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Drug adjuncts for treating alcohol dependence

ABSTRACT

Three drugs are approved by the US Food and Drug Administration for treating alcoholism: disulfiram, naltrexone, and acamprosate. Drugs approved for other indications that are being used experimentally or "off-label" include nalmafene, topiramate, and ondansetron. As we learn more about the pathophysiologic basis of alcoholism, it is hoped that novel drugs can be developed to help people with alcohol dependence achieve abstinence, and as a result, curb alcohol-related morbidity.

KEY POINTS

Better drugs might be developed that target the neurotransmitter systems implicated in the development and perpetuation of alcohol dependence.

The treatment effects of the currently available agents are moderate at best, and not all patients respond.

No drug or combination of drugs is likely to be effective if used by itself. Rather, these drugs should be used as adjuncts to behavioral therapy.

Of the available agents, acamprosate has the best evidence of efficacy; it should be used as early as possible in the course of the illness.

WE HAVE LEARNED MUCH about the neurochemical basis of alcohol dependence over the past 20 years, but we still have only a few medications for treating it. Only disulfiram (Antabuse), naltrexone (ReVia), and acamprosate (Campral) are approved by the US Food and Drug Administration (FDA) for this indication; topiramate (Topamax) and ondansetron (Zofran) are sometimes used "off-label."

Better drugs are needed. Alcoholism is common and difficult to treat and causes serious physical, mental, and social problems. Further, the effect of the available agents is modest at best, and some patients do not respond.

This paper reviews the scope of the problem, the neurochemistry of alcoholism, the available agents, and how physicians can help.

A MAJOR PUBLIC HEALTH PROBLEM

Alcohol dependence is a major public health problem and the fourth leading cause of disability worldwide.[1] So common is alcoholism that physicians in any medical specialty are likely to see alcohol-dependent patients nearly every day.[2]

The diagnosis of alcohol dependence requires a combination of findings that include tolerance or withdrawal symptoms, loss of control over drinking, an inordinate amount of time dedicated to drinking, neglect of other activities, and continued use of alcohol despite adverse consequences.[3]

Alcohol abuse may manifest as recurrent social, interpersonal, or legal problems, dangerous behavior while under the influence, or neglect of important obligations due to continued drinking.[3]

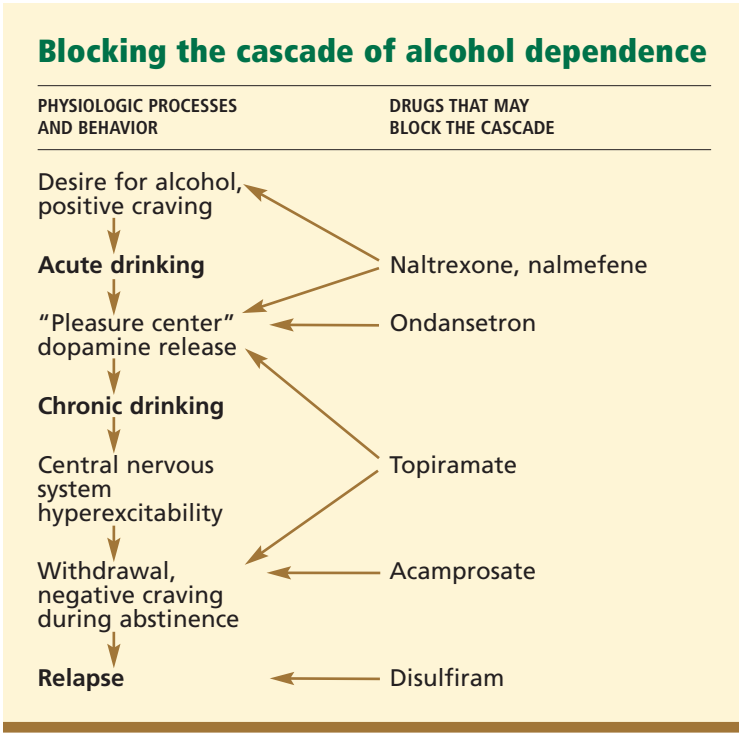

FIGURE 1

Alcoholism is a disease, not a behavioral deficit

Difficult to treat

Alcoholism, being a chronic relapsing disorder with genetic, psychosocial, and environmental influences, is difficult to treat. Historically, its long-term management has been limited to psychosocial interventions such as addiction counseling, behavioral treatments, and self-help groups (eg, Alcoholics Anonymous).

