



*P*harmacology



PHARMACOLOGY

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SEARCHING FOR NEW DETOXIFICATION STRATEGIES

- *Alcohol withdrawal syndrome (AWS) can range from no symptoms to a life-threatening event.*
- *In the United States, anti-anxiety agents called benzodiazepines are the primary treatment for AWS, yet they can also be abused.*
- *In Europe, anticonvulsants are commonly used to treat AWS.*
- *Researchers have found that an anticonvulsant agent called divalproex sodium can significantly reduce the amount of benzodiazepine needed for treating AWS.*

Alcohol withdrawal syndrome (AWS) can range from no symptoms to agitation and intense anxiety to tremors, seizures, delusions, fatal increases in body temperature, and cardiovascular collapse. Benzodiazepines provide an alcohol-like effect, relieving AWS symptoms by substituting for the alcohol that is no longer present in the system. However, benzodiazepines are similar enough to alcohol to have significant potential for intoxication, abuse and even dependence. A study in the September issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines the viability of an anticonvulsant agent called divalproex sodium as an alternative to benzodiazepines for treating AWS.

“Alcohol, benzodiazepines and divalproex sodium all enhance gamma-aminobutyric acid (GABA) neurotransmission, one of the brain systems that becomes unbalanced during alcohol withdrawal,” said Joseph P. Reoux, a psychiatrist with the Veterans Affairs Puget Sound Health Care System and lead author of the study. “More specifically, certain anticonvulsants appear to prevent the nervous system hyperexcitability that develops during alcohol withdrawal. Although an anticonvulsant like divalproex sodium enhances the same brain inhibitory system that alcohol and benzodiazepines do, it does not have the euphoria, abuse potential or as high of a risk for cognition impairment that can occur with benzodiazepines. It also has anti-kindling properties, and tends to be better tolerated than carbamazepine (another anticonvulsant that can be used to treat alcohol withdrawal).”

“Kindling” occurs when the nervous system develops increased sensitivity to a stimulus such as withdrawal from alcohol. (Enhanced withdrawal responses are referred to as a kindling effect because of their similarity to the kindling of brain seizures.) When a nerve cell is repeatedly exposed to a stimulus that is initially too small to cause full nerve excitement, it can become more sensitive, or kindled, to the stimulus and begin to react at lower thresholds. This sensitivity persists over time and can become stronger with continued exposure to the stimulus. The concept of neuronal kindling is used to understand what clinicians may see during alcohol withdrawal: symptoms tend to become worse over time in people who repeatedly expose their brains to withdrawal from alcohol. Certainly kindling can complicate addiction by contributing to an individual’s unwillingness to forego alcohol, even when its ingestion is no longer a source of pleasure.

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SEARCHING FOR NEW DETOXIFICATION STRATEGIES

Researchers gave a primarily male inpatient population either 500 mg of the divalproex sodium formulation of divalproex sodium (also called valproate) or a placebo three times a day. Because the study participants were already experiencing withdrawal symptoms at a level that is normally medicated, they were also given a baseline dose of oxazepam (a benzodiazepine sedative) to ease their discomfort, as well as additional oxazepam if and when the severity of their withdrawal symptoms warranted it. During the seven-day study period, divalproex sodium reduced the amount of the oxazepam needed to adequately treat alcohol withdrawal. Adding divalproex sodium to the treatment regimen also appeared to stop the withdrawal symptoms from becoming worse when compared to giving oxazepam alone.

“The findings certainly support the idea that valproate is a viable treatment option for AWS,” said Reoux, “although it would be more correct to say that this study showed that using divalproex sodium significantly reduces the amount of benzodiazepine needed for the treatment of AWS. One of the more important aspects of this study is that it was scientifically rigorous. Previous studies of valproate for AWS were not randomized double-blind placebo controlled trials, so this study provides the strongest evidence to date supporting the use of valproate in the treatment of alcohol withdrawal.”

The anticonvulsant valproate has been available in Europe for treating AWS since the 1960s, but has only been marketed in the U.S. since 1978. In the U.S., benzodiazepines comprise the drug regimen of choice, despite their potential for abuse.

“Many medications are used differently in other places,” explained Richard K. Ries, a professor of psychiatry and addictions at the University of Washington. “Much of this has to do with what clinicians are used to doing. Sometimes this also has to do with pharmaceutical company marketing. Or sometimes it’s due to what the Federal Food and Drug Administration allows. For example, many meds are available in Europe well before they are available here, which has been true of many of the anticonvulsants.”

