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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Institute on Alcohol Abuse and Alcoholism

FEATURE

NCIG: MAKING DRUG DEVELOPMENT MORE EFFICIENT AT NIAAA



With nearly 18 million people in the United States with an alcohol use disorder and an annual total economic cost of \$235 billion, there is a clear need for more interventions to treat alcohol use disorders. More treatment options can help minimize the negative consequences felt by dependent individuals, their families, workplaces, and society as a whole. One aspect of treatment, in addition to well-known methods such as mutual-help groups and individual therapy, is the use of medications. Several medications are approved by the U.S. Food and Drug Administration (FDA) for treating alcoholism (see accompanying story on page 2), and others show promise.

The drug development process, however, is extremely lengthy (approximately 13 years from discovery to market) and very expensive. To help encourage the development of medications to treat alcoholism, NIAAA founded the Clinical Investigations Group (NCIG) in 2007 to test the safety and effectiveness of promising drugs and to bridge the gap between preclinical

studies and Phase III clinical trials involving larger groups of participants. Additionally, NCIG hopes to serve as a model for pharmaceutical companies by improving the methodology to best detect a treatment's effect with minimal cost and time.

When considering medications to evaluate in the NCIG program, program staff look for signs of efficacy shown in prior research, such as a reduction in drinking or craving for alcohol or other subjective effects. Candidate medications include those already marketed for the treatment of other diseases or disorders as well as new compounds currently in development by pharmaceutical companies. When a compound shows signs of efficacy, staff then work collaboratively with the pharmaceutical industry to increase the likelihood that the drug will be made available to patients.

NCIG has successfully initiated three trials since the program's inception in 2007. Quetiapine, a drug used in treating psychiatric disorders, was examined in 224 very heavy-drinking alcohol-dependent individuals. Results from this study have been analyzed and submitted for publication. Data from a trial of levetiracetam XR (Keppra XR®), an antiseizure drug, are currently being analyzed, and subjects are being recruited for a trial evaluating

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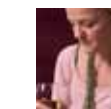
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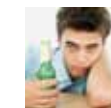
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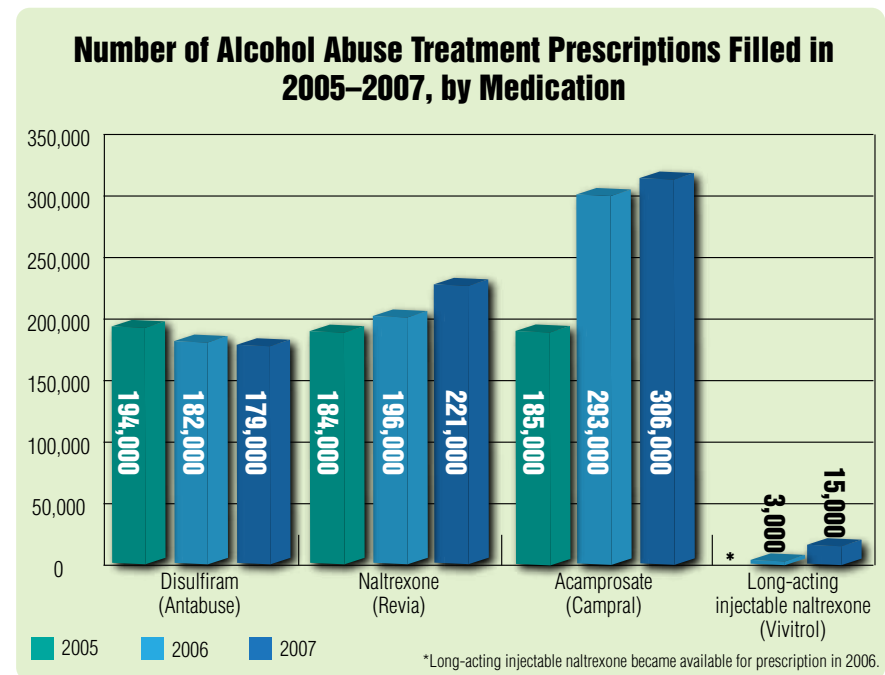
CHARTICLE

ALCOHOLISM MEDICATION PRESCRIPTIONS ARE MODEST BUT GROWING

Only about 1 in 10 people with alcohol dependence in the United States takes an FDA-approved alcoholism medication as part of his or her treatment. Nearly 18 million Americans are dependent on alcohol, according to NIAAA's nationwide survey. Retail pharmacies filled an estimated 720,000 prescriptions for alcoholism medications in 2007* (not counting some prescriptions, such as those dispensed by mail order, hospitals, or clinics).

