

Treatment of Alcohol Dependence With Medications

In recent years, the development of new medications to treat alcohol dependence, representing the combined efforts of neuroscientists and clinical researchers, has begun a new era in alcoholism treatment. Until 1995, the only medical treatment approved for use in the United States (disulfiram) simply provoked intense physical symptoms such as vomiting upon the ingestion of alcohol. In contrast, newer drugs for alcoholism treatment operate at the molecular level of the brain processes that promote and maintain addiction. The targeted actions of these newer drugs offer the possibility of more effective treatment options for the millions of alcohol-dependent persons in our Nation.

Over the past decade, advances in knowledge of the biology underlying drinking behavior have laid the groundwork for new pharmacologic treatments for alcohol dependence. For example, it is now known that multiple chemical messenger systems in the brain, called neurotransmitter systems, are involved in problem drinking. Several medications that affect different neurotransmitter systems have been tested in humans.

In particular, one area of research has focused on a class of medications called “opiate antagonists.” These medications interfere with neurotransmitter systems that produce pleasurable effects, such as feelings of euphoria, upon the use of alcohol and other drugs. If patients resume drinking while taking opiate antagonists, they are not rewarded with the expected “high” from the alcohol. Two of these drugs, naltrexone and nalmefene, have shown promising results for treating alcohol dependence. In 1995 naltrexone (ReVia) was approved by the U.S. Food and Drug Administration (FDA) for treating alcohol dependence, while nalmefene is in the testing phase of development.

In addition, researchers are evaluating medications that target different neurotransmitter systems involved in maintaining dependence

on alcohol. One such medication, acamprosate, holds promise in reducing the return to drinking, following a brief period of abstinence, that typifies alcohol dependence. Moreover, investigators are examining the possibility that combining a medication that reduces the risk of relapse (such as acamprosate) with one that reduces the risk of heavy drinking should relapse occur (such as an opiate antagonist) may increase treatment effectiveness.

Pharmacology research has focused not only on drugs to treat alcoholism itself, but also on medications for coexisting conditions that can threaten recovery. Current research continues to show that antidepressants, both old and new, are powerful agents for helping persons with alcohol dependence who also suffer from depression to gain and maintain abstinence from alcohol. Patients with untreated depression often relapse to drinking, whereas those who take antidepressants generally participate more in treatment programs and respond better. Recent studies in this area have strengthened the findings of previous research by using larger, more diverse patient samples and new types of antidepressants.

Medications hold great promise but at present cannot replace psychological treatments for people with alcohol dependence. These two classes of treatment strategies are complementary rather than competitive, in that studies suggest that pharmacologic agents may be combined effectively with skilled counseling to improve treatment outcomes (O’Malley et al. 1992, 1996). This section focuses on recent advances in pharmacotherapy research in two main areas: (1) medications specifically used to treat alcohol dependence, and (2) medications to treat some patients who suffer not only from alcohol dependence but also from psychiatric disorders, primarily depression. (For an update on research on psychological treatments, see the previous section “Treatment of Alcohol Dependence With Psychological Approaches” in this chapter.)

Medications for Alcohol Dependence

In 1992, alcohol researchers proposed the attributes of a “perfect medication” for treating alcohol dependence (Volpicelli et al. 1992). The drug they were seeking would reduce the craving for alcohol so that an individual would be less motivated to drink. The ideal drug also would block the reinforcing effects of alcohol so that if the individual resumed drinking, pleasant effects would not be felt. In addition, the medication would have few, if any, side effects. With these goals in mind, researchers have made significant progress in recent years.

Blocking the Reward: Opiate Antagonists

The treatment of alcohol dependence has benefited from decades of research that have led to an understanding of the mechanics of addiction and of the way in which certain medications can counter the effects of addictive drugs. Substances like heroin and morphine, called opiates, act like chemicals the brain produces naturally, called endogenous opioids, which stimulate pleasurable feelings and suppress pain. Medications known as opiate antagonists bind with the brain’s receptors for endogenous opioids, thus blocking the desired effects of heroin and similar drugs while having no effect themselves.