Ries is intrigued by the study’s findings because of the potential for valproate to become a new detoxification strategy. “AWS is an immense problem which affects patients in medical, surgical, and psychiatric settings as well as in addiction treatment populations,” he said. “Yet there is a paucity of research documenting new and better ways to deal with it. This pilot study makes a good attempt to address this and highlights the need for more research.”

Article is based on the following published research:

Reoux, J.P.,
Saxon, A.J.,
Malte, C.A., Baer, J.,
& Sloan, K.
(September 2001).
Divalproex sodium in
alcohol withdrawal:
A randomized
double-blind
placebo-controlled
clinical trial.
*Alcoholism: Clinical
and Experimental
Research*,
25(9), 1324-1329.



FINE-TUNING NALTREXONE TREATMENT FOR ALCOHOLICS

- *Naltrexone has proven to be highly effective for many in recovery, but it does not work for everyone.*
- *A recent study has found that individual metabolism may be a factor in Naltrexone's effectiveness.*
- *Its effectiveness can, in turn, be partially determined by measuring blood levels for Naltrexone and its major metabolite, 6-beta-naltrexol.*

Naltrexone is a medication that decreases the rewarding effects of drinking and reduces the craving for alcohol that often leads people to relapse. Yet despite its effectiveness for many recovering alcoholics, it does not work for everyone. A study in the September issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that Naltrexone's effectiveness may be influenced by individual metabolism, and that this may be detected by measuring blood levels for the medication's major metabolite, 6-beta-naltrexol.

"Determining blood levels may be useful for patients who are not helped by the standard Naltrexone dose," explained Mary E. McCaul, associate professor at Johns Hopkins University School of Medicine and lead author of the study. "This study demonstrates the importance of adjusting Naltrexone dosage to ensure that an adequate blood level of 6-beta-naltrexol is achieved. If an individual does not achieve a therapeutic effect at the standard Naltrexone dose of 50 milligrams per day, he or she may want to discuss a dose increase with the prescribing physician."

McCaul explained that drugs can have agonist and/or antagonist properties. Agonists activate a receptor to achieve their effect. Antagonists block the receptor from being activated by another endogenous (produced within the organism) or exogenous (produced outside the organism) chemical, but do not produce any activity of their own. Naltrexone is an opioid antagonist. This means that Naltrexone blocks the opioid receptor from being activated, but does not cause any psychoactive effects for the person taking the medicine.

Naltrexone was first developed in the 1970s as a compound to block heroin and other opioid agonists from activating the receptors for opiates like heroin. In the mid-1980s, Naltrexone was approved for the treatment of heroin addiction. In the late 1980s, researchers began to suspect that drinking alcohol was pleasurable because it released endogenous morphine-like molecules. Joseph R. Volpicelli, associate professor and senior scientist at the Treatment Research Center at the University of Pennsylvania, was one of those original researchers.

"The reward system in the brain involves several neurotransmitters," said Volpicelli, "one of which is the opioid neurotransmitter system." Activation of this system – by alcohol consumption, for example – is associated with pain relief, calming and euphoria. "When opioids are stimulated," he said, "that in turn causes an increase in the neurotransmitter called dopamine." Dopamine activity in the brain center, called the nucleus accumbens, is thought to be key

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FINE-TUNING NALTREXONE TREATMENT FOR ALCOHOLICS

to reward and experiencing the high of a variety of different drugs such as cocaine, amphetamines and nicotine. “What happens is that the brain gets a ‘taste’ of having endorphins or dopamine released, and it wants more of it,” Volpicelli continued. “So first use is like an appetizer for the brain, particularly for people who have a family history of alcoholism and may have a genetic susceptibility for becoming addicted to alcohol.”

Preclinical research has shown that animals treated with an opioid antagonist such as Naltrexone decrease voluntary consumption of alcohol in the laboratory. In human clinical trials, Naltrexone decreases alcohol consumption, slows the onset of relapse, and reduces craving for alcohol in recently abstinent alcohol-dependent patients. Yet researchers couldn’t determine why some alcoholics were helped and others were not, despite their equal commitment to quit drinking. McCaul’s findings may help resolve this mystery.

