Pharmacotherapy for relapse prevention of alcohol use disorder in the Indian setting: A systematic review

ABSTRACT

Alcohol use disorders (AUDs) is an important public health concern as estimates of the prevalence of AUD range at 4%–6% in the Indian population. Currently, there is limited literature on the pharmacotherapeutic interventions for AUD in the Indian setting. It is imperative to identify the possible variations in their effects from Western studies, and hence the current review was attempted to perform a comprehensive evaluation and critical appraisal of the methodology of the evidence on pharmacological strategies of relapse prevention of AUD in the Indian setting. A total of 18 studies were included in the review. Disulfiram was the most common pharmacological agent to be studied. The initial literature before 2000 focused primarily on disulfiram, whereas the studies in the next decade compared it to acamprosate and naltrexone and emerging interest in anticraving agents such as baclofen and topiramate had been noted over the past few years. No studies were available on newer agents such as ondansetron, selective serotonin reuptake inhibitors or formulations such as depot and implants. Deterrent agents were found to be better when compared to anticraving agents in terms of abstinence and relapse, whereas the latter were more effective for control of craving. Among the pharmacological agents studied, the greatest evidence exists for disulfiram for relapse prevention which could be due to affordability of disulfiram and social support in the Indian context. The chief methodological limitations include the lack of randomized trials and objective measures for assessing abstinence.

Keywords: Alcohol use disorder, India, pharmacotherapy, relapse prevention

Address for correspondence:
Dr. Balaji Bharadwaj,
Department of Psychiatry,
De-addiction Clinic, Jawaharlal Institute of Postgraduate Medical Education and Research,
Puducherry, India.
E-mail: balaji.b@jipmer.edu.in

Alcohol use disorders (AUDs) is one of the important public health concerns associated with significant morbidity and mortality. About 3.8% of deaths globally have been found to be attributed to alcohol consumption. Further, alcohol is also found to be responsible for 4.6% of global disability-adjusted life years. More than 1% of gross national product was reported to be spent on alcohol in both high- and middle-income countries. The National Household Survey of Drug Use had reported that the average prevalence of alcohol dependence syndrome is 4% in the Indian population. Recent figures also suggest a similar rate of alcohol dependence of about 6% with about 11% having AUDs (harmful use and dependence). AUDs have been compared to medical illnesses such as diabetes mellitus and asthma in terms of its chronic and relapsing course. Inspite of the relapse prevention strategies, the rates of relapse reported have been as high as 40%–60%.

It is necessary to implement effective measures to counter the burden of alcohol use in the present scenario, especially prevention of relapse in patients following detoxification. Currently, there is limited literature on the pharmacotherapeutic interventions for AUD in the Indian setting. Although it is possible to extrapolate effectiveness of the pharmacological interventions from the Western studies, it is imperative to study them in Indian setting to identify the possible variations in their effects and outcome.
which could have therapeutic implications. Factors such as social support and cost-effectiveness of drugs are more pertinent to the Indian setting. With this background, the current systematic review was attempted to perform a comprehensive evaluation and critical appraisal of the methodology of the evidence on pharmacological strategies of relapse prevention in AUD in the Indian setting.

We searched for studies done in Indian patients with AUDs where the use of at least one medication was studied for its effectiveness in preventing relapse or in reducing craving in the postdetoxification phase. The drug may have been compared with a control group who were not given any pharmacotherapy or may have received another medication as comparison. We took all clinical studies that compared or reported outcomes in at least two groups. We did not restrict to blinded studies or randomized controlled trials alone but also included open-label designs and retrospective chart reviews. We did not include reviews on the topic.

RESULTS

A total of 18 studies were included in the review. Disulfiram was the most common pharmacological agent to be studied for relapse prevention in AUDs. The earliest studies on pharmacotherapy of relapse prevention in AUD date back to year 1982. The older studies in 1980s and 1990s primarily focused on assessing the safety profile and effectiveness of disulfiram. Further, the advent of the 21st century brought out studies which compared disulfiram with acamprosate and naltrexone. Since the last decade, there has been a gradually increasing interest in anticraving agents such as baclofen and topiramate. No studies were available on newer anticraving agents such as ondansetron, selective serotonin reuptake inhibitors (SSRI), or newer formulations such as depot and implants. To summarize, the deterrent agent has been found to be better when compared to anticraving agents in terms of abstinence and relapse. Anticraving agents as expected were found to be better than disulfiram for control of craving. The summary of the 18 studies has been elaborated in Table 1.