Alcohol is not an opiate-like substance, and researchers do not know the exact mechanism by which opiate antagonists affect drinking. Animal studies suggest, however, that these medications block some of alcohol’s rewarding effects. When researchers administered an opiate antagonist (naltrexone) to rats that were later given alcohol, the medication decreased the amount of alcohol-induced dopamine, a neurotransmitter involved in motivation and reinforcement that is available in a reward center in the brain (Benjamin et al. 1993). Moreover, rats given larger doses of naltrexone showed even greater decreases in dopamine. This “dose-dependent” effect demonstrated that the opioid system is an important target for medications to control alcohol consumption and reward. Recent studies on two opiate antagonists, naltrexone and nalmefene, are summarized below.

Naltrexone. Studies in humans also support the hypothesis that opiate antagonists reduce the pleasurable effects associated with alcohol’s stimulation of the endogenous opioid system and related reward systems. Patients given naltrexone described less euphoria, or “high,” from drinking than did patients taking a placebo (Volpicelli et al. 1995*b*). Similarly, social drinkers given naltrexone in a laboratory told researchers they felt fewer stimulant effects of alcohol and more of its sluggish, sedative effects (Swift 1995; Swift et al. 1994). Thus, by reducing the positive reinforcement of drinking and increasing unpleasant effects, naltrexone may help abstinent individuals who relapse to refrain from heavy drinking.

In another study, social drinkers who were pretreated with naltrexone waited longer to have both their first and their second drinks (Davidson et al. 1996*b*). This finding suggests that opiate antagonists block both the chemical changes in the brain elicited by environmental cues before drinking and the “priming” effects of alcohol during drinking—phenomena associated with the urge to drink and loss of control over drinking. Researchers who reexamined data (O’Malley et al. 1995) from two previous clinical trials of naltrexone (O’Malley et al. 1992; Volpicelli et al. 1992) found that patients with alcoholism who took naltrexone and who ultimately returned to drinking refrained a longer time until their first drink and their first episode of heavy drinking than did patients who took a placebo. Among the patients in the study who drank, those using naltrexone drank less frequently and on a significantly smaller percentage of days than did placebo-treated patients, and they were less likely to relapse to heavy drinking.

Persons with alcoholism share two core symptoms: the tendency to drink more than they intend to and drinking at levels that lead to medical, psychological, or social problems, such as missing work and failing to fulfill family responsibilities. Naltrexone appears to have a significant effect on both of these symptoms of alcohol dependence. In two early studies, the researchers gave naltrexone to recently detoxified outpatient

volunteers who came from diverse racial/ethnic and economic backgrounds and who had received different types and intensities of behavioral treatments for alcoholism (O'Malley et al. 1992; Volpicelli et al. 1992). Regardless of differences in demographic traits and behavioral treatments, patients given naltrexone had similar outcomes across all groups: they drank less frequently, and when they drank, they consumed less alcohol.

No medication can be fully effective unless it is used as directed, that is, taken as scheduled and for the full course of treatment. The degree to which patients are compliant in taking medication as directed is a key measure of efficacy in all drug studies. Reasons for noncompliance include unpleasant side effects, expense, and complicated dosing schedules. Recent research suggests that patients' compliance with naltrexone is excellent in a treatment research setting. When naltrexone use was verified by urine testing, it was found that 92 percent of naltrexone-treated patients were compliant, compared with 78 percent of placebo-treated patients (O'Malley et al. 1992). Other investigators noted that naltrexone was especially effective in preventing relapse to heavy drinking among patients who took the medication regularly and who completed the 12-week treatment course (Volpicelli et al. 1997). Patients who took more of their naltrexone pills correctly had lower percentages of drinking days than did patients who did not take all of them correctly.

Investigators have developed an effective new method for monitoring naltrexone and its major metabolite, 6-beta-naltrexol, in human plasma (Davidson et al. 1996a; Huang et al. 1997). The new blood test, analyzed by high-performance liquid chromatography with electrochemical detection, may help researchers to refine naltrexone dosing to improve its efficacy. Some patient groups, such as women and the elderly, often respond much better to medications at lower dosages, whereas other groups require relatively high levels.

Several investigators have examined the side effects of naltrexone. A study of 570 patients

with alcoholism found no serious adverse events associated with naltrexone treatment (Croop et al. 1995). Although no systematic studies have ascertained the range of doses that might be used to treat alcoholism, the typical dose is 50 milligrams per day (mg/day). At a much higher dose—300 mg/day—naltrexone is associated with adverse liver effects (hepatotoxicity). The drug label notes that this medication is not appropriate for patients with acute hepatitis or liver failure.