Long-term management usually involves a detoxification phase followed by a rehabilitation phase in which we try to optimize the chances of achieving long-term abstinence and reducing alcohol-related problems. The outcomes of such treatment, however, have been disappointing, and 40% to 70% of patients return to heavy alcohol use within 1 year after treatment.[4]

THE CHEMISTRY OF ALCOHOLISM

As society has come to accept that alcoholism is a legitimate disease (and not a behavior deficit), researchers have begun to search for its pathophysiologic basis. Over the past 20 years, major discoveries have been made about the neurochemistry of alcoholism. With these advances has come an interest in developing drug treatments for alcohol dependence as adjuncts to standard treatment.

Several neurotransmitter systems have been implicated in initiating and perpetuating alcohol dependence (FIGURE 1), and it is logical to believe that drugs that target these systems might improve treatment. Several of these drugs are now available.

Alcohol increases dopamine, which feels good

One focus of research and treatment is on the reward mechanisms in the brain.

The limbic system is believed to be involved in the pleasurable and stimulating effects of many drugs of abuse, including alcohol. Dopaminergic neurons in this system originate in the ventral tegmental area of the midbrain and project to the nucleus accumbens deep within the forebrain. Alcohol activates these mesocorticolimbic neurons, resulting in release of dopamine and an incentive to consume more alcohol.[5] This experience, often called "positive" craving, can result in compulsive drinking.[6]

Opioid pathways mediated by endogenous beta-endorphin also affect the dopaminergic reward system. Alcohol increases the activity of these pathways and thereby exerts additional influence on the dopamine reward system.[7] Blockade of opioid transmission thus has the potential to modulate drinking behavior.

Serotonin also plays a key role: serotonin receptors influence the dopamine reward system activated by alcohol.[8] Selective blockade of these receptors reduces dopamine release in response to alcohol and offers an additional strategy for reducing alcohol consumption by attenuating its rewarding effects.[9]

Glutamate excites, GABA sedates

Another area of intense research in alcohol dependence is the balance between excitatory and inhibitory neurotransmission in the central nervous system. In mammals, glutamate activity is the major determinant of brain excitability, while gamma-aminobutyric acid (GABA) is the complementary inhibitory neurotransmitter.

Alcohol sedates by blocking glutamate and boosting GABA

Alcohol facilitates GABA transmission and

attenuates glutamatergic transmission.[10,11] Together, these actions result in a depressant effect, which in part explains the acute sedative effects of alcohol intoxication.

But it is not that simple. Alcohol appears to exert its direct effects in the brain primarily by interacting with specific subtypes of receptors for these neurotransmitters.

The biology and pharmacology of glutamate receptors is extremely complex. Most attention in the field of alcohol dependence has focused on the metabotropic glutamate receptor subtype 5 (mGluR5) and on the ionotropic *N*-methyl-*D*-aspartate (NMDA) receptor subtype.

When glutamate levels fall, presynaptic mGluR5 receptors stimulate glutamate release through a phospholipase C-mediated second-messenger system that serves to increase synaptic levels of glutamate.[12] Postsynaptic NMDA receptors mediate excitatory neurotransmission. Acute alcohol intake is believed to reduce NMDA receptor activity as part of its sedative effect.

The brain adapts to chronic drinking

Chronic exposure to alcohol is believed to induce neuroadaptive changes in glutamatergic function geared towards restoring normal excitability in the central nervous system. The basis for this neuronal plasticity is not entirely understood but may involve alterations in NMDA receptor sensitivity to alcohol or increases in the levels of certain co-agonists.[13,14]

Reciprocal changes are believed to occur in the gamma-aminobutyric acidergic system to offset the effect of alcohol.[15] Overall, this neuroadaptation restores normal neuronal functioning in the face of prolonged depression from alcohol by resetting the general level of excitability.

Alcohol withdrawal: Too much glutamate, not enough GABA

A consequence of these adaptive changes is that when a chronic drinker abruptly stops drinking, the elevated level of excitability is left unopposed, leading to the symptoms of the alcohol withdrawal syndrome.

