Acamprosate: a new tool in the battle against alcohol dependence

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Abstract: Acamprosate, a medication that has been used in Europe for years, is the newest drug to be approved by the US Federal Drug Administration for the treatment of alcohol dependence. It has been shown to assist in the maintenance of abstinence in recently detoxified alcohol-dependent individuals. The following review delineates the proposed mechanism of action and pharmacokinetics of the drug. Findings of clinical trials are outlined and topics such as cost effectiveness, comparison with other medications used for the treatment of alcohol dependences as well as combination pharmacotherapy are discussed. In combination with psychosocial treatment, acamprosate is a promising tool for the maintenance of abstinence in alcohol-dependent patients after alcohol withdrawal. This review also illustrates the continued need to search for more effective treatments, as the overall effectiveness of our currently available pharmacotherapies remains limited in the long-term maintenance of recovery from alcohol dependence.

Keywords: acamprosate, alcohol, alcohol dependence, abstinence

Introduction

The effects of alcoholism on the individual as well as the surrounding community constitute a major public health issue. The National Institute on Alcohol Abuse and Alcoholism's (NIAAA) 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions found that the prevalence of alcohol abuse and dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, APA 1994) in 2001–2002 were 4.65% and 3.81% respectively (Grant et al 2004). It was estimated that in 2000 there were 63 718 deaths attributable to harmful drinking, accounting for 4% of all deaths among men and 1.5% among women in the US (Rivara et al 2004). The price of the health care resulting from alcohol abuse in this country is estimated at more than US$26 billion per year (US Department of Health and Human Services 2000). Previous authors have found that alcoholism and resulting medical comorbidities result in more frequent hospitalizations and longer hospitalization stays compared with those without substance dependence disorders (Walker et al 1994). In addition to direct health consequences to the alcoholic, this disease is associated with escalated risk-taking behaviors that can lead to extensive indirect harm. For instance, the 2001 National Household Survey on Drug Abuse found that greater than 1 in 10 Americans aged 12 or older drove under the influence of alcohol at least once in the 12 months prior to the interview (Substance Abuse and Mental Health Services Administration 2002). In addition to alcohol-related motor vehicle crashes, society is affected by crime, fire, destruction, and social welfare administration. The productivity effects due to alcohol-related illness, premature deaths, and alcohol-related crimes have been estimated to be greater than $134 million per year (US Department of Health and Human Services 2000).

The key components in the treatment of an alcohol-dependent individual include safe withdrawal from alcohol (possibly requiring medicated detoxification),

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maintaining abstinence after withdrawal, and reducing craving and risk for relapse. Maintaining abstinence in recently detoxified alcoholic individuals has proven to be a challenging task. It has been estimated that approximately 50% of alcoholic patients relapse within three months after successful detoxification (Whitworth et al 1996). Psychosocial support has been the cornerstone in helping individuals maintain abstinence, and pharmacotherapy is proving to be a valuable addition to this. Prior to the introduction of acamprosate to the US market in 2004, only two medications had the US Food and Drug Administration (FDA) approval for the treatment of alcohol dependence.

Disulfiram

The first, disulfiram, is an alcohol-deterrent drug. It interrupts the metabolism of alcohol by inhibiting aldehyde dehydrogenase, thereby blocking the breakdown of acetaldehyde to acetate. When alcohol is consumed in conjuction with disulfiram, levels of acetaldehyde increase as further metabolism of alcohol is blocked. This increase in acetaldehyde levels results in nausea, vomiting, and changes in blood pressure. The patient's fear of this disulfiram-alcohol reaction serves as a strong reinforcement for abstinence (Shuckit and Tapert 2004). Disulfiram has been used as a treatment for alcohol dependence for over 50 years.

Naltrexone

The second drug, naltrexone, is a pure opioid antagonist. While its mechanism of action is not fully understood, its competive antagonism at the opioid receptor is hypothesized to block the release of dopamine induced by the consumption of alcohol. By reducing the rewarding effects of alcohol, it is thought to reduce craving to drink and loss of control (Sinclair 2001). Naltrexone has been approved in the US since 1994 for the treatment of alcohol dependence.