“This paper is especially important on two fronts,” said Volpicelli. “First, it begins to identify that, for at least blocking the pleasure associated with drinking, doses higher than 50 milligrams may be helpful for some people. There seems to be a huge individual variability in how Naltrexone is metabolized, so those people who may be the more rapid metabolizers may benefit from higher doses of the medication.” He explained that the usual 50-milligrams-per-day dose of Naltrexone for treatment of alcoholism was based on the dosage formerly given to heroin addicts. “Furthermore,” he said, “this study also shows us that we can measure blood levels and know if a person needs a higher dose. We can now dose people specifically to get the best level of beta-naltrexol in their system in order to have the best clinical effect.”

McCaul is planning to continue her studies in this area. “Currently,” she said, “we are using positron emission tomography to scan brain opioid receptors to determine the extent of opioid receptor blockade by Naltrexone. This may vary among individual patients as a function of possible genetic differences, effects of chronic alcohol consumption, and differences in Naltrexone blood levels. We expect that those patients with greater receptor blockade will experience greater alcoholism treatment effectiveness than patients with lower blockade. If so, this will help further elucidate the mechanisms of Naltrexone’s effectiveness in alcoholism treatment.”

“McCaul’s study as well as other studies showing how alcohol affects the brain are very important,” said Volpicelli. “They provide more evidence that alcohol addiction is a medical disease, and medicines like Naltrexone can be helpful in helping people recover.”



**Article is based
on the following
published research:**

McCaul, M.E.,
Wand, G.S., Rohde, C.,
& Lee, S.M.
(September 2000).
Serum 6-beta-naltrexol
levels are related to
alcohol responses in
heavy drinkers.
*Alcoholism: Clinical
and Experimental
Research*,
24(9), 1385-1391.

SEARCHING FOR NEW MEDICATIONS TO TREAT ALCOHOLISM

- *Naltrexone is a prescription medication taken by mouth that helps reduce drinking in alcoholics.*
- *Naltrexone is quickly metabolized in humans by the liver to a metabolite called 6-beta naltrexol.*
- *Researchers have provided the first direct evidence that 6-beta naltrexol may itself effect alcohol consumption.*
- *These results suggest that 6-beta naltrexol is a potential new medication for alcohol dependence.*

Since its 1994 approval by the Federal Food and Drug Administration, Naltrexone remains the sole prescription medication used to reduce drinking in alcoholics. Naltrexone is taken by mouth and quickly metabolized in the liver to a number of different compounds or metabolites that can be measured in blood or urine. Naltrexone's major metabolite is called 6-beta naltrexol. A study in the October issue of *Alcoholism: Clinical and Experimental Research (ACER)* examines if 6-beta naltrexol itself can reduce alcohol consumption.

“Although 6-beta naltrexol is a metabolite that can be measured in human plasma and urine after administering Naltrexone,” explained Margaret R. Rukstalis, assistant professor of psychiatry at the University of Pennsylvania-VA Treatment Research Center and lead author of the study, “it is not known if 6-beta-naltrexol is independently pharmacologically active in reducing alcohol consumption. Studies have shown that high plasma levels of 6-beta naltrexol are critical in preventing relapse to alcoholism. Yet human plasma levels of both Naltrexone and 6-beta naltrexol are highly variable following standardized oral doses of Naltrexone. This is probably related to individual differences in the ability of the liver to metabolize Naltrexone.”

First and foremost, as noted by Raymond Anton, professor of psychiatry and scientific director of the Alcohol Research Center at the Medical University of South Carolina, “alcohol works on cells in the brain. Alcohol alters the function of these cells immediately. While most people's cells return to normal once the alcohol is removed/metabolized, some people (those at risk for developing alcoholism) are likely to have their cells more permanently changed. If this occurs again and again during episodes of intoxication, the cells begin to depend on alcohol. This dependency is manifested in a change in chemical signalling between the cells.”

The reward system in the brain involves several neurotransmitters, one of which is the opioid neurotransmitter system. Activation of this system by alcohol consumption, for example, is associated with pain relief, calming and euphoria. When opioids are stimulated, that causes an increase in the neurotransmitter called dopamine. Dopamine activity in the brain center, called the nucleus accumbens, is thought to be key to reward and experiencing the “high” of a variety of different drugs, including alcohol.

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SEARCHING FOR NEW MEDICATIONS TO TREAT ALCOHOLISM

Drugs can have agonist and/or antagonist properties. Agonists activate a receptor to achieve their effect. Antagonists block the receptor from being activated by another endogenous (produced within the organism) or exogenous (produced outside the organism) chemical, but do not produce any activity of their own. Both Naltrexone and 6-beta naltrexol are opioid antagonists. This means that they block the opioid receptor from being activated.

