INVITED REVIEW

PHARMACOTHERAPY OF ALCOHOLISM: GAPS IN KNOWLEDGE AND OPPORTUNITIES FOR RESEARCH

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(Received 8 December 1999; in revised form 11 June 2000)

Abstract — During the past decade, renewed interest in medications to prevent relapse in alcoholics has yielded a number of promising candidates. Although two of these medications, naltrexone and acamprosate, are currently in clinical use in a number of countries, their effectiveness appears to be limited. Disulfiram, the deterrent medication that was approved 50 years ago for the treatment of alcoholism, has not consistently been shown to be efficacious. However, since inadequate dosing and other modifiable factors may limit its deterrent effects, the identification of a more potent metabolite of disulfiram appears to warrant further evaluation. Studies of serotonergic agonists for treatment of alcoholism have also yielded inconsistent results. There is evidence, however, that subgroups of alcoholics may respond well to such medications, suggesting that treatment matching may enhance their efficacy. In addition, naloxone, a compound with effects similar to naltrexone, as well as a sustained release formulation of naltrexone, may enhance the beneficial effects of opioid antagonist therapy. Despite these developments, much remains to be learned about the pharmacotherapy of alcoholism. The ongoing development and evaluation of novel medications should be given a high priority. However, such basic issues as the optimal dosing strategy and duration of treatment for existing therapies are not known. Similarly, combination therapy, involving either multiple medications or the combination of medication with specific psychotherapies, has not been well studied. The utility of specific pharmacotherapies in women, different ethnic/racial groups, adolescent and geriatric patients, and individuals with co-morbid alcohol and drug use disorders (including nicotine dependence) is also largely unknown, as is the appropriateness of medication therapy for treatment of early problem drinkers. The ultimate aim of these efforts is the development of algorithms for the pharmacological treatment of heavy drinking, which incorporate the characteristics of the patient and of pharmacological and psychosocial treatments with demonstrated efficacy. Although a general framework for such an effort currently exists, much detail is needed before it will be of widespread clinical value.

INTRODUCTION

Among the major challenges in alcoholism treatment is the prevention of relapse into heavy drinking. Individual and group counselling and 12-step programmes are basic elements in the rehabilitation of patients with alcohol dependence. Although medications are commonly used to treat withdrawal from alcohol, their role in the rehabilitation of alcoholic patients remains limited. Pharmacological agents can be used in several ways to prevent alcoholic relapse. Whereas deterrent drugs make the ingestion of alcohol unpleasant, others appear to reduce alcohol intake by reducing the reinforcing effects of alcohol or by reducing the urge or craving to ingest alcohol.

This review is intended to highlight promising areas of investigation and gaps in the literature on pharmacological and combined treatments for alcohol dependence. Although medications are increasingly being used to treat comorbid psychopathology in alcoholics (Kranzler and Rounsaville, 1998), this review will focus on alcoholism pharmacotherapy independent of such comorbidity. This review is not intended to be comprehensive, since space does not permit a discussion of all pharmacological agents that have been examined for treatment of alcohol dependence. In addition, it must be recognized that many studies that yield negative results are never published, an important issue termed ‘the file drawer problem’ (Rosenthal, 1979), which limits the validity of general conclusions.

The brief overview that follows will be extended in subsequent sections to provide a more detailed review of the existing literature, including the limitations of that literature. Since there are few studies of combined treatments for alcohol dependence, they will also be presented as an integral part of the detailed review. The final section of the article is a discussion of the opportunities that exist for research on the pharmacotherapy of alcoholism.

Renewed interest in medications to treat alcoholism, evident over the past decade, has begun to bear fruit, as witnessed by the approval in 1994 by the US Food and Drug Administration (FDA) of naltrexone for treatment of alcohol dependence. Disulfiram, a deterrent agent, was approved for the treatment of alcoholism nearly 50 years earlier (Hald and Jacobsen, 1948). Its use, however, has not been widespread and, although some small-scale studies have shown it to be superior to placebo, the largest controlled trials have failed to demonstrate its efficacy. Although naltrexone was approved in the USA for treatment of alcohol dependence based upon the results of two controlled trials showing the medication to be superior to placebo in the prevention of alcoholic relapse, this medication has also failed to achieve widespread use in the USA. Although there are probably a number of reasons for this lack of commercial success, some recent studies have shown poor tolerability and/or poor compliance with the medication.

Recently a multicentre study of acamprosate was completed in the USA, with the results reported recently in preliminary form (Mason and Goodman, 2000). Acamprosate is the most
intensively studied medication for treatment of alcohol dependence (Mason and Ownby, 2000). Although the drug has not yet been approved for use in the USA, its approval in countries throughout Europe suggests that it is likely to become the second medication approved in the USA for treatment of alcohol dependence in the ‘new era’ of alcoholism pharmacotherapy.

In the face of all of this promise, the lack of clear guidelines for the use of medication, alone or in combination with specific psychosocial treatments, substantially limits the clinical value of pharmacotherapy for alcoholism treatment. Furthermore, despite growing interest by the pharmaceutical industry in medication development for alcohol dependence, funding for such research remains far below that of other therapeutic areas in psychiatry, such as the treatment of major depression or psychosis. The main source in the USA for funding research on the pharmacotherapy of alcoholism remains the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Consistent interest and high levels of industrial support for medication development internationally are essential for a more rapid development of the field.

**REVIEW OF THE LITERATURE ON MEDICATIONS FOR RELAPSE PREVENTION IN ALCOHOLICS**

**Deterrent medications**

These alter the body’s response to alcohol, making its ingestion unpleasant. Disulfiram (Antabuse), the only deterrent medication approved in the USA for the treatment of alcoholism, inhibits aldehyde dehydrogenase (ALDH), the enzyme that catalyzes the oxidation of acetaldehyde to acetic acid. If alcohol is ingested after this enzyme is inhibited, blood acetaldehyde levels rise, which produce the disulfiram–ethanol reaction (DER). The DER is an aversive reaction that varies in intensity both with the dose of disulfiram and the volume of alcohol consumed; it is the prospect of such a reaction that is thought to deter drinking.

