Alcohol Abuse and Alcoholism: An Overview

Joseph R. Volpicelli, M.D., Ph.D.

Alcoholism and alcohol abuse rank among the top 3 psychiatric disorders in the United States. These disorders are associated with significant medical and economic consequences. Furthermore, studies consistently show that an investment in addiction treatment leads to overall cost savings for society. Recent work has identified specific effects of alcohol on several neurotransmitter systems, including γ-aminobutyric acid, serotonin, dopamine, and the opioid receptors. These findings suggest that multiple pharmacologic interventions may be useful for the treatment of alcohol addiction. This article reviews the clinical use of naltrexone and discusses psychosocial programs to enhance treatment retention and adherence. *(J Clin Psychiatry 2001;62[suppl 20]:4–10)*

During the past 2 decades, remarkable progress has been made in understanding the pharmacologic effects of alcohol and in translating this knowledge into more effective treatments. This article reviews the significant medical and economic costs of alcoholism and alcohol abuse and shows how applying current addiction treatment programs can substantially reduce these costs. Next, this review focuses on how recent insights into the effects of alcohol have led to the development of medications, such as naltrexone, that can reduce alcohol relapse rates following detoxification and how these treatments can be effectively applied to help those who suffer from alcohol addiction. Finally, some of the barriers to medical treatment are discussed.

ALCOHOLISM AND ALCOHOL ABUSE ARE IMPORTANT PUBLIC HEALTH CONCERNS

Alcoholism and alcohol abuse have significant medical and economic consequences. Thirteen percent of the adult population in the United States has a history of alcohol dependence or alcohol abuse, and the 12-month prevalence of alcohol dependence is between 4% and 5%.[1] To put this figure in perspective, alcohol dependence ranks with mood and anxiety disorders among the top 3 psychiatric disorders in this country.[2] According to the 1992 National Longitudinal Alcohol Epidemiologic Survey, there are approximately 14 million Americans with alcohol dependence or abuse.[3] Alcohol abuse and dependence cost society approximately $176 billion per year.[4] The majority of this economic burden relates to reduced productivity, premature death, direct treatment expenditures, and legal fees.[5]

In addition to its economic impact, alcoholism leads to significant medical morbidity and mortality. Alcoholism and alcohol abuse are responsible for 105,000 deaths per year in the United States.[6] Alcohol dependence is associated with increased risk for a variety of medical problems including cirrhosis, cardiomyopathy, various cancers, infectious disorders, fetal abnormalities, and neurologic complications including dementia.

CURRENT TREATMENTS ARE MODERATELY EFFECTIVE

In light of the high economic and medical costs of alcoholism, it is important that people with alcohol-drinking problems be identified and referred to effective treatment programs. Current psychosocial treatments for alcoholism are moderately effective. The data from Project MATCH give an excellent overview of state-of-the-art treatments.[7] In this study, 3 types of psychosocial treatment were compared, with over 1700 subjects randomly assigned to receive cognitive-behavioral therapy, motivational enhancement therapy, or 12-step facilitation. The percentage of days that alcohol was consumed decreased from 75% to less than 20% during the year following a 3-month course of alcoholism treatment. Each of the 3 types of alcoholism treatments had similar results and was effective for about 50% of the subjects.[7]

From the Penn/VA Center for Study of Addiction, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia.

Presented at the closed roundtable symposium "Pharmacological Treatment of Alcohol Abuse and Addiction," which was held on February 28, 2000, in Philadelphia, Pa., and supported by an unrestricted educational grant from Forest Laboratories, Inc.

Supported by grant R01-AA07517 from the National Institute on Alcohol Abuse and Alcoholism, Bethesda, Md.

Financial disclosure: Dr. Volpicelli is a consultant for Mallinckrodt.

Reprint requests to: Joseph R. Volpicelli, M.D., Ph.D., University of Pennsylvania School of Medicine, 40 W. Evergreen Ave., Suite 106, Philadelphia, PA 19118-3224.