During alcohol withdrawal, extracellular levels of glutamate in the brain begin to increase within hours. Further, with repeated cycles of alcohol use and withdrawal, the magnitude of this increase becomes greater. At the extreme, this phenomenon may form the basis for alcohol withdrawal-related seizures.[16]

With too much glutamate and not enough GABA, a newly sober alcoholic patient feels nervous and profoundly distressed. This dysphoria is a formidable stimulus for renewed drinking, a phenomenon known as "negative" craving.[17] Most drinking relapses occur in the early months of abstinence, when the aberrations in neuronal excitability are most pronounced. Furthermore, the increases in extracellular glutamate may be sufficient to cause toxic effects and neuronal loss, a process known as excitotoxicity.[18]

PHARMACOLOGIC THERAPY

Currently approved for treating alcohol dependence are disulfiram, naltrexone, and acamprosate. Other drugs that are being investigated or used off-label include nalmefene, topirimate, and ondansetron (**TABLE 1**). None of these agents has proven effective without some form of concurrent behavioral therapy. The need for multimodal therapy requires a collaborative approach between primary care physicians and addiction specialists in the initial phase of rehabilitation.

Disulfiram

Disulfiram was serendipitously discovered to cause an aversion reaction to alcohol nearly 60 years ago. Ethanol is metabolized in a two-step enzymatic process. Disulfiram irreversibly inhibits a key enzyme in the process called aldehyde dehydrogenase, causing accumulation of a toxic intermediate metabolite called acetaldehyde.

If disulfiram is in the body, whenever the patient consumes alcohol, acetaldehyde accumulates and causes a combination of unpleasant effects (eg, nausea, vomiting, flushing, and hypotension) known as the disulfiram-ethanol reaction. This reaction provides a mental and physical disincentive to drink. The severity of the reaction is proportional to the dose of disulfiram and the amount of alcohol consumed.

Modest effect at best. Disulfiram has not been widely used, and few studies have shown

TABLE 1

Drugs used in treating alcohol dependence

Disulfiram (Antabuse)*
- Mechanism: inhibits aldehyde dehydrogenase
- Effect: aversion reaction
- Dosage: 250–500 mg/day
- Contraindications: concurrent alcohol-containing preparations, severe myocardial disease
- Adverse effects: hepatic toxicity, polyneuritis, peripheral neuropathy

Naltrexone (ReVia)*
- Mechanism: opioid receptor antagonist
- Effect: decreased frequency and severity of relapse
- Dosage: 50 mg/day
- Contraindications: opioid dependence or withdrawal, acute hepatitis, liver failure
- Adverse effects: nausea, headache, dizziness, fatigue

Acamprosate (Campral)*
- Mechanism: modulates glutamatergic excitability
- Effect: improves abstinence rates
- Dosage: 1,998 mg/day (999 mg/day with moderate renal impairment)
- Contraindications: severe renal impairment
- Adverse effects: diarrhea, suicidality

Topiramate (Topamax)
- Mechanism: modulation of gamma-aminobutyric acidergic and glutamatergic activity
- Effect: decreased craving and drinking, improved quality of life
- Dosage: initial 25 mg/day; maintenance 300 mg/day in divided doses
- Contraindications: none known
- Adverse effects: metabolic acidosis, renal stones, psychomotor slowing, somnolence, mood disturbances

Ondansetron (Zofran)
- Mechanism: serotonin receptor antagonist
- Effect: reduces alcohol consumption
- Dosage: not established
- Contraindications: none known
- Adverse effects: headache, malaise, constipation

*Approved by the US Food and Drug Administration for treating alcoholism

Most drinking relapses occur early, when neuronal excitability is greatest

it to have a consistent therapeutic benefit. The largest study of disulfiram to date found no significant difference between disulfiram and placebo in terms of various measures of abstinence.[19] In fact, the factor that best predicted complete abstinence at the end of the study was compliance with taking the study medication—no matter if it was active drug or placebo. Other studies found that disulfiram modestly decreased the frequency of drinking, but not the abstinence rate.[20,21] Furthermore, standard doses of disulfiram may not produce an aversive reaction to ethanol in many individuals.[22]

High rate of drug interactions. Disulfiram can interact with a variety of other drugs that are competitively metabolized via the cytochrome P-450 system, and the interactions may cause patients to experience heightened effects or even toxicity. Patients taking theophylline, phenytoin, or warfarin may require dosage reduction of these medications to avoid potentially harmful effects.