Alcoholism medication prescriptions more than doubled between 2003 and 2007, up from 393,000 prescriptions. This growth was driven largely by acamprosate (Campral), introduced in 2005. Campral is the most commonly prescribed medication for alcohol dependence, with over 40 percent of the market.

Naltrexone (Revia) and disulfiram (Antabuse) are also often prescribed for alcohol dependence, at roughly 30 percent and 25 percent of the market, respectively. Far fewer prescriptions



were written for long-acting injectable naltrexone (Vivitrol), introduced in 2006. This lower market share may be related to its higher cost: \$489 per prescription,

roughly five times that of other alcoholism medications. Vivitrol is delivered as a once-a-month injection, rather than as a pill.

*Most recent published data.

Sources:

Mark TL, Kassed CA, Vandivort-Warren R, Levit KR, Kranzler HR. Alcohol and opioid dependence medications: Prescription trends, overall and by physician specialty. *Drug and Alcohol Dependence*;2009 Jan 1;99(1-3):345-9. <http://www.ncbi.nlm.nih.gov/pubmed/18819759>

Grant BF, Dawson DA, Stinson FS, Chou SP, Dufour MC, Pickering RP. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. *Drug and Alcohol Dependence*;2004 Jun 11;74(3):223-34. <http://www.ncbi.nlm.nih.gov/pubmed/15194200>

FEATURE

DRUGS USED IN TREATING ALCOHOL USE DISORDERS

Currently, there are three drugs approved by the FDA for the treatment of alcohol use disorders: disulfiram (sold under the trade name Antabuse), naltrexone (sold as an oral medication under the name Revia and as an injectable under the names Vivitrol and Naltrel), and acamprosate (sold under the trade name Campral). In addition, some benzodiazepines (Valium and Xanax) have been approved to treat

alcohol withdrawal symptoms. A number of other drugs, while not FDA-approved to treat alcohol abuse, have shown promise in reducing drinking.

In 1949, disulfiram became the first drug approved to treat alcoholism. The drug works by increasing the concentration of acetaldehyde, a toxic byproduct that occurs when alcohol is broken down in the body.

Excess amounts of this byproduct cause unpleasant symptoms, such as nausea and flushing of the skin. The anticipation of these effects can help some people avoid drinking while taking disulfiram.

For over 40 years, disulfiram was the only medication physicians could offer to their patients who were battling alcohol abuse and dependence.

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varenicline (Chantix®), a smoking cessation medication. In addition, NCIG staff are in the process of choosing compound(s) for a fourth trial.

The pharmaceutical industry's response to the NCIG program has been positive. Several major pharmaceutical companies have contacted NIAAA with potential compounds for testing via the NCIG program. NCIG has worked with one major pharmaceutical company and is negotiating with another to secure a Cooperative Research and Development Agreement, or CRADA,

to conduct a proof of concept trial with a new molecular entity.

The continued review of data from already conducted NCIG trials provides an opportunity to enhance and improve the methodology for conducting these trials as efficiently and productively as possible. Joanne Fertig, Ph.D., who—along with Daniel E. Falk, Ph.D.—serves as NCIG principal investigator, notes: “What we are learning from these trials gives us additional insights about evaluating future studies that will hopefully improve the evidence base

for treating patients with alcohol use disorders. In addition, as we test more drugs with different neural targets, we gain insight into the mechanisms underlying the development and maintenance of alcohol dependence.”

NIAAA's objective for NCIG has been to make more drugs available to physicians to treat alcohol dependence. Through NCIG, NIAAA seeks to encourage pharmaceutical companies to consider testing compounds for treating alcohol dependence at an early stage of the development process.