Follow-up studies of patients who have used a medication can yield important information about its long-term effects as well as the potential for drug "rebound," which could lead to relapse, when the medication is discontinued. Six months after treating patients for 12 weeks with naltrexone, researchers (O'Malley et al. 1996) interviewed a subset of participants from their earlier study (O'Malley et al. 1992). They found that two-thirds of the patients originally treated with a placebo, but only one-third of naltrexone-treated patients, had resumed drinking to the point that they again met criteria for alcohol abuse or dependence. Naltrexone-treated patients also were less likely to relapse during the first month after they stopped using the medication and less likely to drink heavily during the first 4 months after treatment.

As mentioned, however, the study did find that one-third of the patients relapsed after the 12-week treatment period, suggesting that naltrexone should be continued beyond 12 weeks for some people. At the 6-month follow-up interview, patients were more likely to be abstinent from alcohol if they had been able to sustain abstinence during the initial 12 weeks of treatment with naltrexone (O'Malley et al. 1996). Because establishing abstinence is linked with better treatment outcomes, use of naltrexone beyond the 12-week period may be particularly helpful to patients who have difficulty with abstinence during initial treatment.

In addition, some patients may have no trouble achieving abstinence during initial naltrexone treatment, but they may anticipate periods of

relapse risk, such as an upcoming vacation, or experience sudden stressful events, such as the death of a friend. These patients may benefit by using naltrexone again for short periods until they feel more secure about their coping skills in avoiding relapse. Longer term studies of maintenance treatment with naltrexone are under way to determine the appropriate duration of treatment for different groups of patients.

Determining which patients are likely to benefit from this treatment is prudent because naltrexone is moderately expensive: the standard daily 50-mg tablet for an alcohol-dependent person retails at almost \$5. Additionally, as with any new medication, naltrexone must be used more widely before firm conclusions are drawn about risks and benefits. Early trials suggest that the patients who may derive the greatest benefit from naltrexone are those who experience an intense urge to drink and who have physical symptoms, such as chronic pain or discomfort, coupled with poor cognitive functioning, such as impaired learning skills and memory (Jaffe et al. 1996; Volpicelli et al. 1995a).

A large cooperative study is now under way at 15 U.S. Department of Veterans Affairs medical centers to examine alcoholism treatment with naltrexone for up to 1 year. The 600 veterans assigned to naltrexone or a placebo also will receive a standardized behavioral intervention, the Alcoholics Anonymous-based 12-step facilitation treatment designed for the project Matching Alcohol Treatments To Client Heterogeneity (Project MATCH) (see also the previous section in this chapter, “Treatment of Alcohol Dependence With Psychological Approaches”). The study will also evaluate the cost-effectiveness of naltrexone.

Nalmefene. Nalmefene, a newer opiate antagonist that is not yet approved by the FDA for treatment of alcoholism, is structurally similar to naltrexone but has potential advantages for treating alcohol dependence. Unlike naltrexone, for example, nalmefene has shown no dose-dependent liver toxicity (Mason et al. 1999). In addition, nalmefene is considered a “universal” opiate antagonist, in that it binds more readily with

the three subtypes of opioid receptors that are thought to reinforce alcohol consumption (Charness et al. 1983; Culpepper-Morgan et al. 1995; Emmerson et al. 1994; Michel et al. 1985; Tabakoff and Hoffman 1983), whereas naltrexone specifically binds to just one receptor subtype and may affect the other two only at high doses (Sawynok et al. 1975).

This new study reinforced findings from a small pilot study on nalmefene that showed that alcohol-dependent patients taking 40 mg/day had significantly lower rates of relapse in preliminary studies than did either patients on the placebo or those on 10 mg/day of nalmefene (Mason et al. 1994).

In a recent study of 105 patients, those who were randomly assigned to nalmefene (20 or 80 mg/day) were 2.4 times less likely to relapse to heavy drinking during the 12 weeks of treatment than those who received a placebo. Although one-third of the patients treated with nalmefene did relapse to heavy drinking at least once during the trial, they had fewer subsequent heavy-drinking episodes than did those taking the placebo. The researchers found no significant differences between 20-mg and 80-mg doses of nalmefene, and the patients taking either dose of nalmefene had high rates of compliance and showed no evidence of medically serious side effects (Mason et al. 1999).

