess the degree of motivation. Only then, in consultation and agreement with the patient, the suitable medication must be chosen. Poorly motivated patients need motivation enhancement therapy.

Q5. Patient is willing for total abstinence and is a candidate for disulfiram but he reports intense craving and he fears that he might give into his craving and start drinking leading to the Disulfiram Ethanol Reaction. What should I do?

Ans. In such cases, with informed consent, start disulfiram and also add an anticraving agent. Such a combination is likely to have a better outcome. The Disulfiram will help in cognitive arousal to be on guard, while the anti-craving agent will decrease the craving.

Suggested reading

© Annemans L, Vanoverbeke N, Tecco J, D'Hooghe D (2000). "Economic evaluation of campral (acamprosate) compared with placebo in maintaining abstinence in alcohol-dependent patients." *European Addiction Research*, 6: 71-8.

- ⊙ Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, et al; COMBINE Study Research Group (2006). "Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial." *The Journal of the American Medical Association*, May 3, 295(17):2003-17.
- ⊙ Besson J, Aeby F, Kasas A, Lehert P and Potgieter A (1998). "Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism: a controlled study." *Alcoholism: Clinical and Experimental Research*, 22: 573-9.
- ⊙ Carmen B, Angeles M, Ana M and María AJ (2004). "Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review." *Addiction*, 99: 811-828.
- ⊙ Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, et al; for the Vivitrex Study Group (2005). "Efficacy and Tolerability of Long-Acting Injectable Naltrexone for Alcohol Dependence. A Randomized Controlled Trial." *The Journal of the American Medical Association*, 293:1617-25.
- ⊙ Graham R, Wodak AD and Whelan G (2002). "New pharmacotherapies for alcohol dependence." *The Medical Journal of Australia*, 177: 103-7.
- ⊙ Jaffe AJ, Rounsaville B, Chang G, Schottenfeld RS, Andmeyer RE (1996). "Naltrexone, relapse prevention, and supportive therapy with alcoholics: An analysis of patient treatment matching." *Journal of Consulting and Clinical Psychology*, 64:1044-53.
- ⊙ Janakiraman R, Raguraman KP and Ramamurthy C (2005). "Effects of topiramate in alcohol dependence." *Australian and New Zealand Journal of Psychiatry*, August 39(8):736-7.
- ⊙ Kiefer F, Wiedemann K (2004). "Combined therapy: what does acamprosate and naltrexone combination tell us?" *Alcohol and Alcoholism*, Nov-Dec, 39 (6):542-7.
- ⊙ Kranzler HR (2000). "Pharmacotherapy of alcoholism: gaps in knowledge and opportunities for research." *Alcohol and Alcoholism*, Vol. 35 (6): 537-47.
- ⊙ Kranzler HR, Van Kirk J (2001). "Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis." *Alcoholism: Clinical and Experimental Research*, 25: 1335-41.
- ⊙ Littleton JM (1995). "Acamprosate in alcohol dependence: how does it work?" *Addiction*, 90:1179-88.
- ⊙ Mason BJ (2003). "Acamprosate and naltrexone treatment for alcohol dependence: an evidence-based risk-benefits assessment." *European Neuropsychopharmacology*, 13(6): 469-75.
- ⊙ Srisurapanont M, Jarusuraisin N (2002). "Opioid antagonists for alcohol dependence (Cochrane Review)." In: *The Cochrane Library*, Issue 1. Oxford: Update Software.
- ⊙ Williams SH (2005). "Medications for Treating Alcohol Dependence." *American Family Physician*, 72:1775-80.