FEATURE: Drugs Used in Treating Alcohol Use Disorders. . . Continued from page 2

However, the FDA approved naltrexone as an oral medication in 1994 and as an extended-release injectable in 2006. Naltrexone blocks opioid receptors involved in the pleasant sensations associated with drinking and can reduce alcohol craving.

In 2004, 10 years after the FDA approved naltrexone, it approved acamprostate. Acamprostate is thought to ease the negative effects related to quitting drinking by dampening glutamate activity and reducing some of the brain's hyperexcitability associated with alcohol withdrawal. Similarly, benzodiazepines target the *gamma* aminobutyric acid (GABA) neurotransmitter to curb excitability in the brain during alcohol withdrawal, allowing the brain to restore its natural balance.

Another drug, topiramate (sold as Topomax), targets the

neurotransmitters GABA and glutamate. Topiramate is currently FDA-approved for the treatment of seizures and migraine headaches; however, it appears to be effective in reducing drinking in alcohol-dependent patients. Ondansetron, a drug used to treat nausea and vomiting, has shown promise in reducing drinking in patients who developed alcohol dependence early in life.

Selective serotonin reuptake inhibitors are currently used to treat anxiety and depression and may reduce drinking in patients who developed alcohol dependence later in life. Baclofen, a medication used to treat muscle spasms, may have beneficial effects in encouraging abstinence, especially in alcoholic patients with cirrhosis. Another drug, quetiapine, is used to treat psychiatric disorders. Early-stage studies show that quetiapine might be effective in increasing rates of abstinence,

especially in patients with severe alcoholism or in those who developed alcohol dependence early in life.



NIAAA continues to support studies of other new and existing medications to treat alcohol use and dependence, to provide physicians with additional tools for treating their patients experiencing alcohol use disorders, and to help match the best treatment to the patients most likely to respond to each medication.

NEWS FROM THE FIELD

BINGE DRINKING PATHWAY IN THE RAT BRAIN

Two receptors in the brain may play a role in controlling binge drinking. Receptors are molecules that receive chemical signals which then direct cell behavior. This study, by researchers at the University of Maryland and published in the March issue of the

Proceedings of the National Academy of Sciences, investigated the role of two specific receptors, GABA_A and Toll-like receptor 4 (TLR4). Previous studies have shown that GABA_A receptors appear to play a role in excessive drinking by causing a calm,

euphoric feeling in response to alcohol. TLR4 contributes to the inflammation and brain damage brought on by excessive drinking.

In this study, researchers used gene therapy techniques to target GABA_A

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THE BRAIN: RECEPTIVE TO THE UPS AND DOWNS OF ALCOHOL

The actions of alcohol that cause intoxication and other short-term and long-term behavioral effects occur primarily in the brain, where alcohol disrupts normal communications among the brain's billions of neurons. Under normal circumstances, information is transferred from neuron to neuron by chemical messengers called neurotransmitters, which are released by one neuron, traverse a tiny gap called a synapse, and then are bound by specialized proteins called receptors that are embedded in the membrane of the receiving neuron. This process is depicted to the right.

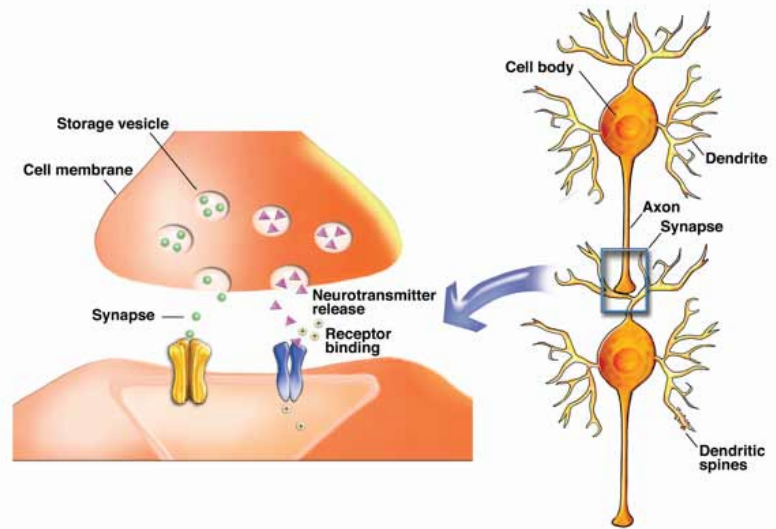
When a neurotransmitter binds to a receptor, it changes the activity of the receiving neuron, either reducing or enhancing the signal it normally transmits. In other words, the receiving neuron can become either excited or inhibited. Multiple subtypes exist for a given receptor, and each subtype may produce a different response to the same neurotransmitter.