Acamprosate

Acamprosate is the newest drug to receive FDA approval for the treatment of alcohol dependence. It has been used in Europe for several years and therefore has an abundant body of literature supporting its efficacy. It has been shown to assist in the maintenance of abstinence and decrease negative symptoms associated with the acute post-withdrawal period in recently detoxified alcohol-dependent individuals (Wilde and Wagstaff 1997; Forest Pharmaceuticals, Inc. 2005). The mechanism by which acamprosate helps to maintain abstinence is not yet fully elucidated. It does not interfere with or substitute for the reinforcing effects of alcohol (Littleton and Zieglgansberger 2003). Unlike disulfiram, it does not produce an aversion to alcohol. It is neither a sedative nor an anxiolytic agent, and does not have anti-depressant effects (Anonymous 2005). It is not addictive and does not provide reinforcing effects of itself (Littleton 1995).

Mechanism of action

While several hypotheses on the mechanisms of action of acamprosate have been described, the exact mechanism of action is still not fully understood. The structure of acamprosate is similar to that of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. It has been found to be active at the N-methyl-D-aspartate (NMDA) receptor (Knopfel et al 1987). A likely mechanism of action is the inhibition of neuronal hyperexcitability mediated by antagonism or modulation of pre- and post-synaptic activity of excitatory amino acids, such as glutamate, particularly via modulation of activity at the NMDA receptor (Scott et al 2005)

Chronic alcohol consumption is believed to negatively impact the equilibrium between the excitatory glutamatergic neurotransmitter system and the inhibitory GABAergic neurotransmitter system. During alcohol intoxication, the GABAergic system is hyperactive, while it is decreased in activity during withdrawal (Ueno et al 2001). During withdrawal, the excitatory neurotransmitter systems, including glutamate, are hyperactive. By functioning to increase GABAergic activity and/or inhibiting glutamatergic activity via modulation of the NMDA receptor, acamprosate may ameliorate alcohol withdrawal symptomotology (Dahchour and De Witte 2000; Boeijinga et al 2004).

Pharmacokinetics

The pharmacokinetics of acamprosate have been investigated in healthy volunteers, in abstinent alcohol-dependent adults and in individuals with renal or hepatic insufficiency (Forest Pharmaceuticals, Inc. 2005). The studies of pharmacokinetics performed by the manufacturer were then reviewed by Saivin et al (1998) and Durbin et al (1995).

Acamprosate is poorly absorbed after oral administration, with an average bioavailability of only 11%. Time to reach steady state occurs within 5 days of dosing.

Steady-state peak plasma concentrations (C_{max}) after standard dosing of acamprosate (two 333 mg tablets 3 times daily) average 350 ng/mL and are reached within 3–8 hours following dosing (Forest Pharmaceuticals, Inc. 2005). While co-administration of acamprosate with food decreases its bioavailability, it is not clinically significant, so that the medication can be taken with or without food.

The volume of distribution of acamprosate following intravenous distribution is estimated to be approximately 1 L/kg (72–109L) (Forest Pharmaceuticals, Inc. 2005). Animal studies indicate that acamprosate crosses the blood-brain barrier (Durbin et al 1995).

Acamprosate does not undergo metabolism. After oral dosing of two 333 mg tablets of acamprosate, the average terminal half-life at steady state ranges between about 20 and 33 hours. The drug is primarily excreted unchanged through the kidneys (Forest Pharmaceuticals, Inc. 2005).

As the drug has little potential for drug-drug interactions, acamprosate appears to be safe in individuals taking multiple medications. In vitro studies indicate that acamprosate does not induce cytochrome P450 (CYP) 1A2 or 3A4, nor does it inhibit CYP 1A2, 2C9, 2C19, 2D6, 2E1, or 3A4 (Forest Pharmaceuticals, Inc. 2005). There are no pharmacokinetic changes in either drug when acamprosate is given with alcohol, diazepam or disulfiram.

When acamprosate is given with naltrexone there is a 33% increase in the C_{max} for acamprosate; however, this is not considered clinically relevant and dosage adjustment is not recommended (Forest Pharmaceuticals, Inc. 2005). Acamprosate does not appear to have any effects on the pharmokinetics of naltrexone.

Special patient populations

No significant differences in pharmacokinetics have been identified based on sex (Saivin et al 1998). As participants in clinical trials were between the ages of 18 and 65 years, the pharmacokinetics of acamprosate have not been evaluated in pediatric or geriatric populations.