Despite the apparent logic of such an approach, there is limited evidence for the efficacy of disulfiram in the treatment of alcoholism. In a multicentre, cooperative study conducted in the Veterans Administration (Fuller et al., 1986), more than 600 male alcoholics were assigned randomly to groups receiving disulfiram (either 1 mg/day or 250 mg/day), or to a control group. Patients assigned to the disulfiram groups were told they were being given the drug, but neither patients nor staff knew the dosage. Results showed that, irrespective of the medication group, complete abstinence in the 1-year treatment trial was related to medication compliance. There were no significant differences among the three groups in terms of length of time to first drink, unemployment rate, social stability, or number of men totally abstinent. However, among patients who resumed drinking, those taking disulfiram 250 mg/day had significantly fewer drinking days than patients in the other two groups, a finding that may have arisen by chance (given the large number of statistical analyses).

Careful efforts to enhance compliance with disulfiram may serve to augment the deterrent effects of the medication. The use of disulfiram by subcutaneous implantation (Wilson et al., 1980) does not appear to yield blood levels that are adequate to produce a DER (Bergstrom et al., 1982).

However, behavioural efforts that may be of value include the use of incentives provided to the patient, contracting with the patient and a ‘significant other’ to work together to ensure compliance, providing regular reminders and other information to the patient, and behavioural training and social support (Allen and Litten, 1992). Azrin et al. (1982) found that a trial programme of stimulus control training, role playing, communication skills training and recreational and vocational counselling improved outcome in disulfiram-treated patients compared with those receiving placebo. Chick et al. (1992) assessed the efficacy of supervised disulfiram treatment as an adjunct to out-patient treatment of alcoholism. During a 6-month treatment period, patients received disulfiram 200 mg/day or placebo under the supervision of an individual nominated by the patient. Under these circumstances, disulfiram significantly increased abstinent days and decreased total drinks consumed; these effects were confirmed by parallel changes in γ-glutamyltransferase levels.

Because there is an increased risk of side-effects and toxic hazards as the dosage of disulfiram is increased, the daily dosage prescribed in the USA has been limited to 250–500 mg/day. However, by titrating the dose of disulfiram in relation to a challenge dose of ethanol, Brewer (1984) found that a substantial number of patients required in excess of 1 g/day of disulfiram to produce the DER. This suggests that for many patients, the standard approach to treatment with disulfiram is inadequate to yield an aversive reaction when combined with alcohol, thereby limiting its potential value as a deterrent medication. It is possible that by enhancing compliance and optimizing the dosage of disulfiram, its efficacy in alcoholism treatment may be substantially increased.

The requirement that disulfiram undergoes a complex process of bioactivation before it can inhibit ALDH (Yourick and Faiman, 1991) may explain the need for a higher dosage in some patients. S-ethyl N,N-diethylthiocarbamate sulphonoxime (DETC-MeSO), a metabolite of disulfiram, appears to be responsible for inhibition of ALDH (Hart and Faiman, 1992). At the dosage that is used clinically, faulty bioactivation in some individuals may yield too low a concentration of DETC-MeSO to inhibit ALDH. There are a number of factors that can interfere with bioactivation. First, bioactivation of disulfiram appears to be inhibited by one of its metabolites (Yourick and Faiman, 1987). Furthermore, some alcoholics, due to liver disease, have reduced levels of the cytochrome P-450 enzymes that are required for bioactivation (Guengerich and Turvey, 1991). Following pretreatment with disulfiram, alcoholics with liver disease showed a diminished response to an alcohol challenge, compared to alcoholics without liver disease (Wicht et al., 1995). In addition, the potential exists for competitive inhibition of disulfiram bioactivation by the co-administration of a variety of widely used medications that are also metabolized by the relevant cytochrome P-450 enzymes (Madan et al., 1995).

The clinical use of DETC-MeSO, the metabolite of disulfiram that directly antagonizes the activity of ALDH should, therefore, eliminate much of the variability in response observed with disulfiram. Furthermore, the metabolism of disulfiram produces several intermediates that are potentially toxic (Erve et al., 1998). Since DETC-MeSO is the end product of disulfiram metabolism, none of these intermediates are produced from it, so that it may also be better tolerated than the parent
Medications that directly reduce alcohol consumption

These appear to influence several neurotransmitter systems that underlie the reinforcing or discriminative stimulus effects of ethanol: endogenous opioids; catecholamines, especially dopamine; serotonin, and excitatory amino acids (e.g. glutamate) (Kranzler, 1995). Although it is likely that these systems interact in complex ways to produce the reinforcing effects of ethanol, efforts to develop medications for alcoholism treatment have focused on agents that are relatively selective for specific neurotransmitter systems.

Serotonergic medications. In contrast to the extensive preclinical literature that links serotonergic neurotransmission to alcohol consumption, data on the effects of serotonergic medications on human drinking behaviour are more limited, and the results are less consistent (Kranzler and Anton, 1994). The serotonergic medications that have been most extensively evaluated are the selective serotonin reuptake inhibitors (SSRIs), particularly fluoxetine and citalopram. A summary of the studies of citalopram and fluoxetine is provided in Tables 1 and 2, respectively.