Potentially serious side effects. Dosing of disulfiram is limited because of the risk of serious side effects, including death. The maximum dosage in the United States is 500 mg/day. The most common side effect appears to be drowsiness,[19] which is usually self-limited and can be managed by taking the dose in the evening.

Idiosyncratic but potentially fatal hepato-

toxicity has been reported with disulfiram in about 1 in 25,000 patients treated per year.[23] Fatal hepatotoxicity typically occurs early in the course of treatment; physicians are advised to monitor liver function at baseline, then at 2-week intervals for 2 months, and after that every 3 to 6 months.[24]

Because of the potential for hypotension during a disulfiram-ethanol reaction, disulfiram should be avoided in patients with significant cardiac or cerebrovascular disease. Diabetes, psychosis, and cognitive impairment are other significant contraindications.

Patients must comply for this drug to be effective, and so disulfiram may be most effective in settings in which its administration is supervised or compliance is emphasized, such as in treatment programs for professionals or other people subject to contingency contracts and special high-risk patients.

Naltrexone

Naltrexone is an antagonist of the mu opioid receptor. It is thought to diminish the desire to drink by blocking the beta-endorphin pathways that facilitate the mesocorticolimbic dopamine reward system. Blockade of opioid receptors prevents such facilitation and may diminish the subjective reinforcing experience associated with alcohol consumption.[25]

Dosage. Naltrexone is generally given at 25 mg/day for 1 to 2 days, then increased to the standard dosage of 50 mg/day.

Longer time to relapse. Most clinical trials showed that patients undergoing substance abuse treatment or counseling engaged in less heavy drinking if they also received naltrexone compared with placebo.[26,27] The most consistent finding in clinical studies is an increase in the time to the first relapse.[28] Not all trials had positive results, however.[29] Naltrexone does not appear to increase the chance of remaining completely abstinent from alcohol but rather reduces the frequency or intensity of drinking. This effect has been attributed to a reduction in the positive reinforcing effects of alcohol, ie, a diminution of "positive" craving.[25]

Some patients may benefit more. In some studies, patients were more likely to benefit from naltrexone if they had a family history of alcoholism, suggesting that genetic influences may modulate the effects of the drug.[30] In addition, patients with greater craving at the beginning of therapy tend to benefit more from naltrexone than patients without many urges to drink.[31] These factors should be considered when choosing a pharmacologic approach to the treatment of alcoholism.

Effects fade after discontinuation. If naltrexone has any beneficial effect, it appears to fade after the patient stops taking the drug.[32] This diminution of effect highlights the chronic relapsing nature of alcoholism, the long-standing learned behavior involved, and the need for concurrent psychosocial and behavioral treatment.[33]

Compliance also affects the efficacy of naltrexone. Beneficial effects have been found primarily among patients who take 70% to 90% of their medication.[33] A long-acting injectable formulation of naltrexone has been developed to improve compliance. Given by intramuscular injection at 4-week intervals rather than daily oral doses, it has shown efficacy in a recent large clinical trial.[34]

Hepatic toxicity a concern. The most prominent adverse effects of naltrexone include nausea, dizziness, and fatigue.[35] As with disulfiram, hepatic toxicity is a concern but is extremely unlikely at the 50-mg/day dose. Nonetheless, naltrexone is generally avoided in patients with hepatic dysfunction, and patients receiving it should have their liver function monitored regularly.

Monitor liver function during disulfiram or naltrexone therapy

Because naltrexone blocks opioid receptors, it may pose problems in clinical practice (eg, when a patient needs general anesthesia). It is contraindicated in patients receiving long-term opioid therapy for chronic pain or heroin dependence.

Nalmefene

Nalmefene, another opioid receptor antagonist, is currently under investigation. It appears to have greater activity than naltrexone at delta opioid receptors. As yet, there is no convincing evidence that nalmefene is more effective than naltrexone, but it appears to be better tolerated and has not been shown to cause liver toxicity.[36] Implantable long-term delivery systems for nalmefene are currently being evaluated.[37]

Acamprosate

Of the agents available for treating alcohol dependence, acamprosate now has the best evidence of efficacy.

The exact mechanism of action of acamprosate is unknown. Although its structure resembles that of GABA, its mechanism of action likely involves inhibition of the glutamatergic system.[38] By attenuating the glutamatergic hyperactivity that occurs during chronic alcohol exposure, acamprosate reduces the negative craving experienced during withdrawal, thereby lowering the incidence or severity of relapses driven by such dysphoria.[39]

Dosage. The recommended dosage of acamprosate is 666 mg three times daily.