The brain's normal balance of neurotransmitters allows the body and brain to function unimpaired. Alcohol causes myriad changes that upset this balance, disrupting normal brain function. Initially, alcohol acts as a stimulant, but as blood alcohol level increases, it becomes a depressant, leading to sleepiness and sedation. Acute intoxication and other short-term effects of alcohol are caused largely by temporary, reversible changes in specific receptors and associated molecules. With repeated alcohol exposure, long-lasting changes occur in receptors

and in the series of downstream chemical interactions as the brain attempts to restore itself to a normal state in the presence of alcohol. If the influence of alcohol is suddenly removed (that is, if a long-term heavy drinker stops drinking suddenly), the brain may have no time to readjust once again, leading to the adverse symptoms associated with alcohol withdrawal, such as experiencing "the shakes" or increased anxiety.

One of the most powerful effects of alcohol is to reduce the pace of brain activity in part by (1) decreasing the excitatory actions of the neurotransmitter glutamate at the glutamate receptor and (2) boosting the inhibitory actions of the neurotransmitter GABA at the GABA_A receptor. These actions are among the reasons that alcohol is often thought of as a depressant. Other neurotransmitters of interest to alcohol researchers include dopamine, serotonin, and opioid peptides. Dopamine appears to play a major role in the pursuit of rewarding stimuli, and alcohol causes dopamine to be released from the nucleus accumbens, one of

PHOTO ESSAY



Source: Clapp P, Bhawe SV, Hoffman PL. How adaptation of the brain to alcohol leads to dependence. *Alcohol Research & Health*; 2008;31(4):310-339.

the brain regions associated with the development of addiction. Serotonin is involved in the regulation of mood, sleep, body temperature, appetite, and a host of other physiological functions.

Animal studies have suggested that alcohol-induced activation of specific serotonin receptor subtypes may contribute to alcohol's rewarding effects. Research also indicates that other serotonin receptors have potential roles in tolerance, withdrawal, and intoxication. Opioid peptides are a class of neurotransmitters that produce effects similar to those of morphine and heroin. High blood levels of certain opioid peptides have been correlated with feelings of euphoria. Alcohol consumption affects the levels of opioid peptides and their receptors, which in turn appears to increase the rewarding effects of alcohol.

NEWS FROM THE FIELD: *Binge Drinking Pathway in the Rat Brain. . . Continued from page 3*



and TLR4 receptors in the brains of rats specially bred and trained to drink heavily. Their findings established that there is a connection between the two receptors—

TLR4 affects the brain cells that are

connected to GABA_A receptors. They also found that silencing the genes for both receptors in certain areas of the brain caused the rats to lose interest in alcohol for about 2 weeks.

The findings are an exciting development both for neuroscience and for alcohol research. These findings could lead the way towards developing medications that target GABA_A and

TLR4 receptors in the same way as in the study, helping to calm people's cravings for alcohol.

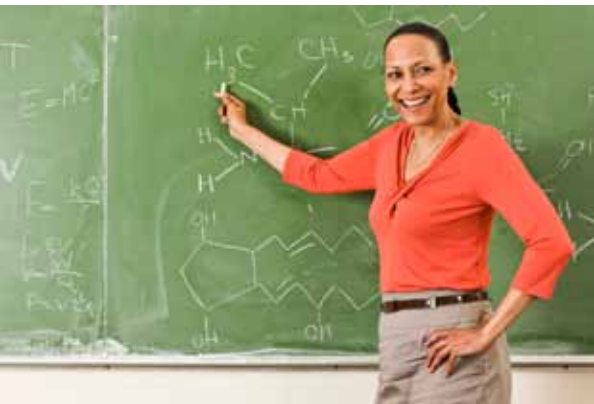
The article abstract can be found here:

