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Cover Story

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Drugs To Fight Addictions

A better understanding of the mechanisms of drug and alcohol dependence is helping to further development and use of pharmacotherapies against addictions

[Ann Thayer](#)

Addictions, especially alcohol dependence, have been treated largely as behavioral disorders. Weaknesses in will, character, or faith were among the factors believed to contribute to an addicted person's dependence. Consequently, for decades, treatment has centered on psychological or behavioral therapy. Only recently, thanks to improved understanding of the neurologic and physiologic aspects of addiction, more medication-based treatments have emerged, along with a gradually expanding willingness to use them.

Pharmacotherapies for treating addictions have actually been around for decades, but only a few medications have been approved specifically for that purpose, and these have found limited use. Within the past few years, the number has nearly doubled as one or two new products each for smoking cessation, opioid abuse, and alcohol dependence have become available. Many researchers working in the field, as well as pharmaceutical companies developing and marketing the medications, believe this growth may herald a new phase in addiction pharmacotherapy.

"I believe we are in the midst of a paradigm shift in how alcohol dependence is perceived and then ultimately how it's treated," says Mark Willenbring, director of the Division of Treatment & Recovery Research at the [National Institute on Alcohol Abuse & Alcoholism](#) (NIAAA). "There is a much more medical approach emerging; treatment for alcohol dependence at this point is similar in some ways to where treatment for depression was about 30 years ago."

Behavioral therapies can be effective, he adds. "Most people don't get treatment, and the treatments we have are not as effective as they need to be," he says. "There are dual problems of expanding access and improving efficacy, and medications are really going to be a key component." The treatment community is grappling with the relatively recent recognition that addiction disorders are chronic, relapsing diseases stemming from genetics and environmental influences and that pharmacotherapies not only are available but can be effective.

NIAAA and the [National Institute on Drug Abuse](#) (NIDA) have been playing critical roles in increasing the neurobiological and neurochemical understanding of addiction disorders, as well as in running clinical studies to show where existing and new therapies offer promise. A resulting change, says Francis (Frank) Vocci, director of NIDA's Division of Pharmacotherapies & Medical Consequences of Drug Abuse, is that "pharmaceutical companies are starting to look at addiction as a viable indication, something worthy of evaluating in terms of developing medications."

Industry's involvement has been limited in the past by several factors, according to many people working in the field. These factors have included deficiencies in the ability to discover and effectively test new antiaddiction drugs, a scarcity of data-driven proof that drug therapies work, a small market size coupled with difficulties in reaching doctors and patients, and even cultural resistance, stigma, and other concerns around such products. The addiction pharmacotherapy market is currently worth only

about \$2 billion, reports the research firm [Spectra Intelligence](#). The market is expected to grow to \$2.9 billion by 2012, fueled by increased need, mounting health care and socioeconomic burdens in the hundreds of millions of dollars, and new products that will add sales and offer proof-of-principle.

About 9% of the U.S. population, or 22.3 million people aged 12 or older, were classified as having a substance dependence or abuse problem in 2005, according to the [Substance Abuse & Mental Health Services Administration](#) (SAMHSA), part of the U.S. Department of Health & Human Services. In its just-released survey—September is National Alcohol & Drug Addiction Recovery month—SAMHSA reports that in this group, 3.3 million used both alcohol and illicit drugs, 3.6 million used just drugs, and 15.4 million used just alcohol. But only 3.9 million people received any kind of treatment, most through self-help groups. Another 71.5 million people used tobacco products.

According to Spectra Intelligence's recent analysis, nearly 35 drug candidates are in the pipeline to treat alcohol, narcotic, and nicotine dependencies. The growing understanding of how addiction plays out is helping improve the design and testing of new and more efficacious medications. Not only are products that are more effective expected to emerge, but also, in a similar manner to how doctors treat other central nervous system (CNS) conditions, these products will provide more options for addressing complex addictive diseases in different patients.

Drugs of abuse are chemically diverse and thus have very different targets, mechanisms of action, and manifestations in the body. But addiction's common underpinning lies in how these molecules ultimately affect the brain's reward pathway, explains [Eric J. Nestler](#) in a review article (*Nat. Neurosci.* **2005**, 8, 1445), prepared with support from NIDA. Nestler is chairman of the department of psychiatry and a member of the Center for Basic Neuroscience at the University of Texas Southwestern Medical Center in Dallas.

Addictive drugs reward their users, an outcome that encourages repeated use, and they produce unpleasant symptoms on withdrawal, Nestler says. Addiction also involves associating drug use with environmental cues and adaptive changes in the brain, believed to contribute to craving and relapse. Evidence suggests the common circuitry is in the brain's limbic system and, in very simple terms, ultimately involves either direct or indirect activation of dopaminergic pathways to increase dopamine levels.

"Because common mechanisms seem to contribute to at least some aspects of all drug addictions," Nestler writes, "it might be possible to develop treatments that would be effective for a wide range of addictive disorders." Drugs targeting the brain's dopamine, glutamate, corticotropin releasing factor (CRF), opioid, or cannabinoid systems might exert the desired effects. At the same time, he cautions that drugs should safely and effectively dampen common mechanisms of reward while not adversely affecting normal function.