“Repeated alcohol exposure in some individuals,” continued Anton, “may increase the cellular release of heroin/opiate-like chemicals called endorphins and enkephalins. This could lead to higher pleasure or a craving for alcohol. Drugs like Naltrexone and 6-beta-naltrexol specifically block this effect of alcohol, so that in individuals that have this type of alcohol dependency, the drug counteracts the alcohol effect.”

Rukstalis said, “Previous studies in humans have shown that plasma levels of 6-beta naltrexol following Naltrexone administration were two to 10 times as high as Naltrexone. Naltrexone is typically given in 50-mg tablets. The dose range of 6-beta naltrexol we tested was comparable to levels of 6-beta naltrexol found in humans following a 50-mg oral dose of Naltrexone.”

In the study, researchers compared the amount of alcohol drinking by rats given 6-beta naltrexol to the amount of alcohol drinking by rats given salt water. They found that alcohol drinking by the rats decreased as the doses of 6-beta naltrexol increased. “These results suggest that 6-beta naltrexol is a potential new medication to treat alcohol dependence,” said Rukstalis.

Both Rukstalis and Anton are optimistic about the future possibilities of 6-beta naltrexol as a treatment for alcoholism. “Naltrexone is so quickly metabolized by the liver that for many people,” said Rukstalis, “there is much more 6-beta naltrexol in the blood than Naltrexone. Currently, Naltrexone is the only way to obtain 6-beta naltrexol. In the future, giving patients 6-beta naltrexol directly may lead to higher and more consistent therapeutic levels compared to the variable levels seen with Naltrexone. Six-beta naltrexol may be easier to give and more effective than currently available medications that help prevent alcohol relapses in alcoholics.”

Anton added, “One nice thing about Naltrexone, even now, is that it needs to be taken only once a day, which is very important for medication compliance, especially in an alcoholic population who may be ambivalent about taking medications to begin with. If 6 beta-naltrexol shows promise, it could potentially be given every other day, or maybe produced in a skin-patch or a long term (depot) injectable format.”



Article is based on the following published research:

Rukstalis, M.R.,
Stromberg, M.F.,
O'Brien, C.P.,
& Volpicellie, J.R.
(October 2000).
6-B-naltrexol reduces
alcohol consumption
in rats.
*Alcoholism: Clinical
and Experimental
Research*,
24(10), 1593-1596.

U SING NALTREXONE TO TREAT ALCOHOLICS WITH A “MEDITERRANEAN DRINKING PATTERN”

- *Naltrexone has been used to treat alcoholism in the United States for close to a decade.*
- *Initial studies of Naltrexone’s effectiveness examined alcohol-dependent individuals who drank primarily on holidays and weekends.*
- *Researchers in Spain examined Naltrexone’s effectiveness on alcohol-dependent individuals who drank throughout the week.*
- *Fewer Naltrexone-treated subjects relapsed to heavy drinking than placebo-treated subjects.*

Many of the original studies of Naltrexone’s effectiveness examined alcohol-dependent patients with a “Scandinavian drinking pattern,” that is, greater drinking on holidays and weekends. Conversely, individuals with a “Mediterranean drinking pattern” tend to regularly consume alcohol during the week, particularly with meals. A study in the September issue of *Alcoholism: Clinical and Experimental Research (ACER)* is among the first to examine the effectiveness and safety of Naltrexone for the treatment of alcoholism among Spanish patients with a Mediterranean drinking pattern.

“Years ago,” said José Guardia, a consultant at the Hospital de la Santa Creu i Sant Pau in Barcelona, Spain and lead author of the study, “there was a clear difference between drinking patterns in the northern and southern countries of Europe. The Anglo-Saxon/Scandinavian tendency was to drink more on holidays and weekends. In France, Italy, Spain and other Mediterranean countries, wine was usually consumed with meals. However, when everyday consumption becomes heavy, and after a long period of time, severe withdrawal and organic consequences of chronic alcohol toxicity are probable. We wanted to see if there would be differences in using Naltrexone for the treatment of alcohol dependency in this population.”