Binge Alcohol Drinking Is Associated With GABA_A Alpha2-Regulated Toll-like Receptor 4 (TLR4) Expression in the Central Amygdala.
<http://www.ncbi.nlm.nih.gov/pubmed/21368176>

NEWS FROM THE FIELD

A SCHOOL'S SCHOLASTIC SUCCESS CAN KEEP KIDS FROM DRUGS, ALCOHOL

For kids who are at risk for drinking, smoking, using drugs, and delinquent behavior, attending a higher-performing school may be protective. A recent study, published



in the March 2011 issue of *Prevention Science*, evaluated the effect of school environment on kids in 61 urban public middle schools in low income, racial/ethnic minority areas of Chicago between 2002 and 2005. The study found that students at schools

with “value-added education,” a measure showing higher than expected academic achievement and better attendance records given the profile of the student body—were much less likely than kids attending similar, but poorer-performing schools to drink, smoke, use illegal drugs, or have behavior problems.

The study measured value-added education based on the proportion of students in each school who meet or exceed the national standards for reading and math and who had better than anticipated attendance during the academic year. Of the 61 schools, 7 were identified as value-added, and 5 were identified as “value-attenuated,” meaning they had lower than average performance. The schools in the middle were termed “normative.”

Students also answered two questions about alcohol use from the National Institute on Drug Abuse annual

Monitoring the Future study. The questions were: “How many times did you drink in the past 30 days?” and “How many times did you have five or more alcoholic beverages in the past 2 weeks?” Based on the researchers’ analysis, value-added education was associated with much lower rates of alcohol use within 2 weeks as well as lower rates of cigarette and marijuana use, stealing, and fighting, when compared with the normative educational environments.

These findings suggest that school environment can serve as a protective factor against underage alcohol use.

The article abstract can be found here:

Preventing the Link Between SES and High-Risk Behaviors: “Value-Added” Education, Drug Use and Delinquency in High-Risk, Urban Schools.
<http://www.ncbi.nlm.nih.gov/pubmed/21360062>

NEWS FROM THE FIELD

STUDY HELPS TARGET NALTREXONE USE

Naltrexone, a common medication for alcohol dependence, may be more effective for women and people who have a particular genetic variant. A recent study published in *Alcoholism: Clinical & Experimental Research* examined the effectiveness of naltrexone based on these variables.

The McGill University-based team recruited 42 healthy social drinkers ages 18 to 50 for the study. Participants received oral naltrexone or a placebo pill for 6 days. On the 6th day, participants completed the “alcohol self-administration task.” Each

participant received one drink and then had the opportunity to earn more drinks by completing tasks on a computer.

In addition, researchers took DNA samples from almost all of the participants, and looked specifically for a specific variant of the *mu* opioid receptor gene (OPRM1). This gene is related to the brain’s system of releasing natural chemicals that produce a feeling of euphoria. Alcohol stimulates the release of these natural chemicals, also called opioids. Naltrexone blocks the brain from producing these feel-good chemicals



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NEWS FROM THE FIELD: *Study Helps Target Naltrexone Use . . . Continued from page 5*

in response to alcohol, which, in turn, helps reduce drinking behavior. Previous studies have shown that this genetic variant appears to influence one's response to naltrexone.

The team found that women and people with the OPRM1 variation who took naltrexone and then drank felt less euphoric than did men, people without the variation, and people in the placebo group who also took naltrexone and

then drank. Interestingly, naltrexone did not affect participants' motivation to earn more drinks, regardless of gender or genotype.

While further research is still necessary, Dr. Marco Leyton, the study's lead investigator, is optimistic that this finding, along with other studies in this area over the next decade, will help inform more personalized treatment

solutions for those suffering from alcohol use disorders.

The article abstract can be found here:

The Effect of Naltrexone on Alcohol's Stimulant Properties and Self-Administration Behavior in Social Drinkers: Influence of Gender and Genotype.