As acamprosate is primarily eliminated via the kidneys, dose adjustment is necessary for individuals with moderate renal impairment (creatinine clearance of 30–50 mL/min). Peak plasma concentrations of acamprosate after a standard dose (666 mg) in individuals with moderate or severe renal impairment were approximately 2-fold and 4-fold higher, respectively, compared with healthy subjects (Forest Pharmaceuticals, Inc 2005). In addition, the half-lives were 1.8-fold and 2.6-fold longer, respectively, compared with healthy subjects. Individuals with severe renal impairment (creatinine clearance <30 mL/min) should not be given acamprosate.

As acamprosate is not metabolized by the liver, the pharmacokinetics of the drug are not altered in individuals with mild to moderate hepatic impairment.

Tolerability

In all of the clinical trials to date, acamprosate has been found to be well tolerated. The drug produces few side-effects, with diarrhea being the most common complaint. Occasionally, headaches, dizziness, and pruritis have been described (Forest Pharmaceuticals, Inc. 2005). Bouza et al (2004) performed a meta-analysis from 10 studies with available data on tolerability and found that gastrointestinal adverse effects were significantly more common in the acamprosate group compared with placebo, but no statistical differences were found between the groups in terms of premature withdrawals from treatment due to adverse events.

Dosage and administration

In the US, as well as Europe, acamprosate is indicated for maintance of abstinence from alcohol in alcohol-dependent patients who are abstinent at treatment initiation. Its efficacy has been demonstrated in the setting of a comprehensive management program that includes psychosocial support. The recommended dosage of acamprosate is two 333 mg tablets (each dose totaling 666 mg) 3 times daily, without regard to food. It should be initiated as soon as possible after alcohol withdrawal. Acamprosate should be initiated during abstinence and should be maintained if the patient relapses (Forest Pharmaceuticals, Inc. 2005).

Dosage in renal impairment

In individuals with moderate renal impairment (creatinine clearance of 30–50 mL/min) the starting dose should be reduced to one 333 mg tablet 3 times daily. Acamprosate should not be given to individuals with severe renal impairment (creatinine clearance of $\leq$30 mL/min) (Forest Pharmaceuticals, Inc. 2005).

Clinical efficacy

Preclinical work with animals has shown that acamprosate decreases voluntary intake of alcohol and preference for alcohol over water (Boismare et al 1984; Heyser et al 1988; Gewiss et al 1991; Spanagel et al 1996; Holter et al 1997; Czachowski et al 2001; Olive et al 2002). In addition, Bachteler et al (2005) found that acamprosate significantly

and selectively reduced alcohol-seeking behavior in rats when these animals were re-exposed to environmental cues predictive of alcohol availability.

The safety and efficacy of acamprosate in humans have been evaluated in 20 controlled clinical trials conducted in 11 European countries. Three of these trials were identified as key registration studies by the FDA. These trials are briefly described in Table 1. In total, the three studies enrolled 1001 alcohol-dependent outpatients who were randomized to double-blind treatment with acamprosate or placebo. In all three studies, psychosocial support was provided in addition to pharmacotherapy (acamprosate or placebo).

The results of the studies have generally been consistent in showing a significant improvement in the rate of total abstinence and in cumulative abstinence duration with acamprosate compared with placebo in association with a variety of different psychosocial interventions. A beneficial effect on time to first drink was also frequently observed.

One large study failed to detect a difference between acamprosate and placebo (Chick et al 2000). This was a 6-month randomized trial undertaken in 20 centers throughout the UK, including 581 participants. Of note, medication was not started until an average of 24 days after the start of detoxification and 32% of patients had already relapsed by this time. Overall compliance was poor and there was a high drop out rate. In this study, no difference was found in abstinent days achieved or in the percentage of those with complete abstinence at 6 months. Also, no effect on consumption was observed. The delay in initiating medication, the high rate of relapse when the medication was started, and the high drop out rate in comparison to other published trials may very well have contributed to the lack of a treatment effect in this study.

Mann et al (2004) performed a large meta-analysis of randomized, placebo-controlled trials of acamprosate. The meta-analysis included 17 studies, with a total of 4087 individuals. This meta-analysis revealed that continuous abstinence rates at 6 months were significantly higher in the acamprosate-treated subjects. At 12 months, the overall pooled difference between acamprosate and placebo for continued abstinence was 13.3%. The effect size in abstinent rates at 3, 6, and 12 months were 1.33%, 1.50%, and 1.95% respectively.