Disulfiram

In the Western studies, disulfiram was used in the dose range of 250–500 mg/day. In Indian studies, disulfiram was employed at slightly lower dose range of 125–500 mg/day and the commonly used dosage was 250 mg/day. It was mostly well tolerated at this dosage. Most common adverse effect reported was tiredness followed by gastrointestinal symptoms, similar to findings of international studies. However, in a study, moderate disulfiram–ethanol reaction (DER) was reported in 42% of patients on 250 mg/day of disulfiram. Complete recovery is usually the case, however, rarely life-threatening adverse effects can occur. There have been reports of developing ischemic stroke as a result of DER. Some of the rare adverse effects reported in India were neuroleptic malignant syndrome, seizures, acute encephalopathy, and hypertension. This is in contrast, with the rare side profile of Western studies such as hepatotoxicity, fulminant hepatitis, optic neuritis, polyneuritis, and peripheral neuropathy. Further, the psychiatric complications such as disulfiram-induced psychosis are more commonly reported from India compared to Western setting. Several case reports of disulfiram-induced psychosis exist. Vulnerable factors identified through these case reports include the past or family history of psychosis. This
Table 1: Indian studies on pharmacological agents for relapse prevention for alcohol use disorders

| Author/place                  | Type of study       | Sample/medication characteristics | Outcome measures                                                                 | Time period specification of outcome/follow-up | Chief findings                                                                 |
|------------------------------|---------------------|-----------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------|--------------------------------------------------------------------------------|
| Bagadia et al. 1982, Mumbai  | Prospective observational study | n=75 adults disulfiram 250 mg     | Severity of DER                                                                  | 6 months                                      | 28% was the dropout rate 54% had good to moderate improvement 42% had moderate DER |
| Srinivasan et al. 1996, Chennai | Prospective observational study | n=158 adults disulfiram 250 mg   | Degree of improvement measured as good, moderate, mild, or nil (Bagadia et al. 1979) | Up to 36 months of follow-up                   | The ADR profile was predominantly mild Most common was tiredness followed by gastrointestinal symptoms No significant difference in compliance was noted in groups of patients receiving disulfiram who took less or equal to 1 month; 1-3 months and 4-36 months |
| Abraham et al. 1997, Puducherry | Prospective observational study | n=60 adults disulfiram 250 mg | ADR Up to 36 months of follow-up                                                                 | 12-15 months                                  | 32.5% belonged to abstinent and nonproblem drinker category 35% belonged to drinking continued but improved category 32.5% belonged to unimproved category Duration of disulfiram was significantly associated with favorable outcomes |
| De Sousa and De Sousa, 2004, Mumbai | Randomized open trial | n=100 adults Randomized to disulfiram 250 mg (50) or naltrexone 50 mg (50) | Outcome as per Heather and Tebbut (1989) classification: Abstinent Nonproblem drinker Drinking but improved Unimproved | 12 months                                      | Significantly higher time to relapse and higher frequency of patients being abstinent was found in disulfiram group compared to naltrexone group Significantly lower craving was found in patients receiving acamprosate compared to those receiving disulfiram |
| De Sousa and De Sousa, 2005, Mumbai | Randomized open trial | n=100 adults Randomized to disulfiram 250 mg (50) or acamprosate 1998 mg (50) | Cumulative days of abstinence Time to first relapse GGT Craving                   | 8 months                                       | Significantly higher time to relapse and higher frequency of patients being abstinent was found in disulfiram group compared to acamprosate group Significantly lower craving and GGT was found in patients receiving acamprosate compared to those receiving disulfiram |
| Basu et al. 2005, Chandigarh  | Retrospective chart review | n=62 Acamprosate (22) Naltrexone (20) No drug (20) | Abstinence                                                                       | 6 months                                       | Unique profile of patients receiving acamprosate: Higher socioeconomic status Lesser family-related problems Lesser comorbid opioid use/other drugs Past history of significantly higher duration of relapse Greater hepatic impairment No significant difference in abstinence was noted among the groups of patients receiving acamprosate or naltrexone or no drug Patients on acamprosate performed significantly better in various domains of functioning at follow-up |