Both acute (Amit et al., 1985) and chronic (Naranjo et al., 1984) administration of zimelidine, an SSRI that was removed from clinical trials due to toxicity, have shown that the drug reduces ethanol consumption. Other SSRIs that have been tested in humans to determine their effects on alcohol consumption include fluoxetine (Naranjo et al., 1990; Gerra et al., 1992; Gorelick and Paredes, 1992; Kranzler et al., 1995; Kabel and Petty, 1996), citalopram (Naranjo et al., 1987, 1992, 1995; Balldin et al., 1994; Tiihonen et al., 1996), visqualine (Naranjo et al., 1989), and fluvoxamine (Kranzler et al., 1993; Angelone et al., 1998).

Naranjo et al. (1990) were the first to report on the effects of fluoxetine on alcohol consumption in heavy drinkers. They found that fluoxetine 60 mg/day reduced average daily alcohol consumption by ~17% from baseline levels; treatment with fluoxetine 40 mg/day or placebo had no effect. When alcoholics on an in-patient unit were given the opportunity to drink alcohol, fluoxetine pretreatment (80 mg/day) initially reduced alcohol consumption, but the effect lasted only 1 week (Gorelick and Paredes, 1992). Using a cross-over design, Gerra et al. (1992) compared the effects of fluoxetine 40 mg/day, acamprosate, and placebo in family-history-positive (FHP) and family-history-negative (FHN) alcoholics. They found that both active medications were superior to placebo in reducing the number

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Table 1. Placebo-controlled trials of fluoxetine (FLX)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Study type</th>
<th>Total n</th>
<th>Study duration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naranjo et al. (1987)</td>
<td>Canada</td>
<td>3,P</td>
<td>29</td>
<td>4 weeks</td>
<td>FLX 60 mg/day (but not 40 mg/day) reduced drinks/day</td>
</tr>
<tr>
<td>Gerra et al. (1992)</td>
<td>Italy</td>
<td>3,C</td>
<td>28</td>
<td>1 month</td>
<td>FLX 40 mg/day reduced drinks/day in family-history-positive patients only</td>
</tr>
<tr>
<td>Gorelick and Paredes (1992)</td>
<td>USA</td>
<td>2,P</td>
<td>20</td>
<td>4 weeks</td>
<td>FLX to a maximum of 80 mg/day transiently reduced drinks/day</td>
</tr>
<tr>
<td>Kranzler et al. (1995)</td>
<td>USA</td>
<td>2,P</td>
<td>101</td>
<td>12 weeks</td>
<td>FLX 60 mg/day was comparable to placebo on all drinking outcomes</td>
</tr>
<tr>
<td>Janiri et al. (1996)</td>
<td>Italy</td>
<td>2,P</td>
<td>50</td>
<td>2 months</td>
<td>FLX 20 mg/day increased proportion abstinent</td>
</tr>
<tr>
<td>Kabel and Petty (1996)</td>
<td>USA</td>
<td>2,P</td>
<td>28</td>
<td>12 weeks</td>
<td>FLX 60 mg/day was comparable to placebo on all drinking outcomes</td>
</tr>
</tbody>
</table>

*aStudy types: 3,P, 3-arm, parallel groups; 3,C, 3-group cross-over; 2,P, 2-arm, parallel groups.

*bTreatment period (for cross-over studies this is the duration of each treatment received).

*cOnly statistically significant differences reported.

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Table 2. Placebo-controlled trials of citalopram (CIT)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Study type</th>
<th>Total n</th>
<th>Study duration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naranjo et al. (1987)</td>
<td>Canada</td>
<td>3,C</td>
<td>39</td>
<td>4 weeks</td>
<td>CIT 40 mg/day increased abstinent days and decreased drinks/day</td>
</tr>
<tr>
<td>Naranjo et al. (1992)</td>
<td>Canada</td>
<td>2,C</td>
<td>16</td>
<td>1 week</td>
<td>CIT 40 mg/day increased abstinent days and decreased drinks/day</td>
</tr>
<tr>
<td>Balldin et al. (1994)</td>
<td>Sweden</td>
<td>2,C</td>
<td>30</td>
<td>5 weeks</td>
<td>CIT 40 mg/day increased drinks/day for lighter drinkers only</td>
</tr>
<tr>
<td>Naranjo et al. (1995)</td>
<td>Canada</td>
<td>2,P</td>
<td>62</td>
<td>12 weeks</td>
<td>CIT 40 mg/day decreased drinks/day for first week only</td>
</tr>
<tr>
<td>Tiihonen et al. (1996)</td>
<td>Finland</td>
<td>2,P</td>
<td>62</td>
<td>4 months</td>
<td>CIT 40 mg/day increased study retention and improved drinking outcomes (by informant report)</td>
</tr>
</tbody>
</table>

*aStudy types: 3,C, 3-group, cross-over; 2,C, 2-group cross-over; 2,P, 2-arm, parallel groups.

*bTreatment period (for cross-over studies this is the duration of each treatment received).

*cOnly statistically significant differences reported.
of drinks consumed. However, the effect of fluoxetine was significant only in the FHN patients, while acamprosate produced a significant reduction only in the FHN patients. Kraenzler et al. (1995) conducted a placebo-controlled trial of fluoxetine 60 mg/day in combination with coping skills psychotherapy in ambulatory alcoholics. These investigators found no overall advantage to the active drug on drinking outcomes. In a further analysis of the data, Kraenzler et al. (1996) found that, among the subgroup of patients with high levels of both pre-morbid vulnerability and alcohol-related problems, fluoxetine appeared to reduce the beneficial effects of coping skills training. Kabel and Petty (1996) showed no effect of fluoxetine 60 mg/day, compared with placebo, among severe alcoholics recruited from an alcoholism treatment programme at a Veterans Affairs Medical Center.