Drugs can have agonist and/or antagonist properties. Agonists activate a receptor to achieve their effect. Antagonists block the receptor from being activated by an endogenous (produced within the organism) or exogenous (produced outside the organism) chemical. Naltrexone acts as an opioid antagonist within the opioid neurotransmitter system, which is a part of the brain’s reward system. When opioids are stimulated, levels of the dopamine neurotransmitter are increased, leading to the “high” that is associated with a variety of drugs. Naltrexone blocks the opioid receptor from being activated. It was first developed in the 1970s to block heroin from activating the receptors for opiates, later becoming approved for the treatment of heroin addiction in the mid-1980s. In the late 1980s, researchers began to suspect it might have uses for the treatment of alcohol addiction.

For the Guardia study, subjects were 202 alcohol-dependent patients (151 males, 51 females),

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U SING NALTREXONE TO TREAT ALCOHOLICS WITH A “MEDITERRANEAN DRINKING PATTERN”

18 to 60 years of age, who were seeking outpatient treatment from seven different treatment centers in Spain. Patients were randomly assigned to 12-weeks of treatment with either 50 mg/day of Naltrexone (n=101) or an identical-looking placebo (n=101). Patient treatment also included a psychosocial intervention, consisting of a weekly session of supportive group therapy, a weekly visit with the study physician and a nurse intervention three times a week. Following treatment, researchers evaluated the relapse rate, alcohol consumption levels, craving, adverse effects, changes in the biochemical markers of heavy drinking and possible toxicity among the final tally of 192 patients considered eligible for evaluation.

Of the Naltrexone-treated subjects, only 7.9 percent (n=8) relapsed to heavy drinking. (Heavy drinking was defined as more than five drinks per day for men, more than four drinks per day for women, or more than five drinking days per week for both genders.) Of the placebo-treated subjects, 18.8 percent (n=19) relapsed to heavy drinking. The adverse effects known to be associated with Naltrexone use (nausea, headache, abdominal discomfort, sleepiness) were low among those treated, confirming previous studies of Naltrexone’s safety and tolerability.

“The most significant finding of our study was that Naltrexone-treated alcohol-dependent subjects showed a reduced relapse rate to heavy drinking,” said Guardia, “in comparison with those patients treated with a placebo. These results demonstrate the synergistic effects of combining pharmacotherapy with psychosocial intervention. We know that alcoholism is a recoverable disease. These results show that when alcohol-dependent patients get the appropriate psychosocial intervention plus pharmacotherapy for a suitable amount of time, they can overcome this addictive disease.”

“These results open up the possibility for European alcohol-dependent patients to receive treatment with Naltrexone,” said José Pérez de los Cobos, a psychiatrist with the Addictive Behavior Unit at the Hospital de la Santa Creu i Sant Pau. In fact, since this study was conducted, Naltrexone has been authorized for the treatment of alcoholism in Spain. “Furthermore,” he added, “once we understand the effectiveness of Naltrexone, we can go on to explore its limitations. That way, future research can examine how combining Naltrexone with other medications, and even more effective psychosocial interventions, can treat alcoholism.”

Article is based on the following published research:

Guardia, J., Caso, C.,
Arias, F., Gual, A.,
Sanahuja, J.,
Ramirez, M., Mengual, I.,
Gonzalvo, B., Segura, L.,
Trujols, J., Casas, M.
(September 2002).
A double-blind,
placebo-controlled
study of Naltrexone
in the treatment of
alcohol-dependence
disorder. Results from a
multicenter clinical trial.
*Alcoholism: Clinical
and Experimental
Research*,
26(9), 1381-1387.





BEHAVIORAL THERAPIES PLUS PHARMACOTHERAPIES CAN ADD UP TO SUCCESS

- *Alcoholism treatment can include behavioral therapies and/or pharmacotherapies.*
- *A new study examines the effectiveness of combining communications, cue exposure and coping skills training with Naltrexone in a treatment program.*
- *Patients who took Naltrexone during aftercare were more alcohol-resistant than placebo recipients.*
- *Patients who received communications, cue exposure and coping skills training were less likely to relapse than education/relaxation training recipients.*

There is no singular approach to treating alcoholism. Treatment professionals can choose from an array of behavioral therapies and pharmacotherapies. However, behavioral therapies may have limited effectiveness because they do not address underlying brain processes at the neurotransmitter level. Conversely, pharmacotherapies may have limited success because they do not address the individual's need to develop coping skills, confidence about staying abstinent in risky situations, and the appropriate responses to high-risk stimuli. A study in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)* combines elements from both approaches – Naltrexone, communication skills training (CST) and cue exposure combined with urge-specific coping skills training (CET) – into a comprehensive program and then assesses its effectiveness.