Table 1. Average Monthly Health Care Costs for Families With and Without an Alcoholic[a]

Years Before (–) and After (+) Alcoholism Treatment	Average Monthly Cost in Dollars	
	Families With an Alcoholic	Families Without an Alcoholic
–1	74.57	6.54
+1	40.72	1.90
+2	9.50	2.45
+3	24.27	3.80
+4	26.30	17.86
+5	12.18	16.60

[a]Data from a Blue Cross/Blue Shield 6-year longitudinal study (1974–1979) through the Health Benefits Division, California Public Employees Retirement System, conducted by Holder and Hallan.[9]

In nonresearch programs it is generally found that about half of the people who go through a treatment program abstain from episodes of excessive drinking during the first 6 months of treatment. While these results are encouraging, there is still considerable room for improvement.

ECONOMIC BENEFITS OF TREATMENT

Studies consistently show that an investment in addiction treatment leads to overall cost savings for society. For example, in a large study of 150,000 enrollees in a health care program in California, the economic costs of alcoholism and the cost offsets associated with treatment were assessed. The average cost of treatment for drug- and alcohol-dependent patients was $1361/patient. However, the cost savings for taxpayers was estimated to be $10,118/patient. Overall, the cost effectiveness of treatment was substantial; for each dollar invested in substance-abuse treatment, taxpayers saved $7 in future costs.[8]

In another study conducted by Blue Cross/Blue Shield, the cost-effectiveness of providing alcoholism treatment was assessed.[9] As Table 1 shows, monthly health care expenses for the family of an alcoholic the year before treatment are about $75, which is about 10 times higher than for families without an alcoholic. After treatment of the alcoholic family member, health care costs dramatically decline and are similar to those of families without an alcoholic member.

RECENT ADVANCES IN UNDERSTANDING THE PHARMACOLOGY OF ALCOHOL CAN IMPROVE TREATMENT OUTCOMES

Historically, it was believed that alcohol's main pharmacologic effect was nonspecific; exposure of nervous tissue to alcohol was thought to increase membrane fluidity, thereby slowing nerve transmission. This theory accounted for the central nervous system (CNS) depression associated with acute alcohol intoxication.

New models of how alcohol exerts its pharmacologic effects and why some people become dependent on alcohol have emerged in the last 2 decades. The current paradigm is based on the specific effects of alcohol on neurotransmitter systems. For example, acute alcohol intoxication can have important effects on γ-aminobutyric acid (GABA) receptor activity, serotonergic activity, endorphin release, and the release of dopamine at the reward centers of the brain. Some of the important pharmacologic effects of alcohol that help us to understand its addictive properties will be reviewed.

SPECIFIC EFFECTS

GABA and NMDA

Acute alcohol administration is a CNS depressant and generally suppresses neuronal activity. With chronic use of alcohol, people develop tolerance to the sedative effects of alcohol. For example, someone may initially feel sedated after drinking just 4 or 5 drinks; after years of drinking, it may take 10 drinks to reach the same level of intoxication.

Acute administration of alcohol is now thought to exert its primary sedative effects by affecting the major inhibitory neurotransmitter, GABA, or the major excitatory neurotransmitter, glutamate. Acute alcohol administration facilitates GABAergic transmission by enhancing chloride conductance through the $GABA_A$ receptor. Conversely, alcohol inhibits glutamate activity by decreasing cationic conductance through the *N*-methyl-D-aspartate (NMDA) receptor. The chronic effects of alcohol on the GABA and NMDA systems are generally opposite to the acute effects; the development of tolerance leads to reduced GABAergic activity and higher levels of NMDA activity.[10]

Serotonin

The clinical observation that many alcoholics have coexisting emotional disorders such as depression, anxiety, and impulsivity[11] first suggested that serotonin may be involved in alcoholism. It was postulated that alcohol may enhance serotonin functioning because these emotional disorders are associated with serotonin dysfunction and because people report that they use alcohol to reduce their symptoms. Animal and clinical studies further supported the notion that there are important interactions between alcohol and serotonin.