Start early, continue use. Acamprosate's putative mechanism of action suggests that it should be used as early as possible during the medical treatment of alcoholism, and it should be continued even if relapses occur to reduce their frequency and severity.

Acamprosate has been found effective only in patients who have undergone detoxification and were abstinent at the start of treatment. In one of the few clinical trials that failed to show acamprosate to be superior to placebo in terms of maintaining abstinence, nearly one third of patients had relapsed before beginning the drug.[39] This suggests that abstinence at the start of therapy may be important if acamprosate is to be effective, and the drug is approved by the FDA for use only in this setting.

Acamprosate reduces negative craving during alcohol withdrawal

Acamprosate should probably be continued for a prolonged time following alcohol withdrawal to allow neuronal excitability to return to normal.

Long-term efficacy. Acamprosate has been demonstrated to be effective in numerous large placebo-controlled trials worldwide with treatment periods of up to 12 months.[40–42] Consistently, it has been more effective than placebo in maintaining complete abstinence. After 12 months, 18.3% of acamprosate-treated patients remained abstinent compared with only 7.1% of those receiving placebo.[41] The effect appears to be maintained for 6 to 12 months after cessation of therapy.[41,42]

Combination with naltrexone is appealing. Until recently, limited data had indicated that acamprosate is about as effective as naltrexone and that combination therapy is more effective than acamprosate alone.[43] However, the Combined Pharmacotherapies and Behavioral Interventions study, a large, multisite controlled trial, recently compared the efficacy of naltrexone and acamprosate in the context of medical management and found no benefit from acamprosate nor any additive effect when combined with naltrexone.[44] The negative results from this trial with respect to acamprosate conflict with those of the aforementioned studies that demonstrated efficacy. This discrepancy may reflect the COMBINE study design, in which the patients were previously untreated or in ambulatory care rather than in rehabilitation centers as in other studies. Many patients had been abstinent very briefly—66% for less than 1 week.

Mechanistically, using both agents simultaneously is appealing because naltrexone appears most beneficial in reducing the frequency and severity of drinking, whereas acamprosate appears better suited for maintaining abstinence.

Renal excretion. Acamprosate undergoes essentially no metabolism and is primarily excreted renally. Dosage reduction is required for patients with moderate renal insufficiency (creatinine clearance 30–50 mL/minute), and the drug is contraindicated in patients with severe renal insufficiency (creatinine clearance ≤ 30 mL/minute).

Side effects are mostly mild and transient. The most frequently reported adverse effect of acamprosate is diarrhea, which tends to be mild and transient. The drug is generally well tolerated, and few patients discontinue treatment because of side effects.

Suicidal thoughts and attempts occurred more frequently in acamprosate-treated patients than with placebo in controlled trials, although they were extremely rare overall and a causal relationship has not been established. Nevertheless, physicians and families are advised to monitor patients for depression or suicidal thinking in the course of recovery from alcoholism.

Topiramate

Topiramate has potent anticonvulsant effects and is currently marketed as an antiepileptic agent.

Topiramate has two important mechanisms of action that may help in treating alcohol dependence: it potentiates inhibitory GABA[45] and it inhibits excitatory glutamate transmission.[46] Through a complex mechanism, these effects are expected to lead to a decrease in dopamine release in the nucleus accumbens in response to acute alcohol ingestion and a reduction in its rewarding effects. Also, topiramate is believed to counterbalance the effects of chronic alcohol consumption on central nervous system excitability, thus lessening the symptoms of withdrawal and making relapse less likely.[47]

Preliminary evidence is encouraging. Relatively little research has been done with topiramate in the treatment of alcohol dependence. Anecdotal reports suggest that some patients feel less craving for alcohol when taking the drug.[48] A recent randomized controlled trial found topiramate superior to placebo in several measures of craving, drinking reduction, and promotion of abstinence.[49] This same trial showed a significant improvement in quality of life and a reduction in harmful alcohol-related consequences in patients taking topiramate.[50] The authors believed this "harm-reduction" to be worthwhile even if complete abstinence was not achieved.

'Harm reduction' may be worthwhile even if complete abstinence is not achieved

Slow titration. Topiramate is given in an escalating schedule beginning with 25 mg/day and increasing to the target dosage of 300 mg/day in divided doses over a course of several weeks.