The other SSRI whose effects on alcohol consumption have been extensively examined is citalopram. Naranjo et al. (1987) first reported that citalopram 40 mg/day reduced the number of drinks consumed per day and increased the number of abstinent days in a sample of non-depressed, early-stage problem drinkers. In this study, citalopram 20 mg/day significantly decreased alcoholic drinks and increased abstinent days. However, when citalopram 40 mg/day was combined with a brief psychosocial intervention in a subsequent study, an advantage for the active drug over placebo on the number of daily alcoholic drinks was found only during the first week of treatment (Naranjo et al., 1995). In this 12-week treatment trial, the overall reduction in drinking was comparable for the citalopram and placebo groups (Naranjo et al., 1995). Balldin et al. (1994) compared the effects of citalopram 40 mg/day with placebo during a 5-week trial in a sample of heavy drinkers. Overall, there was no difference between treatment groups. However, when the data were reanalysed based on the pretreatment level of alcohol consumption, there was an advantage of the active medication on daily alcohol intake in the less heavy drinking subgroup. Tihonen et al. (1996) compared citalopram 40 mg with placebo in a 3-month study. These investigators found that study retention was significantly better in the active medication group, as was the collateral informant report of the patients' condition. There was also a trend for decreased alcohol consumption and γ-glutamyltransferase levels in the citalopram group. Although these investigators found no relationship between alcoholic subtype and medication response, it is unlikely that the small size of the study sample provided adequate statistical power to identify such an interaction.

One possible explanation for the variable findings in studies of SSRIs to reduce drinking behaviour is the diversity of subject samples. The majority of studies by Naranjo and colleagues were conducted in heavy drinkers who were not seeking treatment for alcoholism. These and some subsequent studies suggest that SSRIs are efficacious only in heavy drinkers or in certain subgroups of alcoholics. For example, Gerra et al. (1992) found an effect of fluoxetine only in alcoholics with a positive family history of alcoholism. In contrast, Kraenzler et al. (1996) found that high risk/severity alcoholics had poorer drinking outcomes when treated with fluoxetine, compared to placebo treatment. Balldin et al. (1994) found an effect of citalopram only among heavy drinkers at the lower end of the range of alcohol consumption in their patient sample. Recently, Pettinati et al. (2000) applied an approach similar to that employed by Kraenzler et al. (1996) to examine the interaction of alcoholic subtype with medication effects in a placebo-controlled trial of sertraline. These investigators found that low risk/severity alcoholics drank on fewer days and were more likely to be abstinent in the 12-week treatment trial if they received sertraline than if they were treated with placebo. In contrast, high risk/severity alcoholics showed better outcomes on these measures when treated with placebo, compared with sertraline, though these effects did not reach statistical significance. These findings suggest that prospective studies that aim to match alcoholic subtypes with SSRI treatment may define a role for such medications in the treatment of heavy drinking or mild alcohol dependence.

**Opioid antagonists.** Both naltrexone and naloxene are opioid antagonists with no intrinsic agonist properties. Of these medications, naltrexone has, by far, been studied more extensively. A summary of published studies of opioid antagonists for treatment of alcohol dependence is shown in Table 3.

Naltrexone was approved by the US FDA in 1985 for the treatment of opioid dependence and in 1994 for the treatment of alcohol dependence. Due to poor compliance with the medication, naltrexone maintenance treatment of opioid dependence has been generally unsuccessful in practice. A notable exception to this is its use in opioid-dependent professionals, where it can be combined with contingency contracting to enhance compliance (Stine and Kosten, 1997). Limited compliance with the medication may also limit naltrexone's effectiveness in alcoholism treatment.

In a study of 70 alcohol-dependent veterans, Volpicelli et al. (1992) found that naltrexone 50 mg/day was a useful adjunct to an intensive day treatment programme in the prevention of relapse to heavy drinking. Naltrexone significantly delayed the time to consumption of the first drink following detoxification, and hindered the progression of drinking from initial sampling to operationally defined relapse. Study subjects who drank while taking naltrexone reported less euphoria, which may indicate that naltrexone blocked the endogenous opioid system's contribution to alcohol's 'priming effect' (Volpicelli et al., 1995). In a laboratory study of non-problem drinkers, naltrexone was found to reduce the reinforcing (i.e. stimulant) effects and increase the unpleasant (i.e. sedative) properties of initial alcohol consumption (Swift et al., 1994).

These findings were replicated and extended by O'Malley et al. (1992), who examined the utility of naltrexone in combination with either supportive therapy or relapse prevention skills training. This study appears to be unique, in that it systematically examined combination therapy, i.e. both the pharmacologic and the psychotherapeutic components of treatment were varied. Interestingly, in addition to the main effect of the medication, naltrexone interacted differentially with the psychotherapeutic intervention. Naltrexone was more efficacious in preventing the initiation of drinking when paired with supportive therapy than when used in combination with coping skills training. On the other hand, once the subject sampled alcohol, naltrexone plus coping skills/relapse prevention training was better at preventing a full-blown relapse.
Table 3. Placebo-controlled trials of opioid antagonists for alcohol dependence