Replicating the results of naltrexone studies with this structurally similar compound supports the importance of further research on opiate antagonists to treat alcohol dependence. Nalmefene may be an option for patients who experience adverse side effects from naltrexone or who do not respond to that drug.

Reducing Rates of Relapse: Acamprosate

The medication acamprosate interacts with different biochemical pathways in the brain than those affected by opioid antagonists. Although the precise mechanism of action is still under investigation, acamprosate is known to affect two neurotransmitter systems involved in maintaining alcohol dependence: the glutamate system and

the gamma-aminobutyric acid system. While chronic alcohol exposure disrupts both systems, causing changes that may persist for many months following withdrawal, acamprosate may act by restoring normal activity in these systems (al Qatari and Littleton 1995).

Having been available by prescription in France since 1989, and more recently in more than 30 countries around the world, acamprosate has been used to treat more than 1 million alcohol-dependent people. In the United States, the FDA has granted acamprosate the status of an investigational new drug. A 6-month clinical trial was designed to evaluate the safety and efficacy of acamprosate in the United States across 21 different treatment settings, including psychiatry, internal medicine, and alcoholism treatment programs (Mason and Goodman 1997). This study has recently been completed, and the data are now being analyzed.

Studies of acamprosate in animals and humans have demonstrated many potential benefits. For example, it decreases voluntary alcohol intake with no effects on food and water consumption, no potential for abuse, and no pharmacologic effects other than those involved in reducing alcohol dependence (Soyka 1996). In addition, there is no evidence that acamprosate interacts pharmacologically with alcohol or with other medications prescribed for alcoholism, such as disulfiram, or for depression, anxiety, psychoses, or insomnia (Durbin et al. 1996). Moreover, unlike naltrexone, acamprosate is not metabolized to a meaningful extent in the liver; therefore, patients with liver dysfunction can gain the same therapeutic effects as other patients (Wilde and Wagstaff 1997).

In 11 clinical trials in Europe, which included a total of 3,338 patients from many treatment centers, researchers compared the effectiveness of acamprosate with that of a placebo. In 10 of the studies, patients on acamprosate experienced higher abstinence rates and, for those who did resume drinking, a significantly longer period of abstinence until their first drink than did patients

on the placebo (Geerlings et al. 1997; Lhuintre et al. 1990; Paille et al. 1995; Pelc et al. 1997; Sass et al. 1996; Soyka 1996; Whitworth et al. 1996). Acamprosate produced better outcomes than the placebo in studies in which the drug was administered for as long as 1 year, as well as in follow-up studies in which subjects were reinterviewed 6 to 12 months after stopping the acamprosate treatment (Geerlings et al. 1997; Sass et al. 1996). The single European trial with negative results differed from the other 10 trials in that treatment that is normally initiated immediately after detoxification was delayed up to 2 months. By the time that study began, one-third of the subjects had relapsed (Soyka 1996).

Although some of the 10 positive European trials had stronger results than others, the outcomes consistently favored acamprosate over the placebo in rate and duration of abstinence and other measures. When researchers analyzed pooled data from all 11 trials, the patients on acamprosate were found to have significantly higher rates of abstinence and treatment attendance than those on the placebo, as well as longer alcohol-free periods (Mann et al. 1995). The effects of acamprosate were evident during the first 30 to 90 days of treatment (Ladewig et al. 1993; Sass et al. 1996), the interval in which the risk of drinking is the highest and pharmacologic support may be most effectively implemented (Meyer 1989). In these trials, any additional effect of behavioral therapy could not be evaluated because none of the trials included standardized behavioral therapy; instead, each treatment center provided whatever behavioral therapy it routinely offered (Mann et al. 1995).

Comparing and Combining Acamprosate With Naltrexone

No single study has directly compared acamprosate with naltrexone. However, researchers have compared each medication with a placebo in separate studies that yielded quite similar results. At the end of the 12-week course of medication, 51 percent of the acamprosate-treated patients (Pelc et al. 1997) and 54 percent of the naltrexone-treated patients (O'Malley et al. 1995)

had stopped drinking. The rates for placebo were 26 percent and 31 percent, respectively. Although the abstinence rates achieved by both acamprosate and naltrexone were notably better than the rates with placebo, nearly one-half of the subjects remained at risk for drinking during the treatment study.