Side effects of topiramate in clinical trials included dizziness, psychomotor slowing, paresthesias, and impairment of memory or concentration.[51] All adverse effects were rated as mild to moderate and resolved without intervention.

Topiramate is renally excreted and requires a 50% dosage reduction in patients with a creatinine clearance less than 70 mL/minute. Because it is similar to acetazolamide, it has the potential to cause nonanion gap metabolic acidosis by inhibiting carbonic anhydrase.

Ondansetron

Ondansetron has been the most promising of the serotonergic agents studied for the treatment of alcohol dependence.

Ondansetron is a selective 5-HT3 receptor antagonist currently used for treating refractory nausea and vomiting. As mentioned previously, serotonin receptors exist on the terminals of dopamine-secreting neurons in the nucleus accumbens, where they regulate dopamine release in this region.[9]

5-HT3 receptor antagonists reduced alcohol consumption in a variety of animal models.[9,52] This effect is believed to be due to a reduction in the rewarding subjective effects produced by alcohol and a subsequent decreased desire to drink.[53]

Promising results in early-onset alcoholics. Clinical trials of ondansetron have generally been encouraging.[54–56]

An interesting finding in these trials is that ondansetron seems effective only in early-onset alcoholism,[55,56] distinguished by the onset of alcohol dependence before age 25, significant drinking-related consequences, childhood risk factors, and more severe associated psychopathology including antisocial and impulsive tendencies. Early-onset alcoholics are thought to have a high degree of serotonergic abnormality.[57] Such serotonergic dysfunction results in compensatory potentiation of 5-HT3 receptor function, the blockade of which may be responsible for ondansetron's selective effectiveness in this subgroup.[58]

Studies are under way to determine the precise mechanism of action of ondansetron in alcohol dependence as well as genotypic or phenotypic identifiers associated with differences in the serotonin transporter function in relation to treatment outcome. The optimal dosing has yet to be determined, and dosages have ranged from 1 to 16 μg/kg twice daily in clinical trials.

EVEN WITH SUBOPTIMAL DRUGS, PHYSICIANS CAN HELP

Although many patients may benefit from the use of currently available medications for the treatment of alcohol dependence, their treatment effects are moderate at best, and some alcoholics fail to respond. This to some degree reflects the heterogeneous nature of the alcoholic population and possibly of the disease itself. In the treatment of alcohol dependence, one size does not fit all.

Further, the pharmaceutical industry has moved slowly in alcoholism treatment, and many avenues for drug development remain unexplored. A recent international symposium identified several areas of perceived uncertainty that have limited the enthusiasm of the drug industry in this area, including investment and marketing risk and health liability.[59]

Another major barrier to the development of new medications is that many physicians and patients still do not believe that alcohol dependence is a medical condition or that it can be treated medically. As attitudes change, however, progress might be made, as it has in other areas of mental health. (Annual sales of disulfiram, naltrexone, and acamprosate are dwarfed by sales of other psychotropic drugs used to treat such mental disorders as depression and schizophrenia.[60])

Broader involvement of physicians in the management of alcohol dependence has been cited as a prerequisite for the increased use of pharmacologic treatments.[61] To this end, primary care physicians are encouraged to become more involved in diagnosing and treating alcohol dependence, in conjunction with addiction specialists. This increased involvement would not only engender a paradigm shift towards greater acceptance of treatment for alcohol abuse, but also create more public awareness that effective treatments are available and can offer realistic hope for a healthier and more productive life.

No pharmacologic treatment will likely prove suitable for the stand-alone management of alcohol dependence. No medication to date has been proven effective in clinical trials without some form of concomitant behavioral therapy. Effective behavioral interventions include cognitive behavioral therapy, motivational enhancement therapy, 12-step self-help facilitation, and community reinforcement approaches.[62] Directing alcohol-dependent patients towards effective behavioral treatments combined with thoughtful adjunctive pharmacotherapy may allow a significant proportion to achieve meaningful sobriety, or at least a reduction in the harmful consequences of continued alcohol abuse.

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CME ANSWERS

Answers to the credit test on page 687 of this issue

1 **B** 2 **B** 3 **C** 4 **B** 5 **C** 6 **D** 7 **E** 8 **D** 9 **C** 10 **D** 11 **C** 12 **E** 13 **E** 14 **E**