Table 1 Key studies leading to FDA approval of acamprosate

Study	Design	Study subjects	Main findings
Pelc et al 1997	90-day, double-blind, placebo-controlled trial. Participants randomly assigned to 1 of 3 groups: acamprosate 1998 mg/day, 1332 mg/day, or placebo. Study medication initiated during 14-day inpatient detoxification program.	188 alcohol-dependent males and females (18–65 years, weighing >60 kg). Subjects were included after a 14-day inpatient detoxification program, during which the study medication was started.	Acamprosate superior to placebo ($p<0.001$) in maintaining abstinence, prolonging time to first drink. Trend towards a better effect at higher dosage. Acamprosate appeared to be extremely safe.
Sass et al 1996	48-week, double-blind, placebo-controlled trial. Participants randomized to acamprosate were dosed by weight (weight >60 kg received 1998 mg/day; weight <60 kg received 1332 mg/day). Study medication initiated after 14- to 28-day inpatient detoxification period.	272 newly detoxified alcohol-dependent patients from 12 psychiatric outpatient clinics in Germany. Subjects had to be abstinent from alcohol for a minimum of 14 days and maximum of 28 days, and be free of withdrawal symptoms.	Those receiving acamprosate showed higher continuous abstinence rate ($p=0.05$) and longer mean abstinence duration ($p<0.001$). Few side-effects with acamprosate were recorded.
Paille et al 1995	52-week, double-blind, placebo-controlled trial. Participants randomly assigned to 1 of 3 groups: acamprosate 1998 mg/day, 1332 mg/day, or placebo. Study medication initiated after 7- to 28-day detoxification period.	538 alcohol-dependent males and females (18–65 years). Subjects had to have undergone detoxification, be abstinent at the time of enrollment, and be participating in specialized outpatient treatment for alcoholism. These subjects were predominantly male and tended to have a stable lifestyle in terms of family and occupation.	Those on high dose acamprosate were more likely to remain abstinent than those on low dose or placebo (and those on low dose acamprosate were more likely to remain abstinent than placebo). Statistical difference at 6 months ($p<0.02$) but not at 12 months ($p=0.096$)

Another meta-analysis was conducted to evaluate the efficacies of disulfiram, the opioid antagonists naltrexone and nalmefene, acamprosate, various serotonergic agents (including selective serotonin reuptake inhibitors), and lithium for the treatment of alcohol dependence (Garbutt et al 1999). Of 375 articles evaluated, 41 studies and 11 follow up or subgroup studies were included. Naltrexone reduced the risk of relapse to heavy drinking and the frequency of drinking compared to placebo, but did not substantially enhance abstinence (the avoidance of any alcohol consumption). Acamprosate reduced drinking frequency, but its effects on enhancing abstinence or reducing time to first drink were less clear. Controlled studies of disulfiram were mixed; it did reduce drinking frequency but there was minimal evidence that it improved continuous abstinence rates. Most studies of the serotonergic agents were confounded by high rates of comorbid mood disorders. Lithium lacked efficacy in the treatment of alcohol dependence.

Cost effectiveness

To date, there have been 5 analyses of the cost-effectiveness of adding acamprosate to pre-existing alcohol rehabilitation regimens. All 5 studies consistently found that adding acamprosate to rehabilitation strategies reduces the overall total costs of treatment (Poldrugo et al 2005). In particular, Palmer et al (2000) performed a cost-effectiveness analysis of alcohol abstinence with either standard counseling therapy or standard therapy plus 48 weeks of adjunctive acamprosate in detoxified alcoholic patients. Important complications of alcoholism were considered in the analysis including relapse, alcohol-related liver disease, acute and chronic pancreatitis, acute and chronic gastritis, oropharyngeal carcinoma, esophageal carcinoma, alcoholic cardiomyopathy, alcohol-related peripheral neuropathy, alcoholic psychosis, accidental death, and suicide. The analysis was done on a male cohort with an average age of 41 years, 80% with fatty liver, 15% with cirrhosis, 22% with chronic pancreatitis, and 1% with alcoholic cardiomyopathy at baseline. The authors found that life expectancy was increased in the acamprosate group compared with those who did not take the drug (15.9 compared with 14.7 years) and average total lifetime costs per patient were lower in those on acamprosate therapy.