Several lines of animal research suggest that alcohol drinking is associated with serotonin deficiencies. For example, low levels of serotonin activity, particularly in the CNS, are associated with increased alcohol preference.[12] Also, drugs that reduce serotonergic activity are often associated with an increase in alcohol drinking, and drugs that enhance serotonergic activity (selective serotonin reuptake inhibitors [SSRIs], serotonin agonists) are associated with reduced alcohol drinking.[12]

Human studies on the effects of serotonergic agents on alcohol drinking have been less consistent. For example,

in social drinkers, SSRIs such as citalopram and fluoxetine have demonstrated modest short-term reductions in alcohol drinking.[12] In longer-term clinical studies, however, SSRIs did not reduce alcohol drinking relative to placebo.[13] There may be subgroups of alcoholics, however, that benefit from serotonergic drugs. For example, buspirone, a 5-HT_{1A} receptor partial agonist, reduced anxiety and drinking in a group of anxious alcoholics.[14] Similarly, fluoxetine reduced both depressive symptoms and alcohol drinking in one study among depressed alcoholics.[15] The use of serotonergic medications to treat alcoholics with comorbid depression remains uncertain, because one recent study showed that nefazodone reduced depressed symptoms but not alcohol drinking in depressed alcoholics.[16] Also, sertraline may be associated with increased alcohol drinking in severe, comorbid alcoholics, whereas it is effective in reducing alcohol drinking in less severe alcoholics.[17] In summary, clinical data suggest that the serotonergic medications may have a role in the treatment of specific subtypes of alcoholics.

Dopamine

The intake of alcohol, like that of virtually all other drugs of abuse, is associated with an increase of dopamine at the nucleus accumbens.[18] Since dopamine release is thought to be involved in the reinforcing properties of drugs of abuse, this pharmacologic effect may be particularly important in understanding why some people become addicted to alcohol. To support this notion, mice lacking D_2 receptors do not show a preference for alcohol.[19,20] Alcohol may increase dopamine release directly at the nucleus accumbens or, more likely, indirectly through its effects on opioid or GABA receptors.[18]

Opioid Receptors

Acute administration of alcohol has been shown in many animal and human experiments to stimulate the release of endogenous opioids such as β-endorphin.[21] Alcohol-treated rats show an increase in the release of β-endorphin both in the peripheral blood and in the brain. This enhanced opioid receptor activity is especially apparent in animals with a high alcohol preference[22] and in humans who are at risk for alcohol dependence because of a strong family history of alcoholism.[22] If one has a strong family history of alcoholism and drinks alcohol, there seems to be a larger increase in the release of endogenous opioids, which may contribute to the risk for abusing alcohol.

SUMMARY OF PHARMACOLOGIC EFFECTS OF ALCOHOL

To summarize, research during the past 2 decades has led to a new paradigm with which to understand the pharmacologic effects of alcohol. Alcohol's effect on the GABA and NMDA systems may mediate the sedative and anxiolytic properties of alcohol. Alcohol may be used to compensate for serotonergic dysfunction, and specific subpopulations of patients may use alcohol to reduce unpleasant affective states such as anxiety or depression. Dopamine and the endogenous opioids appear to be related to the alcohol "high," or the rewarding aspects of alcohol drinking. Thus, alcohol has a variety of specific effects on neurotransmitter systems, suggesting that multiple pharmacologic interventions may be useful in the treatment of alcohol addiction. For example, to counter the effects of alcohol withdrawal, medications such as benzodiazepines are used to enhance GABA activity. Medications that reduce NMDA activity, such as acamprosate, are also being used (primarily in Europe) to enhance abstinence rates. Patients using alcohol to cope with anxiety or mood disorders are prescribed medications such as SSRIs to help reduce the risk of relapse. Finally, opiate antagonists are used to reduce alcohol craving and relapse.