<table>
<thead>
<tr>
<th>Referencea</th>
<th>Study typeb</th>
<th>Total n</th>
<th>Study durationc</th>
<th>Commentd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volpicelli et al. (1992)</td>
<td>2,P</td>
<td>70</td>
<td>12</td>
<td>NTX 50 mg/day orally delayed time to first drink and reduced risk of heavy drinking</td>
</tr>
<tr>
<td>O’Malley et al. (1992)</td>
<td>2,P</td>
<td>101</td>
<td>12</td>
<td>NTX 50 mg/day orally resulted in fewer drinking days and heavy drinking days. NTX and ST particularly efficacious in preventing initiation of drinking; NTX and CBT particularly efficacious in preventing relapse to heavy drinking</td>
</tr>
<tr>
<td>Oslin et al. (1997)</td>
<td>2,P</td>
<td>44</td>
<td>12</td>
<td>NTX 50 mg/day orally reduced risk of relapse to heavy drinking</td>
</tr>
<tr>
<td>Volpicelli et al. (1997)</td>
<td>2,P</td>
<td>97</td>
<td>12</td>
<td>NTX 50 mg/day orally = PLA in ITT analysis. In highly compliant subjects, NTX prevented drinking and heavy drinking and reduced total drinks</td>
</tr>
<tr>
<td>Hersh et al. (1998)</td>
<td>2,P</td>
<td>64</td>
<td>8</td>
<td>NTX 50 mg/day orally = PLA on drinking and cocaine use in subjects with co-morbid alcohol and cocaine use disorders</td>
</tr>
<tr>
<td>Kranzler et al. (1998)</td>
<td>2,P</td>
<td>20</td>
<td>8</td>
<td>Sustained release NTX injection reduced frequency of heavy drinking</td>
</tr>
<tr>
<td>Anton et al. (1999)</td>
<td>2,P</td>
<td>131</td>
<td>12</td>
<td>NTX 50 mg/day orally reduced drinking frequency and drinks/drinking day and delayed relapse to heavy drinking</td>
</tr>
<tr>
<td>Kranzler et al. (2000)</td>
<td>3,P</td>
<td>183</td>
<td>12</td>
<td>NTX 50 mg/day orally associated with more adverse effects, poorer medication compliance and greater attrition from treatment than PLA; NTX = NEF = PLA on drinking outcomes</td>
</tr>
<tr>
<td>Mason et al. (1994)</td>
<td>3,P</td>
<td>21</td>
<td>12</td>
<td>NALM 40 mg/day orally superior to NALM 10 mg/day orally or PLA in prevention of relapse to heavy drinking</td>
</tr>
<tr>
<td>Mason et al. (1999)</td>
<td>3,P</td>
<td>105</td>
<td>12</td>
<td>NALM 20 mg/day orally = NALM 80 mg/day orally; together NALM-treated subjects less likely to relapse to heavy drinking</td>
</tr>
</tbody>
</table>

Notes:

a All studies were conducted in the US and were single-site studies.
b Study types: 2,P, 2-arm, parallel groups; 3,P, 3-arm, parallel groups.
c Treatment period only (weeks).
d Only statistically significant differences reported.

CBT, cognitive–behavioural therapy; ITT, intention-to-treat; NALM, nalmefene; NTX, naltrexone; PLA, placebo; ST, supportive therapy.

Analysis by these investigators of the reasons for relapse during this initial study period supports the notion that naltrexone differentially affects alcohol craving and urges, its reinforcing properties, the experience of intoxication, and the chances of continued drinking following a relapse (O’Malley et al., 1996a). These investigators also found that naltrexone may be most beneficial among alcoholics with higher levels of craving and poorer cognitive functioning (Jaffe et al., 1996).

During a post-treatment follow-up period, O’Malley et al. (1996b) found that the beneficial effects of naltrexone diminished gradually over time. Furthermore, abstinence during treatment strongly predicted whether subjects met criteria for alcohol abuse or dependence at a 6-month, post-treatment follow-up visit. These findings suggest that patients who are unable to remain abstinent during acute treatment might benefit from naltrexone treatment for longer than the 12-week duration of treatment in these initial studies.

Subsequently, Oslin et al. (1997), in a study of older veterans, found that naltrexone was superior to placebo in reducing the risk of relapse. However, Volpicelli et al. (1997) found no overall advantage to naltrexone over placebo in the treatment of alcohol dependence. These investigators found that compliance with naltrexone treatment was variable, and that only among highly-compliant subjects was the active medication significantly better than placebo with respect to the percentage of patients who drank, the percentage of patients who relapsed, and total drinks consumed. These findings, together with the evidence of a major effect of compliance in studies of disulfiram, underscore the need for a better understanding of factors that underlie medication compliance among alcoholics. Furthermore, well-informed efforts to enhance medication compliance are essential, if medication therapy is to be of value in the routine clinical care provided to alcoholics.

More recently, Hersh et al. (1998) failed to show an advantage for naltrexone over placebo on measures of substance use or craving among patients with co-morbid alcohol and cocaine use disorders. Kranzler et al. (1998) found that alcoholics treated with a sustained-release formulation of naltrexone had detectable plasma concentrations of the drug for more than 30 days following injection. Furthermore, the active formulation was superior to placebo in reducing the frequency of heavy drinking in these patients. However, in another study by Kranzler et al. (2000) comparing oral naltrexone with the serotonergic antidepressant nefazodone, neither active medication was superior to placebo on measures of alcohol consumption. In fact, in that study, naltrexone treatment resulted in significantly more adverse effects, poorer medication compliance, and a greater rate of early discontinuation of treatment than placebo. Despite these negative results, Anton et al. (1999) found that, when combined with cognitive–behavioural psychotherapy, naltrexone was superior to placebo on a variety of measures: percentage of days abstinent, number of drinks per drinking day, and time to relapse to heavy drinking during the 12-week treatment trial. The observed effects were, however, generally small in magnitude. Furthermore, time to the first alcoholic drink and the likelihood of abstinence throughout the trial did not differ significantly by group, nor did objective measures of heavy drinking (i.e. γ-glutamyltransferase and carbohydrate-deficient transferrin).

A pilot study by Mason et al. (1994) showed an advantage for the opioid antagonist nalmefene 40 mg/day over nalmefene 10 mg/day or placebo in the prevention of relapse to heavy drinking in a small sample of alcohol-dependent subjects. Subsequently, these investigators (Mason et al., 1999) compared nalmefene (20 mg/day or 80 mg/day) with placebo treatment in a larger sample of alcohol-dependent subjects.
They found no difference between the two active treatment groups, though when combined, nalmefene-treated subjects were significantly less likely to relapse to heavy drinking than were placebo-treated subjects. Outcomes on other, related measures of risk of heavy drinking were consistent with this finding. However, although the study was designed as a three-arm trial, unfortunately, the data are not presented separately for the nalmefene groups, so that it is not possible to assess the relative effects of the two dosages vis-à-vis one another or in relation to placebo.