“It is generally recognized that a pharmacotherapy should not be used alone without providing some behavioral treatment or counseling,” said Peter M. Monti, professor of medical sciences and director of the Center for Alcohol and Addiction Studies at Brown University and lead author of the paper. “However, behavioral treatments are often used without pharmacotherapy for alcoholism. The usual reasons are that the patient does not want to use a medication, the counselor or treatment program does not believe that the medication would be useful for the patient, or the patient is not eligible for the medication for medical reasons.”

In this study, researchers looked at the effects of prescribing Naltrexone versus a placebo during the 90 days after alcoholics completed a two-week daily alcohol treatment program. The two-week program consisted of either CST/CET training, or educational discussions and relaxation training.

“Alcoholics who took Naltrexone for at least two months of the 90 days that they were prescribed it, drank alcohol significantly less heavily as compared to alcoholics who were given a placebo,” said Monti. “While Naltrexone did not affect whether alcoholics had any drinks at all, alcoholics using Naltrexone had fewer heavy drinking days, had fewer drinks if they drank, and had fewer urges to drink. The beneficial effects of Naltrexone lasted only while the alcoholics were taking Naltrexone, suggesting that it would be helpful to prescribe Naltrexone for longer than 90 days.”

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EHAVIORAL THERAPIES PLUS PHARMACOTHERAPIES CAN ADD UP TO SUCCESS

Naltrexone acts as an opioid antagonist within the opioid neurotransmitter system, which is a part of the brain's reward system. When opioids are stimulated, levels of a neurotransmitter called dopamine are increased. Dopamine activity is thought to be key to experiencing the "high" of a variety of different drugs, including alcohol. Naltrexone decreases the rewarding effects of drinking and reduces the craving for alcohol that often leads people to relapse.

"One thing that is new about this study," said Stephanie O'Malley, professor of psychiatry at Yale University School of Medicine, "is the sequencing of therapies. The behavioral interventions were provided during day hospital treatment, while the pharmacotherapy occurred after discharge when the patient had brief contacts with a physician for 12 weeks. The results suggest that Naltrexone may be a useful aftercare strategy that, in conjunction with new communication skills and strategies for coping with urges, will help patients maintain their improvements in the long term."

Patients who received the communications, cue exposure and coping skills training were significantly less likely to report a relapse day than patients who received the education/relaxation training. Furthermore, CST/CET patients also reported fewer heavy drinking days at six- and 12-month assessments.

CST is designed to help alcoholics develop more healthy social networks in order to make relapse to drinking less likely. This is necessary for primarily two reasons: alcoholics often damage their family relationships, and many of their friends also drink heavily. Alcoholics are taught communications and conversation skills that can be used to improve their close relationships, such as learning to accept criticism and resolve conflicts gracefully, and to increase their sober friendships.

CET is designed to help alcoholics practice "bringing down" the urge to drink when they are in high-risk situations. For example, patients practice thinking about specific effects that sobriety would have for them (such as spending more time with their children), and by thinking of specific things they could do to minimize the urge to drink (such as calling a sober friend or playing basketball). These methods are individualized for each person's needs. Many treatment programs currently use some form of coping skills training, and to a lesser degree communication skills training, however, the cue exposure treatment approach is not currently used in the United States.



Article is based on the following published research:

Monti, P.M.,
Rohsenow, D.J.,
Swift, R.M., Gulliver, S.B.,
Colby, S.M., Mueller, T.I.,
Brown, R.A., Gordon, A.,
Abrams, D.B.,
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& Asher, M.K.
(November 2001).
Naltrexone and cue
exposure with coping
and communication
skills training for
alcoholics:
Treatment process
and 1-year outcomes.
*Alcoholism: Clinical
and Experimental
Research*,
25(11), 1634-1648.