<http://www.ncbi.nlm.nih.gov/pubmed/21410481>

NEWS FROM THE FIELD

STRESS DRINKING LINKED TO EARLY ALCOHOL USE



People who begin drinking at a young age also may drink heavily during stressful events later in life. Results from a recent study published in the June 2011 issue of *Alcoholism: Clinical & Experimental Research* found an interaction between an early age of first drink and drinking patterns later in adulthood.

The research team examined data from the Mannheim Study of Children at Risk, a German-based longitudinal

study that tracked the outcome of early risk factors from infancy through young adulthood. Participants surveyed at ages 15 and 19 reported the age when they first had more than just a few sips of alcohol. The earliest age of first drink in the study was 8 years old, and about half of the participants began drinking before age 14.

At age 22, participants answered questions about their drinking behavior, including how many days in the past month they drank alcohol and how much they drank on those occasions. The researchers also asked questions about whether participants experienced major stressful life events, including family, health, job, and legal troubles, and daily hassles, such as bad weather or sleep problems.

Results showed stress doesn't necessarily cause people to drink more often but it does cause them to drink larger quantities when they do drink. Daily hassles proved to be unrelated to drinking behavior.

In addition, the age of first drink had a significant influence on both the number of drinking days and the total

amount of alcohol consumed in the last month. People with an earlier age of first drink had more frequent and higher consumption levels than people who began drinking at an older age.

Dorothea Blomeyer, a first author on the study, hypothesizes that adolescents who drink may learn to use alcohol as a way of dealing with stress. "Research indicates that during adolescence, drinking is particularly rewarding under stressful circumstances."

As a result, Blomeyer explains, "This study extends our knowledge on how the connection between early age of first drink and later drinking problems might develop."

The article abstract can be found here:

Age at First Drink Moderates the Impact of Current Stressful Life Events on Drinking Behavior in Young Adults.

<http://www.ncbi.nlm.nih.gov/pubmed/21410482>

5 QUESTIONS WITH...



MARKUS HEILIG, M.D., PH.D.

Dr. Heilig is NIAAA Clinical Director.

1. How do clinical trials fit into the overall research mission of NIAAA?

Clinical trials are a critical part of the bench-to-bedside process, which is the hallmark of research at the National Institutes of Health (NIH). They test the safety and effectiveness of medications and other treatment methodologies and help bring potentially life-saving medications directly to the patient.

Clinical trials are usually conducted in different phases, and each phase has a different purpose and tries to answer different questions. In Phase I trials, researchers test an experimental drug or treatment with a small group of people for the first time to evaluate its safety, correct dosage range, and possible side effects. In Phase II, the experimental study drug or treatment is given to a larger group of people (more than 100) to evaluate effectiveness and to further evaluate its safety. In Phases III and IV, the drug or treatment is given to large groups of people (over 1,000) to confirm effectiveness, monitor side effects, make comparisons with commonly used treatments, and collect safety information so that the drug can receive FDA approval.

Our clinical work at NIAAA focuses on bridging the large research gap between basic neuroscience discovery and early clinical development—often called the research “valley of death.” So we focus on what some refer to as Phase 2a, or as I prefer to call it, experimental medicine.

Phase III studies are expensive and complicated and many organizations, including those in the pharmaceutical industry, are reducing their investment in this area. This causes many promising mechanisms to languish

before they can be translated into clinical advances. This is particularly frustrating because there are still many unmet medical needs and many advances in basic science. So, in order to help bridge this gap, NIAAA is focusing on “early translational” studies. We hope that information gleaned from these hybrid studies will provide the necessary rationale to justify the substantial investments that must be made, by government and industry, in the large-scale Phase II and III trials that ultimately bring medications and treatments to clinical practice.

2. How do you promote clinical trials and what type of people do you recruit? Can potential subjects contact you directly?

Clinical trials recruitment is always a challenge, and we use a range of methods to spread the word about these studies. Clearly, advertising is an important part of our recruitment strategies. Referrals from physicians have also been an important way to find patients who can participate. To keep our research relevant, we need to conduct studies with real patients with real alcohol use disorders. So we work diligently with community treatment providers to establish relationships that can lead to referrals. And yet, even though we provide state-of-the-art care and treatment, it remains an enormous challenge to establish a steady stream of patients from these treatment programs.