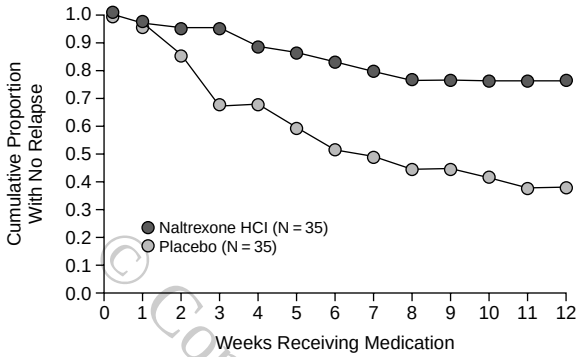
NALTREXONE AS AN EXAMPLE OF A PHARMACOLOGIC TREATMENT FOR ALCOHOLISM

The clinical use of naltrexone is a good example of how our basic understanding of alcohol's pharmacologic effects has led to a new effective treatment. Preclinical studies performed in the 1980s showed that opioid antagonists such as naloxone or naltrexone could decrease alcohol preference,[23–25] particularly in animals with high alcohol preference.[22] It was also discovered that rats genetically engineered to lack opioid receptors do not self-administer alcohol.[26] Finally, a low dose of morphine was found to increase the desire to drink alcohol in animal models.[27] These results suggested that the cycle of alcohol addiction might be triggered by the enhancement of opioid receptor activity—that alcohol drinking in some people creates the need for more drinking by increasing the release of endorphins.[28] It was therefore suggested that opioid antagonists might be capable of disrupting the addiction cycle in humans by blocking the effects of endorphins released during alcohol drinking (for a review, see Ulm et al.[26]).

The first clinical trial using naltrexone for the treatment of alcoholism was started in 1986.[29] At the outset, the authors hypothesized that naltrexone most likely would not reduce the number of people who would sample alcohol, but would substantially reduce relapse rates by decreasing the reward associated with drinking. A person was considered to have relapsed if they experienced (1) a blood alcohol concentration greater than 100 mg/dL during a treatment visit, (2) 5 or more days of drinking in the same week, or (3) 5 or more drinks during 1 drinking occasion.

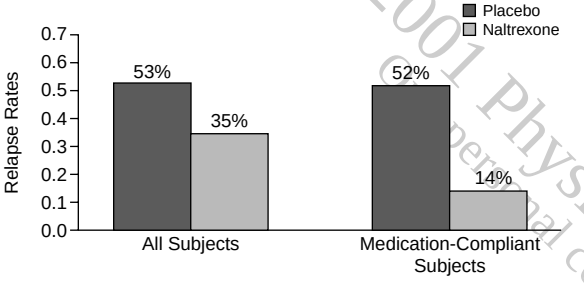
As Figure 1 shows, during the 12 weeks of treatment, approximately half of the group that received the placebo tablets relapsed. This 50% relapse rate was consistent for patients who participated in the standard psychosocial treatment at the Veterans Affairs Medical Center. The stan-

Figure 1. Relapse Rates During 12 Weeks of Treatment With Naltrexone or Placebo[a]



[a]Reprinted, with permission, from Volpicelli et al.[29]

Figure 2. Relapse Rates During 12 Weeks of Treatment With Naltrexone (50 mg/day) or Placebo[a]



[a]Data from Volpicelli et al.[31]

dard program included intensive outpatient treatment in which patients came to treatment daily for several hours each day for the first month of treatment and then for twice-weekly group therapy. Treatment included group therapy modeled after an Alcoholics Anonymous (AA) approach to alcoholism. For subjects taking naltrexone, relapse rates were reduced to less than 25%. This was the first double-blind study demonstrating that a medication could improve treatment outcomes for alcoholism.[29] These results were replicated in a similar study conducted among a nonveteran population by O'Malley and colleagues.[30]