A N ANTI-NICOTINE DRUG REDUCES THE REWARDING EFFECTS OF ALCOHOL

- *Mecamylamine is a drug that blocks the effects of nicotine in the brain.*
- *Mecamylamine is believed to reduce the rewarding effects of cigarette smoking.*
- *A new study has found that mecamylamine also reduces self-reported stimulant and euphoric effects of alcohol in humans, as well as their desire to drink more.*

Mecamylamine is a central nicotinic receptor antagonist that is believed to reduce the rewarding effects of cigarette smoking. Scientists have suspected for some time that common mechanisms may be involved in both nicotine and alcohol reward. Furthermore, prior research has suggested that mecamylamine blocks the reinforcing effects of alcohol in animals. A new study, published in the May issue of *Alcoholism: Clinical and Experimental Research (ACER)*, has found that mecamylamine reduces the self-reported stimulant and euphoric effects of alcohol in humans, and also decreases their desire to drink more.

“Of all the drugs that act in the brain to produce their rewarding effects,” said Harriet de Wit, associate professor in the department of psychiatry at the University of Chicago and corresponding author for the study, “alcohol has some of the most complex and varied effects on neurotransmitter receptor systems. One of the receptor systems where alcohol may act is the nicotinic acetylcholine (NACH) receptor system, the same system where nicotine acts. By acting at these NACH receptors, alcohol also increases the activity of another neurotransmitter system, the dopamine system, which is where most drugs are thought to produce their rewarding effects. We hypothesized that mecamylamine would block the effects of alcohol on the NACH receptors which would, in turn, reduce the activity of the dopamine system, resulting in a dampening of the rewarding effects of the alcohol.”

Researchers recruited 27 (14 males, 13 females) non-smoking social drinkers to participate in six laboratory sessions lasting roughly four hours each. At the beginning of each session, study subjects received either a placebo or one of two doses of mecamylamine (7.5 or 15 mg), followed two hours later by either an alcohol (0.8 g/kg) or a placebo beverage. For two hours following beverage consumption, physiological and subjective-effect measures were taken at 30-minute intervals. The physiological measures included heart rate and blood pressure; subjective effects included stimulation and euphoria.

“Our findings extend previous observations made in animals,” said de Wit, “that alcohol produces its mood-altering effects, in part, through actions on the nicotinic receptor system. These findings also fit nicely with observations that alcohol users are often also smokers, and smokers tend to drink more than non-smokers. This suggests that these associations may have a biological basis, that is, they reflect shared actions on some of the same receptor systems.”

Only one other published human study, by authors Ola Blomqvist and Henry Kranzler, has previously examined the effects of mecamylamine on subjective responses to alcohol. The

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present study expanded on their findings by testing another dose of mecamylamine, and by including a placebo beverage as a control condition.

“Clearly this study extends our findings,” said Kranzler, a professor in the department of psychiatry at the University of Connecticut Health Center, “and provides another step in linking preclinical animal findings with the effects of alcohol in humans. The study sample is also larger, which helps to validate our initial findings. It should be noted, however, that as with our study, the humans were healthy subjects, so additional work is needed to evaluate the clinical significance of these findings in heavy drinkers. It is likely, based on other research, that these effects can be extended to heavy drinkers.”

Researchers also found some unexpected gender differences in the results. “First, we found that male subjects reported more of a stimulant effect from the alcohol than the females,” said de Wit, “regardless of whether they were pretreated with mecamylamine. Second, mecamylamine reduced the stimulant effects of alcohol more in men. Third, women reported more effects from the mecamylamine alone, specifically, self-reported feelings of sedation.” Both de Wit and Kranzler cautioned, however, that these differences may be due to gender differences in pharmacokinetics.

“We gave the women the same amount of alcohol as we gave to the men,” said de Wit, “and there is evidence that women attain a higher concentration of alcohol because of differences in body composition. This could have accounted for some of the sex differences we saw in responses to alcohol. We also gave the same dose of mecamylamine to men and women. Although doses of most drugs – except alcohol – are usually not adjusted for sex or body weight, it is possible that the greater response to mecamylamine in the women could be related to their smaller size.”

“Developments in the pharmacotherapy of alcoholism have been limited by the paucity of agents with demonstrated effects on alcohol reinforcement,” said Kranzler. “This study, in conjunction with other research findings, shows that the nicotinic cholinergic system is a promising one for evaluation as a pharmacotherapeutic target in alcoholism.” Kranzler cautioned that “mecamylamine is not particularly well tolerated in high doses ... however, other, possibly more selective drugs that are active at the nicotinic receptor are becoming available, and may provide better tolerability.”



Article is based on the following published research:

Chi, H., de Wit, H.
(May 2003).

Mecamylamine
attenuates the subjective
stimulant-like effects
of alcohol in social
drinkers.