Fortunately, in this age of personal technology and patient empowerment, we no longer need to rely solely on referrals and the mass media. Self-referrals are becoming increasingly popular, and NIH’s clinical trials Web site (<http://www.clinicaltrials.gov>) makes the process simple and straightforward. Through this site, patients can contact us directly and

begin discussions with our clinical specialists about their suitability for our studies.

The types of subjects we recruit often will depend on the specific study in question. Recently, for example, we have been studying alcohol use by women suffering from depression and anxiety, and are recruiting accordingly. We are devoting major efforts right now to another population—patients with post-traumatic stress disorder and alcoholism.

However, we also need participants with no alcohol use disorder to serve as comparison groups. This aspect of clinical research is critical to confirming that study outcomes are the result of the medications and treatments themselves, and not a placebo effect of simply participating in a study. We greatly appreciate all the volunteers who help advance the science in this important field by participating in our clinical studies.

3. If the purpose of a clinical trial is to develop medications for future use, does the participant benefit at all?

While it is true that the primary purpose of clinical research is to develop effective treatments for future patients, we believe that participation in our studies provides a valuable experience for the research subjects themselves. All participants in our studies receive comprehensive diagnostic evaluations under the supervision of specialized team of physicians and other providers, all at no cost. The state-of-the-art assessments provided in our studies are more thorough and comprehensive than a patient is likely to receive anywhere else.

Meanwhile, many of these studies offer participants groundbreaking medication and treatments, often with life-saving potential, years before they would be

available in the community. Our trials are also a pathway to early treatment. When patients with an alcohol use disorder are recruited, they are entitled to a 4-week intensive treatment program regardless of whether they are suitable for any specific drug protocol at that time. Then, based on the severity of the disorder, we refer them to appropriate community-based long-term treatment and recovery programs. So we believe that participants in our clinical studies do receive many important health benefits while also contributing greatly to the advancement of care and recovery for alcohol use disorders.

4. How has clinical research helped develop medications and practices that physicians use to treat alcohol use disorders today?

Both naltrexone and acamprosate, the two modern medications that are approved for treatment of alcoholism, were brought forward through academic clinical research. Several other medications are in development as well, and look promising. Clinical research also is offering the promise of helping us use already available medications

better. For instance, recent clinical trials have helped match particular medications with participants who had specific genetic profiles—resulting in better outcomes for all patients. Take, for example, the drug naltrexone. In many early studies, researchers continually found only modest success rates overall. However, research also showed that certain patients responded very well to the treatment. As genetics research advanced, we learned that we could identify the patients who were likely to have this positive response, and then selectively use this treatment option to get much better outcomes than we would derive from the general population. This ability to personalize medicine is a key to effective treatment and recovery.

5. What led you to consider alcohol research as a field, and clinical work in particular?

My interest has always been in learning how the brain makes people feel the way they feel and do the things they do, and in learning more about the effects of stress on the human

brain and body. And alcoholism is in many ways a stress disorder. So while I don't consider myself to be an alcohol researcher exclusively, alcohol has proven to be an area where my particular interests coincide, providing a window into these complex neurobiological processes. And from a clinical perspective, alcohol is an area with great unmet needs and human suffering. So working in this area offers a phenomenally rewarding combination of satisfying my inherent curiosity, while hopefully being able to make a difference by helping individuals who suffer terribly from alcohol use disorders.

And through my clinical studies, I have the privilege of maneuvering between two worlds—the laboratory and “real life.” It's enormously satisfying to bring advances in basic science to the patients, and also to bring clinical observations back to the lab to sharpen our focus as we move forward.

ABOUT US

NIAAA Spectrum is NIAAA's first-ever webzine. With engaging feature articles, short news updates, and colorful graphics, *NIAAA Spectrum* offers accessible and relevant information on NIAAA and the alcohol research field for a wide range of audiences. Each issue includes feature-length stories, news updates from the field, charticles and photo essays, and an interview with an NIAAA staff member or alcohol researcher. *NIAAA Spectrum* is published three times a year.

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