In a second clinical naltrexone trial, my colleagues and I[31] looked at a new, heterogeneous sample of alcoholics that included women. All subjects participated in once-a-week individual addiction therapy, which mimicked standard addiction treatment programs in the community. Subjects received naltrexone (50 mg per day) for 12 weeks. The results of this study were similar to those of our first study in that naltrexone reduced relapse rates. However, inspection of the data showed that the effectiveness of naltrexone was much more pronounced among subjects who were more medication-compliant. As Figure 2 shows, among subjects who took 80% or more of their prescribed medication (medication-compliant subjects), naltrexone had a much more dramatic effect than placebo on treatment outcome. While placebo subjects relapsed at about a 50% rate, the relapse rate for the naltrexone-compliant subjects was only 14%. In interviews with the subjects, we found that some of the patients would stop taking their naltrexone so that they could experience the alcohol-induced euphoria. While naltrexone was pharmacologically effective in reducing the pleasurable effects of alcohol, its clinical effectiveness was dependent on the motivation of the subject to abstain and to adhere to the prescribed regimen. These results suggest that psychosocial treatments that enhance the motivation to remain sober and comply with therapy improve treatment outcomes.

BRENDA APPROACH

The importance of medication compliance in using pharmacologic treatments for alcohol addiction treatment led my colleagues and I to design a psychosocial treatment to enhance treatment retention and adherence. We call the approach "BRENDA," an acronym for the various stages used to improve compliance:

Biopsychosocial evaluation
Report/responsibility
Empathy
Needs assessment/goals
Direct advice
Assess response to advice (motivation to change)

Biopsychosocial Evaluation

The first step in the approach is to do a thorough biopsychosocial evaluation of patients who come for treatment. This is important because many patients who have alcohol problems have coexisting medical problems or coexisting psychiatric problems; a thorough biopsychosocial evaluation gives the clinician a good sense of the patient's situation.

Report/Responsibility

The next step is to report back to the patient what has been found in the evaluation. Simply presenting the results of such an evaluation is often effective in motivating patients to reduce their alcohol drinking.[32] In addition, giving people feedback—a report of how their alcohol drinking is affecting their lives—breaks down resistance to therapy and helps motivate healthy behavioral changes.[33]

Empathy

The next step is to show an empathic understanding of the problem. Often, patients who are shown the evidence that alcohol drinking is causing serious problems deny that they are alcoholics. Most people think of an alcoholic as someone on "skid row." Thus, many patients will justify their denial by pointing out that they are employed and

that their life has not fallen apart. So rather than confronting the patient by saying that they are in denial, the therapist should try to understand, from the patient's perspective, how they feel about what was just reported to them. For example, one might say to the patient, "It is true that you are employed and you are still with your wife, so I can understand why, from your definition of an alcoholic, you feel that you're not that bad."

Needs Assessment/Goals

The next step is to work collaboratively to determine the patient's needs. Assuming that there are no emergent medical or psychiatric problems, our approach is to ask the patient to tell us what problems they feel that they are having, rather than dictate to the patient what they should be doing. For example, we may state, "Although I understand why you do not feel that you are an alcoholic, the fact is that you have been having alcoholic binges, you showed up for work with a hangover last week, and you state that you often drink more alcohol than you intend to. Also, your blood work shows that there is an elevation in liver enzymes, most likely due to excessive drinking." The patient may not be bothered by the effect of drinking on work, but may be concerned that his or her blood work shows liver damage. For this patient, the "hook" may be physical health issues; by focusing on this concern, one is more likely to engage the patient in treatment.