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Table 1: Contd...

| Author/place | Type of study | Sample/medication characteristics | Outcome measures | Time period specification of outcome/follow-up | Chief findings |
|--------------|---------------|-----------------------------------|------------------|-----------------------------------------------|----------------|
| Narayana et al. 2008 | Prospective observational study | n=118 soldiers Topiramate (100-125 mg)=41 Naltrexone (50 mg)=37 Acamprosate (1332-1998 mg)=40 | Complete abstinence | 12 months | Complete abstinence was significantly higher in patients receiving topiramate (76.3%) compared to acamprosate (60.7%) and naltrexone (57.7%) |
| De Sousa and De Sousa, 2008, Mumbai | Randomized open trial | n=58 adolescents Randomized to disulfiram 250 mg (29) or naltrexone 100 mg (29) | Time to first relapse craving | 6 months | Significantly higher time to relapse in disulfiram group compared to naltrexone group Lower craving was found in patients receiving naltrexone compared to those receiving disulfiram |
| De Sousa and Jagtap, 2009, Mumbai | Randomized open trial | n=100 elderly patients (age>60 years) Randomized to disulfiram 250 mg (50) or naltrexone 100 mg (50) | Cumulative days of abstinence Time to first relapse GGT Craving | 6 months | Significantly higher time to relapse and higher frequency of patients being abistent was found in disulfiram group compared to naltrexone group Significantly lower craving and GGT was found in patients receiving naltrexone compared to those receiving disulfiram |
| De Sousa et al. 2008, Mumbai | Randomized open trial | n=100 adults Randomized to disulfiram 250 mg (50) or topiramate 150 mg (50) | Cumulative days of abstinence Time to first relapse GGT Craving | 9 months | Significantly higher time to relapse and higher frequency of patients being abistent was found in disulfiram group compared to topiramate group Significantly lower craving and GGT was found in patients receiving topiramate compared to those receiving disulfiram |
| Singh et al. 2008, Chandigarh | Naturalistic study | No pharmacoprophylaxis=9 Disulfiram=18 Naltrexone=31 Disulfiram + Naltrexone=3 | Time to relapse | 8-20 months | No significant difference in time to relapse was found among the four groups |
| Palatty and Saldanha, 2011, Mangalore | Prospective observational study | n=51 adults Disulfiram 125 mg under supervision | Frequency of drop out (relapse) ADR Liver function test Hemogram Lipid profile | 0 days 30 days 60 days | 76.5% completed the treatment at the end of 60 days 45% patients did not report of ADR Most common ADR was drowsiness followed by tiredness Significant increase in SGOT, SGPT, and GGT was found at end of 60 days compared to baseline |
| Grover et al. 2014, Chandigarh | Cross-sectional study | n=4830 patients received disulfiram 18 patients received baclofen | Sexual functioning by Arizona Sexual Experience Scale | - | Sexual dysfunction was significantly greater in baclofen group (38%) compared to disulfiram group (10%) |
| De Sousa and De Sousa, 2014, Mumbai | Randomized open trial | n=52 adolescents Randomized to disulfiram 250-500 mg (26) or naltrexone 100 mg (26) | Cumulative days of abstinence Time to first relapse GGT Craving | 4 months | Significantly higher time to relapse and higher frequency of patients being abistent was found in disulfiram group compared to naltrexone group Significantly lower craving was found in patients receiving naltrexone compared to those receiving disulfiram |

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Table 1: Contd...