In summary, naltrexone appears to produce a modest effect on drinking behaviour among alcoholics. The small effect may explain why significant medication effects have not been observed in some published studies. Furthermore, the number of patients treated in double-blind studies of the drug has been comparatively few, and longer-term outcome studies are lacking. A number of studies are currently underway to further evaluate the range of patient groups for which naltrexone is efficacious, its optimal duration of use and the most appropriate psychosocial treatments to be used in combination with the medication. In addition, based upon promising initial results in the treatment of alcoholism obtained with the opioid antagonist nalmefene (Mason et al., 1994, 1999), further research with that medication is underway. Sinclair (1998) has argued that for opioid antagonists to be efficacious in alcoholism treatment, they must be administered to individuals who are actively drinking, rather than in the context of relapse prevention. Additional empirical evaluation of this hypothesis is warranted.

Acamprosate (calcium acetylhomotaurinate). This amino acid derivative is another promising therapeutic agent. It is approved for use in a number of European countries and a multicentre trial was recently completed in the USA. Table 4 summarizes placebo-controlled trials of acamprosate for alcohol dependence. A detailed summary of acamprosate studies was recently compiled by Mason and Ownby (2000).

Acamprosate affects both γ-aminobutyric acid (GABA) and excitatory amino acid (i.e. glutamate) neurotransmission. Based upon its profile of clinical effects, Littleton (1995, 1996) has argued that acamprosate works by decreasing craving related to conditioned alcohol withdrawal. While ‘craving’ has long been criticized as a non-specific, overused term (Kozlowski and Wilkinson, 1987), Littleton (1995, 1996) has elaborated a theory of the phenomenon that is based on empirical findings from both the laboratory and the clinic.

Initially evaluated in a single-centre trial in France, acamprosate was shown over a 3-month treatment period to be twice as effective as placebo in reducing the rate at which alcoholics returned to drinking (Lhuinêtre et al., 1985). Subsequently, a 3-month, multicentre study in France (Lhuinêtre et al., 1990) showed that treatment with acamprosate produced a greater reduction in γ-glutamyltransferase level than placebo treatment; however, data on drinking behaviour per se were not reported. A large, multicentre study in France (Paille et al., 1995) showed a dose–response relationship for the medication over 12 months of active treatment, followed by 6 months of single-blind placebo. Overall, in this study, acamprosate was associated with significantly better rates of clinic attendance and more abstinent days, with the high-dose acamprosate showing the best outcomes, the placebo group the poorest outcomes, and the low-dose acamprosate group intermediate on these measures.

Three placebo-controlled studies of acamprosate for alcohol dependence have also been conducted in Belgium. Roussaux et al. (1996) found no difference in drinking outcomes or biochemical measures in a 3-month, placebo-controlled trial with 127 alcoholics recruited from an in-patient setting. However, acamprosate was shown to enhance treatment retention and the maintenance of abstinence among alcoholics in a 6-month study by Pelc et al. (1996). In a second study, Pelc et al. (1997) compared two dosages of acamprosate (1332 mg/day or 1998 mg/day) to placebo in a 90-day multicentre study in 188 alcohol-dependent patients. Both acamprosate-treated groups had significantly better outcomes than placebo-treated patients on abstinent days, proportion of patients achieving abstinence for the entire trial, time to first alcoholic drink, and liver enzyme levels. Although there were some trends for the higher dosage of acamprosate to be superior to the lower dosage of that medication, these did not reach statistical significance.

In a multicentre study in Belgium, The Netherlands, and Luxembourg, alcoholics were treated with either acamprosate or placebo for 12 months and were then followed up for an additional 6 months (Geerlings et al., 1997). Acamprosate-treated patients were significantly more likely to complete treatment and to remain abstinent during the treatment period than were placebo-treated patients. The beneficial effects, although evident at follow-up, did not reach statistical significance during the post-treatment period.

In a multicentre study in Austria (Whitworth et al., 1996), alcoholic patients were treated with acamprosate or placebo for 12 months and then followed up for an additional 12 months. During treatment, acamprosate-treated patients were significantly less likely to return to drinking, an effect that persisted during the post-treatment follow-up. Sass et al. (1996) conducted a multicentre study in Germany, which also included 12-month treatment and post-treatment follow-up periods. These investigators found that acamprosate was superior to placebo with respect to treatment retention. Patients receiving the active medication were also more likely to remain abstinent during both the active treatment and follow-up periods.

Poldrugo (1997) reported the results of a multicentre study of acamprosate in Italy, in which patients were randomly assigned to receive either acamprosate or placebo for 6 months, and were followed for 6 months after treatment was discontinued. Acamprosate significantly enhanced treatment retention, and the percentage of acamprosate-treated patients that was continuously abstinent during active treatment was nearly double that of the placebo group. In this study, significantly more patients in the acamprosate group were continuously abstinent during the post-treatment follow-up period as well. Another multicentre study conducted in Italy was recently reported by Tempesta et al. (2000). These investigators treated 310 patients with either acamprosate or placebo for 6 months, followed by a 3-month post-treatment follow-up period. Acamprosate-treated patients relapsed to drinking significantly later in the trial than did placebo patients. The active treatment group was also more likely to maintain continuous abstinence, though this effect was not statistically significant during the follow-up period. Cumulative days of abstinence also favoured the acamprosate group, an effect that persisted during the post-treatment period. Among patients
who drank during treatment, treatment with acamprosate was associated with fewer drinking episodes and a lower mean quantity of alcohol consumption than placebo.