Direct Advice

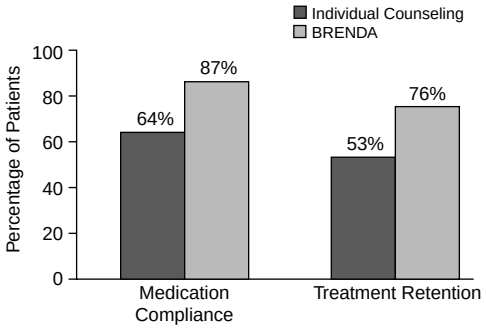
Once the patient's needs are established, the clinician is in a position to give direct advice. For example, the clinician may advise the patient to abstain from or reduce drinking, to use medications to reduce the risk of relapse, to seek help from community support groups, or to attend family, couple, individual, or group counseling (or some combination of these). Patients are more likely to follow through with the treatment recommendation and reduce their drinking if they are given an informed choice of treatment options without confrontation.[34]

Assess Response to Advice

The final step in the approach is to assess the patient's response to direct advice. Some people will say that they are not yet ready to make a change, placing them at a precontemplative stage of change. Some people are very motivated to change. It is not appropriate to give up on someone who is not ready to change. In many typical treatment programs, if someone is not very motivated, they are encouraged to come back when they are ready. My colleagues and I prefer to work with people to try to motivate them to change. We do so by repeating the preceding steps.

My colleagues and I used the BRENDA approach in our third naltrexone trial and evaluated medication adherence and treatment retention for the first 3 months of treatment.[35] As shown in Figure 3, the BRENDA condition was associated with better treatment compliance and better treatment retention compared with the type of individual counseling used in our previous study.[31] This suggests that the BRENDA approach can enhance the success of therapy. We are currently conducting a study in which we are directly comparing the BRENDA approach with traditional counseling and simple physician medication management.

Figure 3. Treatment Compliance and Retention in Patients Undergoing Individual Counseling or the BRENDA Approach[a]



[a]Data from Pettinati et al.[35]

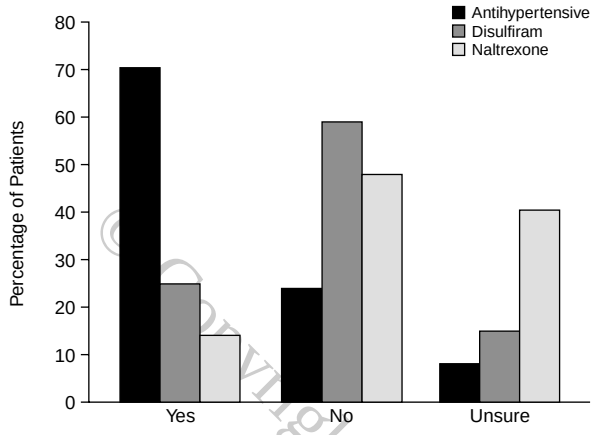
BARRIERS TO INTEGRATING PHARMACOTHERAPY IN ALCOHOL ADDICTION TREATMENT

Despite empirical data showing that medications such as naltrexone can significantly reduce alcohol relapse rates, medications are not widely used to treat alcoholism following detoxification. To put this into perspective, consider that the population of people needing treatment for alcoholism is comparable in size to the population of people with major depression (approximately 20 million each). In the United States, over 1 billion doses of medication are dispensed for the treatment of depression annually, while fewer than 5 million naltrexone doses are dispensed annually. Why do medications for the treatment of alcoholism receive such little clinical attention? Three important challenges make the introduction of medications for alcoholism treatment difficult.

First, unlike medications that treat emotional distress, there is no relief of symptoms from medications (e.g., naltrexone) that block the reinforcing effects of drugs. While a reduction in craving may provide some relief for the patient, there are no inherently rewarding properties associated with taking naltrexone. If a medication helps a patient feel better immediately or even over the next few weeks, then the immediate relief, or the promise of imminent relief, reinforces the benefit of the drug. If the drug merely blocks the high from drinking, then there is no inherent reinforcement or promise of reward.