Rychlik et al (2003) conducted an open, prospective, cohort study in Germany to evaluate the costs of treating alcohol dependence under real-world conditions over one year. Of 814 recently detoxified alcohol-dependent patients, 540 were treated with adjuvant acamprosate in addition to psychosocial rehabilitation support (274 received psychosocial rehabilitation support but no pharmacotherapy). Thirty-three percent of acamprosate patients remained abstinent over the study compared with only 21.1% in the standard cohort. The mean total costs per patient treated with acamprosate were significantly less than those in the standard cohort (€1631.49 and €2068.83 respectively). In this study, direct costs amounted to 76.9% of the total costs, with a 27% difference between the cohorts. The cost savings were generated mainly by a reduced rate of hospitalization.

Comparison of acamprosate with naltrexone and disulfiram

The three medications currently FDA approved for the treatment of alcohol dependence are each unique for mechanism of action, drug interactions, tolerability, and adverse reactions. Each of the three drugs has its own advantages and disadvantages. Table 2 outlines some of the main differences between the drugs. Acamprosate has the most benign tolerability of the three agents. Naltrexone and disulfiram offer the ease of 1 tablet, once-daily dosing, whereas acamprosate therapy consists of 2 tablets dosed 3 times daily (a total of 6 tablets per day). While the multiple daily dosing schedule and pill burden of acamprosate could affect compliance, compliance for acamprosate in placebo-controlled trials was very good.

Kranzler and Van Kirk (2001) performed a meta-analysis to compare the efficacy of naltrexone and acamprosate. Their analysis included 9 placebo-controlled naltrexone trials and 11 placebo-controlled acamprosate trials. They found that both medications significantly, although modestly, affected drinking outcomes. The strongest effect of both medications appeared to be on the frequency of the drinking, reflected by the percentage of drinking days in the naltrexone studies and by cumulative abstinent days in the acamprosate studies. Bouza et al (2004) also performed a meta-analysis which included 13 studies of acamprosate and 19 studies of naltrexone. This meta-analysis found that acamprosate significantly improved abstinence rates and days of cumulative abstinence compared with placebo. Short-term use of naltrexone reduced the relapse rate significantly. While short-term use naltrexone was not associated with a significant modification in abstinence rates, there were insufficient data to ascertain naltrexone's efficacy over more prolonged periods.

Table 2 Comparison of the three medications currently approved by the FDA for the treatment of alcohol dependence.

	Acamprosate[a]	Naltrexone[b]	Disulfiram[c]
Mechanism of action	Restores balance between excitatory glutamate and inhibitory GABA neurotransmitter systems	Opioid receptor antagonist	Inhibits alcohol dehydrogenase, a key enzyme in alcohol metabolism
Interactions with alcohol	None	None	Severe adverse reaction includes nausea, vomiting, flushing, tachycardia
Drug interactions	No clinically significant interactions	Opiates	Phenytoin, oral anticoagulants, isoniazid
Common side-effects	Diarrhea, asthenia, nausea, pruritis, flatulence	Elevated liver function tests, nausea, headache, dizziness, nervousness, fatigue, insomnia, vomiting	Hepatitis, occasional skin eruptions, transient mild drowsiness, fatigueability, impotence, headache
Serious adverse events	None known	Hepatitis	Hepatitis, optic neuritis, peripheral neuritis, polyneuritis and peripheral neuropathy
Contraindications	Severe renal impairment	Hepatitis or liver failure	Hepatitis or liver failure. Current use of metronidazole, paraldehyde, alcohol, or alcohol-containing preparations.

[a] Forest Pharmaceuticals, Inc. 2005
[b] RiVea (naltrexone hydrochloride) Tablets patient package insert (Mallinckrodt 2005).
[c] Antabuse (disulfiram) Tablets patient package insert (Odyssey Pharmaceuticals, Inc. 2005).
Abbreviations: GABA, gamma-aminobutyric acid.