Recently, Besson et al. (1998) compared acamprosate with placebo in a 12-month, multicentre study in Switzerland. Although patients were randomly assigned to receive acamprosate or placebo, stratification was used for patients who were taking disulfiram concomitantly, since the investigators felt that random assignment on this variable was not feasible. Acamprosate was shown to be superior to placebo on measures of total abstinence and on cumulative abstinence days. Interestingly, although only exploratory given the study design, the group receiving both acamprosate and disulfiram showed a significantly greater percentage of abstinence days than any of the other three groups. One explanation offered by the investigators for the marked effect of combination therapy was...
that acamprosate reduced the need to drink, whereas disulfiram enhanced the cognitive effects of self-control over drinking. Additional studies of this combination therapy appear warranted.

Finally, a recent publication describes the results of a multicentre comparison of acamprosate with placebo in 581 alcoholics conducted in the UK (Chick et al., 2000). This study included a 6-month active treatment period, followed by a 1-month post-treatment follow-up period. Unlike other multicentre studies of acamprosate, this protocol allowed patients to be randomly assigned to medication group for as long as 5 weeks after the initiation of detoxification. Consequently, nearly a third of patients had relapsed to drinking by the time of randomization. This may explain the failure to find any beneficial effects on drinking behaviour as a function of medication condition. Transient beneficial effects of acamprosate were observed on desire to drink and on anxiety symptom ratings. Subgroup analysis failed to show a differential effect of the medication based on the typology proposed by Lesch and Walter (1996) as a useful predictor of treatment response.

Together, studies in more than 3000 patients provide generally consistent evidence of the efficacy of acamprosate in alcoholism rehabilitation. Whereas studies of acamprosate have not used standardized psychotherapeutic approaches, the consistent, though modest, advantage of the active medication can be expected when the medication is used in routine clinical settings. However, as greater efforts are made to use specific psychosocial therapies as a platform for pharmacotherapy, greater medication effects may emerge. Furthermore, since acamprosate has a benign side-effect profile, with gastrointestinal symptoms being most prominent, it appears to have a prominent role to play in the treatment of alcohol dependence. However, further studies are needed to determine whether subgroups of alcoholics may be more responsive to treatment with acamprosate (cf. Lesch and Walter, 1996; Chick et al., 2000). This is underscored by the findings of Gerra et al. (1992), who found that acamprosate was efficacious in reducing the number of drinks consumed only in patients with no family history of alcoholism.

OPPORTUNITIES FOR RESEARCH

Two recent, critical reviews evaluated the literature on the pharmacotherapy of alcoholism (Moncrieff and Drummond, 1997; Garbutt et al., 1999). These reviews underscored the need for methodological rigor in the conduct of research in this field. Other authors (Kranzler et al., 1997) have provided guidelines for resolving some of the methodological complexities that are inherent in treatment trials with alcoholics. In addition, Moncrieff and Drummond (1998) reviewed the most highly cited controlled clinical trials (including, but not limited to, pharmacotherapy studies). These authors developed a reliable scoring system, with which they evaluated the methodological quality of 25 trials. In contrast to these reviews, the focus of the present article is on gaps in knowledge and potential strategies to address them. As such, it depends on the author’s subjective appraisal of the importance of the issues that exist and the articles to be considered, rather than specific criteria for the identification of studies for review and for rating the quality of the research findings.

Despite the fact that a number of medications have been shown to be of value in the treatment of alcohol dependence, pharmacotherapy has not yet had a demonstrably large effect on alcoholism treatment. This is due, in part, to a widely held view among the public and large segments of the alcoholism treatment community that alcohol dependence is not a medical disorder. From this follows the belief that the disorder is not amenable to pharmacological treatment, nor is it desirable to complicate the process of recovery by the introduction of medication. Moreover, the pharmaceutical industry has been slow in developing medications to treat alcoholism, due to its scepticism over the potential profitability of such medications. These factors have seriously limited research activity in this area, despite a systematic effort by the US National Institute of Alcohol Abuse and Alcoholism (NIAAA) to develop medications for relapse prevention.

It has been argued that a consistent foundation of psychosocial treatment is necessary for the evaluation of medication effects in substance abuse trials (Carroll, 1997). The main reasoning behind this argument is that manual-guided psychotherapy reduces error variance, so that medication effects are more readily observable. However, virtually all research on the pharmacotherapy of alcoholism, while increasingly attentive to the need for systematic attention to the psychosocial treatment provided to study patients, has focused on main effects of medications. This is so, despite evidence that the nature and intensity of psychosocial treatment can directly affect the efficacy of medications in the treatment of substance abuse (O’Malley et al., 1992; McLellan et al., 1993). Project Combine, a large multicentre study supported by NIAAA, can be expected to provide information on the effects of acamprosate and naltrexone in alcohol dependence, using more or less intensive therapies. However, there are numerous other combinations of medication and psychotherapy, the interactive effects of which are of considerable theoretical and clinical importance, which warrant intensive study.

It is clear that the development of clinically useful pharmacological treatments will require large-scale clinical trials, which provide for statistical power adequate to draw valid conclusions on the efficacy of medications. This is particularly true in the evaluation of combination treatments, both those involving multiple medications and those examining the interaction of medications with well-defined psychotherapeutic treatments. Such large-scale studies also hold promise for the elucidation of patient features that may predict response to individual and combined treatments.