| Author/place | Type of study | Sample/medication characteristics | Outcome measures | Time period specification of outcome/follow-up | Chief findings |
|--------------|---------------|-----------------------------------|------------------|-----------------------------------------------|----------------|
| Shukla et al. 2015, Bengaluru | Chart review | n=549 male cases Patients who received acamprosate=201 Patients who received baclofen=348 | Time to first drink | 1 year | Time to first drink was significantly greater in patients receiving baclofen compared to acamprosate |
| Rozatkar et al. 2016, Chandigarh | Chart review | n=113 adult males receiving 20-40 mg baclofen | Persistent craving Alcohol consumption | 1 month | Persistent craving decreased to 15% from 70% at baseline 34% patients continued alcohol use in dependent pattern compared to 100% at baseline |
| Lohit et al. 2016, Bengaluru | Prospective follow-up study | n=101 males and 1 female | Anticraving medication adherence assessed by self-report medication diary and simplified medication adherence questionnaire Abstinence | 1st week, 3rd week, 8th week, 12th week | Acamprosate 132-1998 mg was the most common agent to be used (74%) followed by naltrexone 25 mg (7%) and disulfiram 125-500 mg (7%) Decrease in adherence to acamprosate and naltrexone was associated with significantly higher increase in relapse rate and decrease in days to alcohol abstinence compared to those who were adherent Significantly lower rates of adherence were noted in patients with younger age group Self-decision to stop medication was the most common reason for nonadherence (39%) |
| Gupta et al. 2007, New Delhi | Randomized open-label study | n=122 Randomized to baclofen 30 mg/day (72) or benfotiamine (50) | Time to first relapse Days of heavy drinking Total duration of abstinence Craving | 0, 2, 4, 8, 12 weeks | Patients who received baclofen had significantly better outcomes with regard to days of heavy drinking, abstinence, and craving compared to those receiving benfotiamine |

ADR – Adverse drug reaction; DER – Disulfiram–ethanol reaction; GGT – Gamma‑glutamyl transferase; SGOT – Serum glutamic-oxaloacetic transaminase; SGPT – Serum glutamic-pyruvic transaminase

warrants need for assessment of potential role of genetic factors in our population.

**Naltrexone**
The dosage of naltrexone in the Indian studies ranged from 25 to 100 mg/day. The most commonly employed dose of 100 mg/day was higher to the common dose of 50 mg/day reported in the Western setting. Dose of 100 mg/day was relatively well tolerated in Indian patients. The commonly reported side effects are headache, dizziness, fatigue, and nausea similar to the Western studies. There were no studies on injectable naltrexone in the Indian setting.

**Acamprosate**
The dose range and side effect profile reported in Indian studies were similar to that reported in international studies. The Indian studies commonly employed the dosage of 1332–1998 mg/day. It was well tolerated and was commonly used in patients with deranged liver parameters. The frequently reported adverse effects included diarrhea and flatulence. There have been reports of Parkinson's symptoms at high-dose range (1998 mg/day) in the Indian setting.

**Baclofen**
The dose range of baclofen varied across Indian studies with 20–40 mg/day in one study and a mean dosage of 50.76 mg/day in another study. Western studies have commonly employed baclofen at a dosage of 30 mg/day. It is well tolerated similar to findings reported in the Western literature which has highlighted its nonabuse potential. The commonly reported side effects include drowsiness, nausea, and abdominal pain. There have been reports of baclofen-induced psychosis at a dose of 20 mg/day in the Indian setting.

**Topiramate**
Topiramate was used in two studies with dose range of 100–150 mg/day. It had a relatively tolerable safety
Records identified through database searching (n = 235)

Records after duplicates removed (n = 235)

Records screened (n = 235)

Records excluded (n = 222)

Additional records from cross references (n = 5)

Full-text articles assessed for eligibility (n = 13)

Studies included in qualitative synthesis (n = 18)

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**Figure 1: PRISMA flow diagram outlining the selection of studies**

Profile. The Western literature has reported a dose range of 200–800 mg/day. The side effects reported such as dizziness, paresthesia, altered perception of taste, psychomotor retardation, and memory impairment are similar those reported in Western studies.[27]