*Alcoholism: Clinical
and Experimental
Research,*
27(5), 780-787.



PROMISING NEW TREATMENT OPTIONS FOR PEOPLE WITH CO-EXISTING ALCOHOL USE AND PSYCHIATRIC DISORDERS

- *The United States has typically separated services for mental health from those associated with addictions.*
- *A selective serotonin reuptake inhibitor (SSRI) called paroxetine shows promise in the treatment of social anxiety in alcohol-dependent subjects.*
- *Researchers have found that an anticonvulsant mood stabilizer called sodium valproate, may be useful for both stabilizing mood states and decreasing alcohol use among bipolar alcoholics.*

Individuals who have co-existing alcohol use and psychiatric disorders must overcome a number of significant hurdles on their way to recovery: multiple health and social problems, double the stigma, a poor response to traditional treatments, a lack of joint treatment options, and a chronic cycle of treatment entry and re-entry. Symposium proceedings published in the February issue of *Alcoholism: Clinical and Experimental Research (ACER)* examine treatment options for this group.

“The United States has typically separated services for mental health from those associated with addictions,” said Charlene E. Le Fauve, symposium organizer and health scientist administrator at the National Institute on Alcohol Abuse and Alcoholism. “Because of this separation, when a person with comorbid disorders enters one type of care, they are inadequately treated for the other condition. If one disorder goes untreated, both usually worsen and additional complications occur, which can include serious medical problems.”

Symposium speakers at the June 2003 Research Society on Alcoholism meeting in Fort Lauderdale, Florida presented findings from recent trials and clinical studies:

- A selective serotonin reuptake inhibitor (SSRI) called paroxetine shows promise in the treatment of social anxiety in alcohol-dependent subjects.

“Since this was the first study to examine the effectiveness of paroxetine in this dual-diagnosis population,” said Le Fauve, “we need to see if the results can be replicated by other researchers before we can determine how promising the results are.”

- Response to SSRIs among people with co-existing alcohol dependency and depression seems to depend on various factors, including the severity of the depression, whether the depression is primary or secondary to the alcohol use, alcoholic typology (Type A or B) and gender.

“When someone is severely depressed, addicted to alcohol, needs inpatient mental health treatment, and has a history of attempting suicide,” explained Le Fauve, “SSRIs are effective at

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PROMISING NEW TREATMENT OPTIONS FOR PEOPLE WITH CO-EXISTING ALCOHOL USE AND PSYCHIATRIC DISORDERS

improving the depression and decreasing alcohol consumption. Whereas, for alcoholics who do not need inpatient treatment because their symptoms of depression are mild to moderate, SSRIs are not very effective at treating both disorders. On the other hand, a heavy drinker who does not require formal addiction treatment may take SSRIs and notice that they will substantially reduce their alcohol intake.”

Research indicates that gender may also play a role in the effectiveness of SSRIs, in that women with both alcohol and depressive disorders tend to respond better than men. In addition, the type of alcoholic receiving SSRIs – Type A versus Type B – can influence its effectiveness. Type As become alcoholics at a later age, have less severe symptoms or fewer psychiatric problems, and have a better outlook on life than Type Bs.

“Type B alcoholics are considered to be more severe and at greater risk for poor health outcomes,” said Le Fauve. “Type B alcoholics also significantly worsen when they are treated with SSRIs when compared to Type A alcoholics. Clearly, SSRIs will not be the best method of treatment for all people who have both depression and alcoholism.”

- In the first study of its kind, researchers found that an anticonvulsant mood stabilizer called sodium valproate, used previously to treat bipolar disorder, may also be useful for both stabilizing mood states and decreasing alcohol use among bipolar alcoholics.

- Researchers have also found that treatment with the antipsychotic clozapine is associated with a decrease in alcohol and other substance use in patients with schizophrenia.

“Atypical or ‘novel’ antipsychotics are generally safer and better tolerated than older or typical antipsychotic medicines,” explained Le Fauve. “Emerging studies suggest that atypical antipsychotics can also be effective for a broad range of psychiatric syndromes beyond the primary indication of schizophrenia. So, it is not entirely surprising that a new atypical antipsychotic such as clozapine ... may be a useful treatment modality for a broad range of non-psychotic conditions, including alcoholism.” Le Fauve noted that researchers are just beginning to unravel the complexities of how to treat people with comorbid mental illness and alcohol use disorders.



Article is based on the following published research:

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