Table 3 briefly describes the trials that have been done comparing acamprosate directly with naltrexone and disulfiram. Naltrexone and acamprosate were compared in a randomized, 12-month, single-blind study involving 157 recently detoxified alcohol-dependent men with moderate dependence and a stable family environment (Rubio et al 2001). The results of this study favored naltrexone. While there was no difference in mean time to first drink, time to first relapse (5 or more drinks in a day) was significantly greater in the naltrexone group (63 days) compared with the acamprosate group (42 days) (p=0.02). At the end of the 12-month study 41% of the naltrexone group compared with 17% of the acamprosate group had not relapsed (p=0.009). The cumulative number of days of abstinence were significantly greater in the naltrexone group, and severity of craving and percentage of heavy drinking days was significantly lower in the naltrexone group compared with the acamprosate group.

Kiefer et al (2003) conducted a 3-month, double-blind, double dummy, placebo-controlled trial comparing the efficacy of these two agents with each other, as well as in combination. One hundred and sixty patients were either randomized to acamprosate 1998 mg/day as 3 divided doses, naltrexone 50 mg/day, a combination of the two drugs at the same doses, or placebo. In this study there was no significant difference between time to first drink and time to relapse between acamprosate and naltrexone, and both were superior to placebo. Time to first drink was significantly lower in the acamprosate, naltrexone, and combination groups compared with placebo.

De Sousa and De Sousa (2005) performed an open, randomized trial in India comparing the efficacy of acamprosate and disulfiram in preventing alcoholic relapse. The study included 100 alcohol-dependent males with highly involved family members who agreed to supervise the ingestion of the medication and attend appointments with the patient. In this study, relapse occurred significantly later in the disulfiram group and a greater proportion of those in the disulfiram group remained abstinent at the end of the year long study compared with acamprosate. The results of this study are difficult to generalize given the extensive family involvement of the patients. Previous work has found that without supervised ingestion of disulfiram, compliance is much lower and therefore the medication is much less effective.

Combination of naltrexone and acamprosate

As discussed extensively up to this point, acamprosate has demonstrated efficacy in maintaining abstinence in individuals' status post acute detoxification. Naltrexone has been shown to reduce relapse into heavy drinking (Kranzler and Van Kirk 2001; Streeton and Whelan 2001). As neither acamprosate nor naltrexone prove successful for 100% of alcohol-dependent individuals, there has been interest in whether the concomitant use of the two drugs would prove

more effective in maintaining abstinence than either drug alone. A hypothesized theory for this suggests that the two agents attenuate different aspects of craving. Naltrexone is an opioid antagonist that indirectly interferes with dopaminergic neurons in the ventral tegmental area projecting to the limbic system, and it therefore may relieve reward craving (Kiefer and Wiedemann 2004). Acamprosate has been postulated to modify the balance between the excitatory glutamatergic system and the inhibitory GABAergic system, thereby diminishing "relief craving" (Dahchour and De Witte 2000; Boeijinga et al 2004; Scott et al 2005).

As discussed previously, Kiefer et al (2003) performed a double-blind, placebo-controlled trial of 160 alcoholics who were randomized to naltrexone, acamprosate, naltrexone plus acamprosate, or placebo for 12 weeks. They found that naltrexone, acamprosate, and the combined medication were significantly more effective than placebo. While the naltrexone group showed a tendency for a better outcome for time to first drink and time to relapse, the combined medication was most effective, with significantly lower relapse rates than placebo and acamprosate but not naltrexone. Kiefer and Wiedemann (2004) evaluated 3 pre-clinical and 4 clinical studies published on either combined tolerability or efficacy of acamprosate and naltrexone. None of these revealed any severe adverse events during combined treatment. Diarrhea and nausea were the most significant side-effects. Whereas the preclinical data on efficacy of combined treatment was inconclusive, clinical data revealed that combined therapy was superior to both placebo and acamprosate monotherapy.

The combination of acamprosate and disulfiram has been evaluated in a small double-blind trial (Besson et al 1998). The authors found that combination was well tolerated, with no adverse reactions between acamprosate and disulfiram. In this small study, the subgroup who received both medications had a better outcome on cumulative abstinent days than those on only one or no medication. Additional investigation in this area is warranted.