**DISCUSSION**

**Efficacy**

The comparison of efficacy of deterrent agent with anticraving agents has always been controversial and subject to debate. In Indian studies, supervised disulfiram administration was found to be better than acamprosate and naltrexone in terms of higher rates of abstinence and greater time to relapse. This is in conformity with results of open-labeled trials, where supervised disulfiram administration was found to be better than naltrexone and acamprosate or unsupervised disulfiram. While one randomized open trial comparing the naltrexone and disulfiram found that patients on disulfiram remained abstinent for a longer time before they relapsed.[28]

One naturalistic study found no significant difference in drinking outcomes among patients receiving no pharmacoprophylaxis or disulfiram, naltrexone, or combination of disulfiram and naltrexone.[29] However, several studies have documented the better evidence base for acamprosate or naltrexone when compared to disulfiram in the Western setting.[30] An important issue worth critically appraising is that these results were not replicated in blinded trials. This discrepancy has been often linked with the debate if the efficacy of disulfiram is due to the psychological effect of its aversive potential or pharmacological action.[31,32] A recent study reported that decrease in adherence to acamprosate and naltrexone was associated with significantly higher relapse rate and decreased abstinence.[33] There have been controversial findings regarding lack of efficacy of acamprosate and naltrexone. One retrospective chart review from India found no significant difference in abstinence rates between the patients receiving acamprosate and naltrexone. Similar finding was reported by a recent meta-analysis of 123 studies.[34] Several meta-analyses report that acamprosate is better than naltrexone for maintaining or supporting abstinence and naltrexone is better than acamprosate in reducing craving and heavy drinking.[35–37] A single Indian study on soldiers reported that abstinence rate was significantly higher in patients receiving topiramate compared to acamprosate or naltrexone.[38] However, conclusion cannot be drawn from a single study due to the study design as well as lack of generalizability. Topiramate was found to be effective in veterans with AUD with posttraumatic stress disorder (PTSD).[39] Topiramate is recognized as one of the effective treatment options for PTSD.[40] Further, the prevalence of PTSD symptoms and PTSD in Indian soldiers was found to be 75% and 25%, respectively.[41] Therefore, it would be worth exploring the efficacy of topiramate in a particular subset such as army soldiers identifying the putative role of PTSD as meditational factor. In Western literature, the effect size of topiramate was found to range from small to medium with greatest effect size for abstinence followed by heavy drinking.[42]

Two recent clinical chart reviews found baclofen to be effective in maintaining abstinence and reducing craving.[20,22] Baclofen was found to be superior in terms of days of abstinence, heavy drinking, and craving compared to benfotiamine in a randomized, open-labeled trial.[43]

**Issues relevant to the Indian context**

The success story of disulfiram in Indian setting could possibly be attributed to two main reasons, cost and the supportive role of the family. Disulfiram has been found to be cheapest pharmacological agent for relapse prevention in AUD. This is of definite relevance to the low- and middle-income group countries including India. A month’s supply of disulfiram was found to be at least 20–30 times cheaper compared to acamprosate and naltrexone.[44] However, there have been no Indian studies assessing cost-effectiveness of pharmacological relapse prevention strategies. The disulfiram–ethanol reaction is often feared and it is often the fear of this reaction that
helps patients keep away from alcohol. The actual instances of disulfiram–ethanol reaction leading to life-threatening complications or death are rare and limited to case reports.

The role of Indian families in treatment seeking for substance users has been found to be different from Western families. The difference starts right from the family members taking the responsibility in seeking treatment for the otherwise unmotivated patient. Further, the support from family members is tremendous in terms of supervision, encouragement in abstinence promoting religious practices such as Ramzan or Navratras, and efforts to keep the patient away from substance using peers.\[44\]

In the Indian setting, quacks have been found to sell disulfiram under the garb of indigenous medications or “Herbal powders.” Family members surreptitiously administering these preparations and the patients developing DER on consuming alcohol is not uncommon in routine clinical practice. Surprisingly, the dose of disulfiram in these preparations was found to be almost 1500–2000 mg/day which is at least ten times the usual prescribed dose.\[45\] The highly prevalent sociocultural beliefs and unchallengeable faith of the patients’ family members toward the traditional practices in the background of decreased availability and accessibility of trained addiction specialist services, further fuel such kind of unregulated practices. The surreptitious administration of high doses of disulfiram in a possibly unmotivated patient can be life-threatening.