Because several neurotransmitter systems are involved in maintaining alcohol dependence, the effect of any single medication on alcohol intake may be modest. Both acamprosate and naltrexone are well tolerated by patients, and the medications' affinities for different neurotransmitter receptors may lead to different effects on drinking outcomes (such as preventing relapse to heavy drinking or prolonging abstinence). Thus, the National Institute on Alcohol Abuse and Alcoholism is currently funding a cooperative, multicenter study that will test acamprosate and naltrexone, both alone and in combination, and evaluate their use (vs. a placebo) in conjunction with behavioral interventions of either moderate or minimum intensity.

Evaluating Serotonergic Agents for Treatment of Alcohol Dependence

The neurotransmitter serotonin affects multiple actions in the brain, including the regulation of mood states, appetite, and sleep. The exact nature of the relationship between serotonin and alcoholism is unknown. One theory suggests that individuals with alcohol dependence are naturally deficient in brain serotonin. According to this view, alcoholism may represent an attempt to increase brain serotonin levels. Another theory suggests that serotonin either directly influences the reinforcing effects of alcohol and other drugs or exerts an indirect influence through an effect on the neurotransmitter dopamine. A third suggestion is that low levels of serotonin lead to impulsive behavior, including an inability to modulate alcohol intake. Abnormalities in the brain's serotonin system may contribute to anxiety, potentially leading to "self-medication" of anxiety symptoms with alcohol. Finally, serotonin may affect general appetite behaviors.

Researchers have examined whether alcohol intake could be reduced by medications that increase the amount of serotonin available for binding with receptors on nerve cells in the brain. Among the "serotonergic" agents that have been evaluated for alcoholism treatment are sertraline (Zoloft), fluoxetine (Prozac), and several other "selective serotonin reuptake inhibitors" (SSRI's), a class of drugs developed in the 1980's to treat depressive disorders. These drugs act at the molecular level where nerve cell endings release serotonin, which then binds to specialized receptors—of which at least 14 different subtypes have been identified—on adjacent nerve cells (Fuller 1996). Normally, the nerve cells that release serotonin also reabsorb some of it, but SSRI's inhibit that reuptake so that more serotonin is available to bind with receptors on other nerve cells.

In addition to medications that inhibit reuptake of serotonin, other agents take advantage of different mechanisms in the serotonin system. For example, a "serotonin receptor antagonist" that blocks a specific receptor subtype (called 5-HT₃) has been shown to reduce one of the reinforcing effects of alcohol, the release of the neurotransmitter dopamine in the brain (Campbell and McBride 1995; Yoshimoto et al. 1991).

Thus far, studies on the effectiveness of serotonergic agents in reducing alcohol intake have shown only a mild and transient effect in moderate drinkers and no effect in alcohol-dependent patients (for a review of these studies, see Litten et al. 1996). In one multicenter study involving 423 alcohol-dependent patients, researchers examined ritanserin, a drug that blocks a serotonin receptor called 5-HT₂, and found it no more effective than a placebo in controlling alcohol craving and consumption (Johnson et al. 1996). Because patients on higher doses of ritanserin had abnormalities in their electrocardiograms, no further study of this drug was undertaken.

Similarly, when researchers gave fluoxetine, a widely used SSRI, to 28 male inpatients with

severe alcohol dependence, they found it to be no better than a placebo in reducing relapse rates (Kabel and Petty 1996). These findings confirmed those of an earlier study of 101 patients in which fluoxetine was not any more effective than a placebo in reducing alcohol consumption (Kranzler et al. 1995).

Although serotonergic agents have not fulfilled the promise they once seemed to offer in treating alcoholism, a recent study in animals suggests this as an area for further research. The researchers gave rats a combination of fluoxetine and a serotonin receptor antagonist called WAY 100635, which is still in development (Zhou et al. 1998). This combination of medications reduced the rats' alcohol consumption more than either compound alone. The authors speculated that combining these drugs increased the available serotonin to a level not achievable by fluoxetine alone.

Overall, however, clinical findings to date suggest that the serotonergic agents studied thus far are not effective for treating alcohol dependence itself, but rather, as described next, for the treatment of cooccurring psychiatric conditions such as depression.