Second, many patients and clinicians believe that people with sufficient willpower should be able to conquer

Figure 4. Results From a Survey Questioning Patients Whether They Would Take an Antihypertensive, Disulfiram, or Naltrexone[a]



[a]Data from Swift et al.[36]

their addiction on their own. Often, taking medicine is considered to be "cheating" or a "crutch." This stigma may explain why it is difficult to introduce medications into the addiction-treatment market. A recent survey by Swift et al.[36] which asked members of AA if they would take an antihypertensive medication, disulfiram, or naltrexone illustrates the point. As Figure 4 shows, about 70% said that they would use antihypertensives, 22% said that they would refuse treatment, and 6% were unsure. In contrast, only 25% would agree to take disulfiram, while 60% would refuse. Strikingly, only 14% of the respondents said that they would take naltrexone. A fair percentage of people—all in treatment and going to AA meetings—said they would never take a medication to help in their addiction treatment.

The third and perhaps most important reason naltrexone is not more widely prescribed is simply the lack of knowledge about the drug. Forty percent of the respondents to the AA survey simply did not know if they would take the medication. It is among this group that educational programs and effective marketing would increase clinical interest in naltrexone and other medications that are developed for alcoholism treatment.

CONCLUSIONS

Given the significant medical and economic consequences resulting from alcoholism and alcohol abuse, it is important to use available therapies. Current treatments are effective for about half of patients and lead to significant cost reductions. Advances in the understanding of the pharmacology of alcohol have led to the development of effective medications such as naltrexone to improve treatment outcomes. While naltrexone is not widely used to treat alcoholism, increased understanding and the development of other medications and treatment strategies for use alone or in combination with naltrexone promise to dramatically change the clinical practice of alcoholism treatment.

Drug names: citalopram (Celexa), disulfiram (Antabuse), fluoxetine (Prozac), naloxone (Narcan and others), naltrexone (ReVia), nefazodone (Serzone), sertraline (Zoloft).

REFERENCES

1. Grant BF. Prevalence and correlates of alcohol use and DSM-IV alcohol dependence in the United States: results of the National Longitudinal Alcohol Epidemiologic Survey. J Stud Alcohol 1997;58:464–473
2. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
3. Grant B, Harford TC, Dawson DA, et al. Prevalence of DSM-IV alcohol abuse and dependence, United States 1992. Alcohol Health Res World 1994;18:243–248
4. Rice DP. Economic costs of substance abuse, 1995. Proc Assoc Am Physicians 1999;111:119–125
5. Burke TR. The economic impact of alcohol abuse and alcoholism. Public Health Rep 1988;103:564–568
6. McGinnis JM, Foege WH. Mortality and morbidity attributable to use of addictive substances in the United States. Proc Assoc Am Physicians 1999; 111:109–118
7. Project MATCH Research Group. Matching alcoholism treatments to client heterogeneity: treatment main effects and matching effects on drinking during treatment. J Stud Alcohol 1998;59:631–639
8. Gerstein DR, Johnson RA, Larison CL. Alcohol and Other Drug Treatment Outcomes for Parents and Welfare Recipients: Outcomes, Benefits, and Costs. Washington, DC: US Dept Health Human Services, Office of the Assistant Secretary for Planning and Evaluation; 1997
9. Holder HD, Hallan JB. Impact of alcoholism treatment on total health care costs: a six-year study. Adv Alcohol Subst Abuse 1986;6:1–15
10. Nevo I, Hamon M. Neurotransmitter and neuromodulatory mechanisms involved in alcohol abuse and alcoholism. Neurochem Int 1995;26:305–336; discussion 337–342
11. Bucholz KK. Nosology and epidemiology of addictive disorders and their comorbidity. Psychiatr Clin North Am 1999;22:221–240
12. Naranjo CA, Bremner KE. Serotonin-altering medications and desire, consumption and effects of alcohol-treatment implications. EXS 1994;71: 209–219
13. Kranzler HR, Burleson JA, Korner P, et al. Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. Am J Psychiatry 1995;152:391–397
14. Kranzler HR, Burleson JA, Del Boca FK, et al. Buspirone treatment of anxious alcoholics: a placebo-controlled trial. Arch Gen Psychiatry 1994;51: 720–731
15. Cornelius JR, Salloum IM, Ehler JG, et al. Fluoxetine in depressed alcoholics: a double-blind, placebo-controlled trial [see comments]. Arch Gen Psychiatry 1997;54:700–705
16. Roy-Byrne PP, Pages KP, Russo JE, et al. Nefazodone treatment of major depression in alcohol-dependent patients: a double-blind, placebo-controlled trial. J Clin Psychopharmacol 2000;20:129–136
17. Pettinati HM, Volpicelli JR, Pierce JD Jr, et al. Improving naltrexone response: an intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. J Addict Dis 2000;19:71–83
18. Cowen MS, Lawrence AJ. The role of opioid-dopamine interactions in the induction and maintenance of ethanol consumption. Prog Neuropsychopharmacol Biol Psychiatry 1999;23:1171–1212
19. Herz A. Endogenous opioid systems and alcohol addiction. Psychopharmacology (Berl) 1997;129:99–111
20. Phillips TJ, Brown KJ, Burkhart-Kasch S, et al. Alcohol preference and sensitivity are markedly reduced in mice lacking dopamine D_2 receptors. Nat Neurosci 1998;1:610–615
21. Gianoulakis C. Endogenous opioids and excessive alcohol consumption. J Psychiatry Neurosci 1993;18:148–156
22. Gianoulakis C, de Waele JP, Thavundayil J. Implication of the endogenous opioid system in excessive ethanol consumption. Alcohol 1996;13:19–23