Patient-selection characteristics

Previous work supports the theory that pharmacotherapies may be more successful if pharmacologic agents are matched to particular characteristics in an alcoholic individual. Verheul et al (1999) proposed a psychobiological model of craving for alcohol which included reward craving (desire for the rewarding or stimulating effects of alcohol), relief craving (desire for the reduction of tension or arousal), and obsessive craving (lack of control over intrusive thoughts about drinking). They proposed that individual differences

Table 3 Studies comparing acamprosate with naltrexone and disulfiram

Study	Design	Study subjects	Main findings
Rubio et al 2001	12-month, randomized, single-blind study comparing naltrexone and acamprosate	157 recently detoxified alcohol-dependent men with moderate dependence and a stable family environment	Time to first relapse was greater in the naltrexone group than acamprosate group (p=0.02). At end of study, greater percentage of naltrexone group had not relapsed compared with acamprosate group (p=0.009). Cumulative number of days of abstinence was greater in naltrexone group, and severity of craving and percentage of heavy drinking was lower in naltrexone group than acamprosate group.
Kiefer et al 2003	12-week double-blind, double-dummy, placebo-controlled trial comparing efficacy of naltrexone, acamprosate, and combination of both with either alone.	160 recently detoxified alcohol-dependent patients randomized to acamprosate, naltrexone, both, or placebo.	Acamprosate, naltrexone, and combination therapy were superior to placebo. No significant difference in time to first drink and time to relapse between acamprosate and naltrexone. Combined medication resulted in significantly lower relapse rates than placebo and acamprosate but not naltrexone.
De Sousa and De Sousa 2005	1-year open, randomized trial comparing efficacy of acamprosate and disulfiram (taken for a 8-month period).	100 alcohol-dependent males with highly involved family members who agreed to supervise medication compliance and attend appointments with patient.	Relapse occurred later in the disulfiram group than acamprosate group (p=0.0001). Greater proportion of those in the disulfiram group remained abstinent at the end of study than acamprosate group (p=0.0002).

would create distinct pathways toward and manifestations of cravings. Understanding these differences could help tailor specific pharmacotherapies for specific individual characteristics and thereby increase pharmacotherapy efficacy. For example, Johnson et al (2000) demonstrated that ondansetron, a 5-HT3 antagonist, is a successful treatment in early-onset, compared with later-onset, alcoholics. They speculated this was due to the drug modifying underlying serotenergic dysfunction. In addition, Monterosso et al (2001) found that individuals with high levels of alcohol craving or a strong family history of alcoholism were more likely to benefit from naltrexone treatment. Gerra et al (1992) found that non-familial alcoholics significantly reduced drinking with acamprosate, while familial alcoholics significantly reduced alcohol intake with fluoxetine, but not with acamprosate. In addition, the findings of Lesch and Walter (1996) support the matching of patient characteristics to increase efficacy of acamprosate. However, in a pooled analysis of 7 randomized controlled trials comparing acamprosate with placebo, Verheul et al (2005) did not find statistical differences in potential predictors of efficacy with acamprosate in alcoholic individuals.

Acamprosate may be particularly useful in alcohol-dependent individuals with hepatic impairment or liver disease. However, to date no pharmacokinetic data are available in those with severe hepatic impairment. Naltrexone and disulfiram must be used with caution or contraindicated in this population because of the risk of hepatotoxicity. Naltrexone is also contraindicated in those needing administration of opioid analgesics. On the other hand, as acamprosate is excreted renally, it is contraindicated in those with severe renal impairment and must be used cautiously with decreased doses in those with moderate renal impairment. Naltrexone and disulfiram may be used in this patient population.

Conclusions

Acamprosate has been shown to be safe, well tolerated, and efficacious to help alcohol-dependent individuals achieve abstinence from alcohol after detoxification. In combination with psychosocial and behavioral management programs, it can be an important tool in the armamentarium of the provider treating this difficult disease. It has also been shown to be safe and well tolerated when used in combination with naltrexone, and may provide even greater benefit in maintaining abstinence in alcohol-dependent individuals than monotherapy. Further work is needed to clarify patient characteristics that may allow individuals to optimally benefit from one pharmacotherapy versus another. At present there are conflicting data in the literature on the optimal time to start acamprosate and further work to clarify this would be of utmost utility. In addition, this review demonstrates that the current pharmacotherapies available for the treatment of alcohol dependence are of limited clinical utility, particularly in the absence of psychosocial treatments. The continued search for effective treatments of this debilitating disease is of greatest importance.

Disclosures

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