However, small-scale, exploratory studies remain important for the development of new candidate medications or formulations. Although there is consistent evidence that acamprosate is efficacious in reducing the number of days drinking, its effects are modest. In contrast, while the effects of naltrexone in some studies have been robust, evidence of its efficacy has been less consistent. Consequently, there is a pressing need to identify medications with unique modes of action, as well as those with greater potency than existing medications in producing effects that may be of value in alcoholism treatment. Once such medications are identified, their potential must be demonstrated in preliminary clinical trials, before they are subjected to large-scale investigation. For example, evidence that disulfiram must undergo bio-transformation to produce aversive effects when alcohol is...
consumed (Yourick and Faiman, 1991) suggests that DETC-MeSO, the active metabolite of disulfiram (Hart and Faiman, 1992), may be more efficacious as a deterrent than the parent compound. Since the safety of this metabolite has been demonstrated in preclinical toxicologic studies, it is now possible to evaluate its effects in humans. Obviously, however, evidence of its safety and efficacy in small-scale clinical studies is needed before large-scale evaluation of DETC-MeSO is warranted.

Given the likely advantage of combining medication and psychosocial treatments (O’Malley et al., 1992; McLellan et al., 1993), attention to the factors that influence the integration of these approaches is also important. Combining medications with self-help group participation may represent a particular challenge (Meza and Kranzler, 1996). Abstinence-oriented groups such as Alcoholics Anonymous often see deterrent agents such as disulfiram as supportive of their goal of total abstinence. As a consequence, group members may be willing to work with physicians around the issue of proper dosage, compliance, and early detection of side-effects. The use of medications to reduce the risk of relapse through direct effects on craving or drinking behaviour may also be potentially additive or synergistic to self-help efforts. The factors that influence the acceptability of medication therapy to both self-help groups and the alcohol treatment community should, therefore, be an important focus of research.

It is likely that efforts to identify factors that predict poor compliance and appropriate efforts to remedy these will be of value generally in the pharmacotherapy of alcoholism. In addition to efforts that focus on medication compliance, research is needed to identify other factors that influence the efficacy and effectiveness of medications with demonstrated utility in relapse prevention. Specifically, it is unclear for which patient groups acamprosate and naltrexone are most useful and which dosage schedules and concomitant psychosocial treatments are optimal. Although the literature on the selective serotonin reuptake inhibitors has not been consistently positive, these medications may have a role in the treatment of some heavy drinkers or alcoholics. Clarification of whether these medications are efficacious in subgroups of heavy drinkers or alcoholics may help to resolve the discrepant findings in the literature, yielding both theoretical and clinical advantages. Furthermore, little is known about the safety and efficacy of combining medications for relapse prevention in alcoholics. In addition, these issues must be examined in women, in different ethnic/racial groups and in adolescent and geriatric samples. Data on pharmacotherapy for relapse prevention in these groups are virtually non-existent (Gorelick, 1993).

Optimal duration of therapy is also not well defined. Most trials are of comparatively short duration, in order to demonstrate initial efficacy before the expense of a long-term trial is assumed; however, alcohol dependence is clearly a chronic, relapsing illness. Given evidence of the efficacy of some medications over shorter periods of time, longer studies of these agents are needed. Ultimately, it will be necessary to determine whether medication treatment substantially alters the natural history of alcohol dependence over the lifetime of the individual.

Medication development has focused on individuals with moderate-to-severe alcohol dependence, in an effort to prevent relapse. Little is known concerning the efficacy of medications to reduce drinking in individuals who drink heavily, but who are not alcohol dependent, or who meet criteria for alcohol dependence but have not experienced substantial problems related to their drinking. In short, the role of pharmacotherapy in secondary prevention efforts remains to be defined.

Alcoholics with co-morbid drug use disorders are often excluded from alcoholism treatment trials. This is ironic, given the high degree of overlap in the prevalence of alcohol and drug use disorders (Kessler et al., 1997). In view of the pressing clinical need represented by co-morbid drug use disorders, a sustained effort is needed to identify medications, alone and in combination, that are efficacious and effective in such dually dependent groups. In addition, optimal combinations of medications and psychosocial treatments are needed for this population.

The ultimate goal of these efforts to develop medications for the treatment of alcohol dependence is a series of algorithms for characterization and pharmacological treatment of heavy drinkers/alcoholics, including a variety of medications combined with specific psychosocial treatments. Guidelines for initiation, maintenance and discontinuation of treatment and for managing poor or partial response are necessary. Consideration of combination therapy should include combination of medication and psychosocial treatment, as well as combination pharmacotherapy. Ultimately, such information will be useful in the elaboration of algorithms for the pharmacological treatment of heavy drinking and alcohol dependence, which incorporate the characteristics of the patient, as well as the medications and psychosocial treatments that have been shown to be efficacious. Although a general framework for such an effort currently exists, much detail remains to be added before these algorithms will be of widespread clinical value.

Acknowledgements — The preparation of this manuscript was supported in part by US National Institutes of Health Grants RO1-AA11062, K02-AA00239, P50-AA03510 and M01-RR06192. The manuscript is a revised version of a lecture delivered at the Ninth Congress of the International Society for Biomedical Research in Alcoholism, Copenhagen, Denmark, June, 1998. Ola Blomqvist, MD, PhD, Vania Modesto-Lowe, MD, and Morris Faiman, PhD provided helpful comments on the manuscript.

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Note added in proof

Recently, Johnson (Johnson et al., 2000) found a dose-related effect of ondansetron, a selective 5-HT3 antagonist, on drinking behaviour in early-onset alcoholics (i.e. those with onset at age 25 years or younger). At a dosage of 4 μg/kg twice daily, ondansetron was superior to placebo on the proportion of days abstinent (~40% greater than for placebo) and on the intensity of alcohol intake (~40% lower in the active medication group). Levels of carbohydrate deficient transferrin were also significantly lower in the ondansetron-treated group. In contrast, among late-onset alcoholics (i.e. those with onset after the age of 25), the effects of ondansetron on drinking behaviour were comparable to those of placebo. This provides further support for a clinically important interaction between serotonergic medications and alcoholic subtype.