Medications for Patients With Both Alcoholism and Depression

People with alcohol dependence often experience symptoms of depression when they stop drinking. For most individuals, these symptoms disappear or wane during the first 1 or 2 weeks of abstinence. However, studies have shown that patients who continue to report serious depressed feelings after the 1st week of abstinence are likely to have a depressive disorder that coexists with their alcohol dependence. These patients are often referred to as having "comorbid depression" or a "dual diagnosis." If the depression is left untreated, many will relapse to drinking. Thus, accurate diagnosis of depression and its swift treatment are critical in the care of alcohol-dependent patients.

Investigators have examined different types of antidepressant agents for dually diagnosed

patients, including the older tricyclic antidepressants such as imipramine and desipramine, which have been available since the 1960's, and the newer SSRI's such as sertraline and fluoxetine. The availability of SSRI's has allowed more aggressive treatment of depression in alcohol-dependent patients because these medications have few side effects and can be taken safely by individuals who continue to drink, unlike tricyclic and other antidepressants that interact significantly with alcohol (Schottenfeld et al. 1989).

As described below, studies show that regardless of the type of antidepressant used, depressed alcohol-dependent patients who take antidepressants have better outcomes in terms of their drinking than do those who take a placebo. Clinical trials of antidepressants for dually diagnosed patients tend to have small sample sizes, which limits the extent to which the findings can be generalized to larger and more diverse patient groups. However, the scientific methods used in these small studies are generally rigorous, and, taken as a whole, the findings suggest significant progress in refining treatment for this subgroup of persons with alcohol dependence who are at increased risk for illness and death because of their dual disorders.

Recent studies of imipramine (McGrath et al. 1996) and fluoxetine (Cornelius et al. 1997) confirm previous work showing that depressed people with alcoholism who are given antidepressants experience greater decreases in depression and alcohol consumption than do those given a placebo (Kranzler et al. 1995; Mason and Kocsis 1991; Mason et al. 1996; Nunes et al. 1993). Some participants in these antidepressant trials continued to drink even though their depression lifted, which demonstrates the need for additional interventions specific to drinking.

In making decisions about diagnosis and treatment of alcohol-dependent patients, some clinicians distinguish between primary depression, which occurs before the onset of alcoholism, and secondary depression, which occurs afterwards.

Studies of both types of depressed patients with alcoholism have shown essentially the same findings: antidepressant medications improve mood and reduce drinking whether the patients' depression is primary (McGrath et al. 1996; Nunes et al. 1993) or secondary (Mason et al. 1996).

Finding the optimal dosage of antidepressants for dually diagnosed patients has also been an area of investigation, because ineffective treatment of depression may lead to relapse during the early stages of abstinence. Many patients with a long-term history of alcoholism have liver dysfunction, which may alter their metabolism of certain medications so that they require higher or lower dosages. A 6-month study examining the metabolism of antidepressants by patients with and without current alcoholism found that alcoholic patients without cirrhosis may benefit from higher dosages of antidepressants, because changes in their liver functioning during early abstinence speed up their metabolism of these drugs (Mason 1996).

In Closing

Alcohol's precise effects on the reward centers of the brain are still not fully understood, but laboratory studies and clinical trials continue to increase our knowledge of new medications to augment behavioral therapies for alcohol dependence. In recent years, these studies have shown that: (1) naltrexone and a similar compound, nalmefene, help reduce the chance of heavy drinking when abstinent individuals relapse; (2) acamprosate can prevent relapse by making it easier to maintain abstinence; (3) SSRI's are not useful in treating alcohol dependence itself; and (4) not only SSRI's, but also other antidepressants, are successful in treating coexisting depression that may lead patients with alcohol dependence to relapse if the depression is left untreated.

Currently, clinical trials are under way to search for new and more effective pharmaceutical agents to treat alcohol-dependent individuals. Among

these are trials designed to explore whether combining acamprosate and naltrexone, two highly tolerable and effective drugs, can enhance treatment outcomes when they are provided along with behavioral therapies; to test the safety and efficacy of different dosages of acamprosate; and to study sertraline as a representative of the safe and tolerable SSRI's for treating depression that coexists with alcoholism.

Studies will also be needed to identify the most appropriate medications for different subgroups. Current research has confirmed that alcohol is metabolized differently by women (see review by Romach and Sellers 1998) and by older adults (see review by Ownby et al. 1996) than it is by younger men, who have constituted the majority of subjects in studies of the pharmacotherapy of alcoholism. Future research will need to examine data from women, older adults, and other subgroups to determine the medications that are most effective and acceptable, with the fewest adverse side effects, for different groups of patients.

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