23. Altshuler HL, Phillips PE, Feinhandler DA. Alteration of ethanol self-administration by naltrexone. Life Sci 1980;26:679–688
24. Myers RD, Borg S, Mossberg R. Antagonism by naltrexone of voluntary alcohol selection in the chronically drinking macaque monkey. Alcohol 1986;3:383–388
25. Volpicelli JR, Davis MA, Olgin JE. Naltrexone blocks the post-shock increase of ethanol consumption. Life Sci 1986;38:841–847
26. Ulm RR, Volpicelli JR, Volpicelli LA. Opiates and alcohol self-administration in animals. J Clin Psychiatry 1995;56(suppl 7):5–14
27. Reid LD. Endogenous opioids and alcohol dependence: opioid alkaloids and the propensity to drink alcoholic beverages. Alcohol 1996;13:5–11
28. Volpicelli JR. Uncontrollable events and alcohol drinking. Br J Addict 1987;82:381–392
29. Volpicelli JR, Alterman AI, Hayashida M, et al. Naltrexone in the treatment of alcohol dependence [see comments]. Arch Gen Psychiatry 1992;49: 876–880
30. O'Malley SS, Jaffe AJ, Chang G, et al. Naltrexone and coping skills therapy for alcohol dependence: a controlled study. Arch Gen Psychiatry 1992;49:881–887
31. Volpicelli JR, Rhines KC, Rhines JS, et al. Naltrexone and alcohol dependence: role of subject compliance [see comments]. Arch Gen Psychiatry 1997;54:737–742
32. Hester RK, Miller WR. Handbook of Alcoholism Treatment Approaches: Effective Alternatives. Boston, Mass: Allyn & Bacon; 1995
33. Miller WR. Increasing Motivation to Change. Boston, Mass: Allyn & Bacon; 1995
34. Miller WR, Benefield RG, Tonigan JS. Enhancing motivation for change in problem drinking: a controlled comparison of two therapist styles. J Consult Clin Psychol 1993;61:455–461
35. Pettinati HM, Volpicelli JR, Kranzler HR, et al. Sertraline treatment for alcohol dependence: interactive effects of medication and subtype. Alcohol Clin Exp Res 2000;24:1041–1049
36. Swift RM, Duncan D, Nirenberg T, et al. Alcoholic patients' experience and attitudes on pharmacotherapy for alcoholism. J Addict Dis 1998;17:35–47