There have been no studies which have compared the efficacy of drugs in patients consuming Indian-made foreign liquor and country-made liquor. There might be differences in the drug and dose requirements of the patients consuming these unique forms of alcohol owing to differences in concentration and type of alcohol. Hence, there is a need for studies assessing the efficacy of pharmacological agents in patients consuming local and indigenous forms of alcohol specific to India.

**Critical appraisal of the methodological aspects of the studies**

It is essential to interpret the results with caution, considering various methodological issues noted in the studies. Five striking themes of methodological concerns could be identified. First, lack of randomized controlled trials with blinding is of the most important methodological flaws. The studies have largely been cross-sectional as well as prospective-observational studies\[26,27,33,34-40\] and retrospective chart reviews.\[20,21,49,50\] There were few randomized open-labeled trials.\[18,25,51,52\] The lack of blinding and matched controls has high potential for introduction of bias. However, the difference in the mechanism of action between the deterrent agents and anticraving agents makes it difficult to conceptualize and conduct a blinded trial.

This is because physicians decide on the particular treatment after considering the overall clinical profile of the patient and few patients may be candidates for either line of treatment.

Second, majority of the studies have relied on self-report outcome measures. The lack of objective measures for assessing abstinence is one of the major limitations. Third, all the four randomized open-labeled trials were reported from a single center in Mumbai which might limit the generalisability of the study findings. The data from premier deaddiction centers in India has been largely limited to retrospective chart reviews. Hence, there is a need for studies with rigorous study methodology from academic institutes and tertiary care centers which are bound to have differences in patient profile as well as quality of deaddiction services compared to other settings.

Fourth, most of the patients received psychosocial and psychotherapeutic interventions such as supportive group psychotherapy. Concomitant nonpharmacological interventions can become an important confounder, especially when the study is trying to assess the stand-alone efficacy of the pharmacological agent.\[53\] Further, in some of the studies, patients were also receiving SSRI for management of comorbid depression.\[25,52,54\] This needs to analyzed carefully considering the potential of SSRI as novel anticing agent due to its established efficacy craving in animal models.\[59\] Fifth, there was variation in sample size characteristics across various studies. The sample size across the studies was small, ranging from 51 to 549 with only one study having sample size more than 200. The study periods ranged from 1 month to 3 years. Hence, there is a need for studies with greater sample sizes and longer follow-up periods. There was heterogeneity in the sample characteristics in type of setting, variation in selection criteria, comorbid substance use, etc. Exclusion of patients suffering from medical illness also limits the generalizability of study findings to the real world scenario.

**Limitations of the current review**

We have used four databases/search engines for finding articles for the review to cover a wide time period. However, it is possible that there may have been inadvertent missing of articles based on a screening of the titles and abstract alone. We have limited the main review to include studies that have investigated the effectiveness or efficacy or medications for relapse prevention in the Indian setting. However, we have had to include case reports and other articles in some cases for the purpose of highlighting the adverse effect profile of drugs in the Indian context. Since
most of the studies are not randomized, double-blinded, controlled trials, we could not assess the strength of the studies using Jadad scores.

Future directions
Pharmacoprophylaxis (relapse prevention) in alcohol dependence includes at least three broad classes of medications: (1) deterrents such as disulfiram, (2) ant lucraving agents such as naltrexone and acamprosate, and (3) Gamma-aminobutyric acid agents with possible substitution effects, such as baclofen and topiramate. Hence, the future studies in this field may have to investigate the potential role for selection of one of these classes of drugs depending on the patient characteristics. The pharmacogenetic influences on the efficacy of these medications also need to be studied to guide better and personalized choice of medications for patients.

CONCLUSION
Among all the pharmacological agents for relapse prevention in AUD, the greatest evidence exists for disulfiram. This is unique to the Indian setting considering the therapeutic nihilism associated with disulfiram in Western settings. This could be mainly due to the affordability of disulfiram and the family support meted out by Indian families. The chief methodological limitations in the studies conducted so far are lack of randomized trials with blinding and objective measures for assessing abstinence.

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Conflicts of interest
There are no conflicts of interest.

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