Existing pharmacotherapies, he also points out, are specific for the target or receptor of the drug of abuse, and no treatment aimed at a common mechanism has yet been fully validated across a range of

addictions. Meanwhile, along with identifying various molecular and cellular pathways, receptors, and neurotransmitters, scientists have found links between genes and the risk of dependence and other factors involved in addiction. Now they are trying to relate these genetic variations to behavioral phenotypes of addiction.

In turn, they are creating more predictive and robust animal models. And they are exploring targets and pharmacotherapeutic agents that run the gamut from agonists, partial agonists, antagonists, and modulators of appetitive systems in the brain to monoclonal antibodies and even vaccines (*Eur. J. Pharmacol.* **2005**, 526, 101). The goal is to find pharmacotherapies that not only halt a drug's acute effect and prevent withdrawal but also block craving and other factors that cause relapse.



ISTOCK PHOTO

SMOKING CESSATION. Nicotine replacement therapies (NRTs) have dominated pharmacological treatment for smoking. These are patches, gums, lozenges, nasal sprays, and inhalers for delivering controlled doses of the addictive drug itself. The [Food & Drug Administration](#) approved the first NRT gum for prescription use in 1984, followed by the first patch in 1991. In 1996, both the gum and patches became over-the-counter (OTC) products. According to NIDA, all NRT products are equally effective, working about 20% of the time.

Although NRTs ease withdrawal symptoms, they don't control neurotransmitter release or blunt the addictive effects of nicotine. An option is bupropion, a norepinephrine- and dopamine-reuptake inhibitor. [GlaxoSmithKline](#) (GSK) sells the off-patent drug as Wellbutrin for depression and, since 1997, as Zyban for smoking cessation. Nortriptyline, a tricyclic antidepressant and norepinephrine reuptake inhibitor, has been studied and is sometimes used for smoking cessation but isn't approved for this use.

In 2005, GSK had \$611 million in sales of OTC smoking cessation products, primarily NRTs. [Pfizer](#) has been the other leading producer of NRTs, but these products are part of the consumer health business the company is selling to [Johnson & Johnson](#). The total market for nicotine addiction therapies was about \$1.5 billion in 2005, according to Spectra Intelligence, with sales of existing therapies expected to grow modestly.

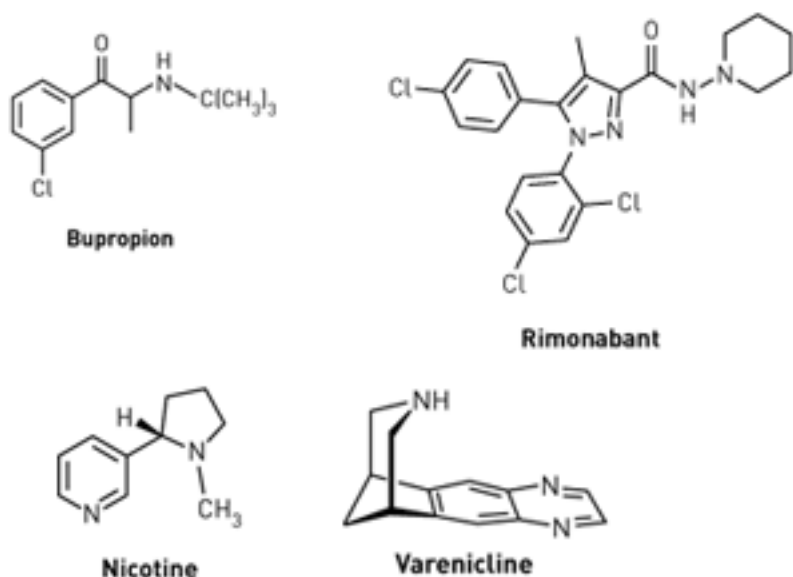
The need for new therapies is tremendous, and the market potential is enormous. According to the

[World Health Organization](#), there are 1.3 billion smokers worldwide. Tobacco-related illnesses are the second leading cause of death among all people, accounting for about 5 million deaths per year. In the U.S. alone, about 60 million people smoke cigarettes. An estimated 70% say they want to quit, and 40% try each year. The [Centers for Disease Control & Prevention](#) lists smoking as the leading preventable cause of death.

The first new nonnicotine treatment to come along in a decade is varenicline, launched in August by Pfizer as the prescription drug [Chantix](#). Its discovery and development took roughly one decade, says Martin R. Jefson, Pfizer's vice president for CNS discovery. The drug is a pharmacologically unique chemical entity that works through the same nicotinic receptor population used by the substance of abuse, he explains. But whereas nicotine is a full agonist, or activator, of the receptor, varenicline is only a partial agonist, which may be key to its ability to help patients quit and avoid relapse.

"There is good scientific evidence that nicotine targets nicotinic acetylcholine receptors located in a region of the brain thought to be very central to the process of reward and habituation," Jefson says. A specific abundant subtype called $\alpha_4\beta_2$ is believed to mediate the reinforcing properties of nicotine. It does so by binding nicotine and then releasing dopamine; the pleasurable outcome of this event leaves a smoker wanting to do it again.

"We were looking for something that might offer the benefits of an antagonist, which would block the rewarding effects of nicotine taken in by relapse smoking, but also something that served as an activator or agonist of the receptor and provide some relief from the craving and withdrawal that comes with abrupt cessation," Jefson explains. A partial agonist does this by competing with nicotine itself for the receptor with comparable or even superior affinity and activating the receptor some but not nearly as much as the full agonist.

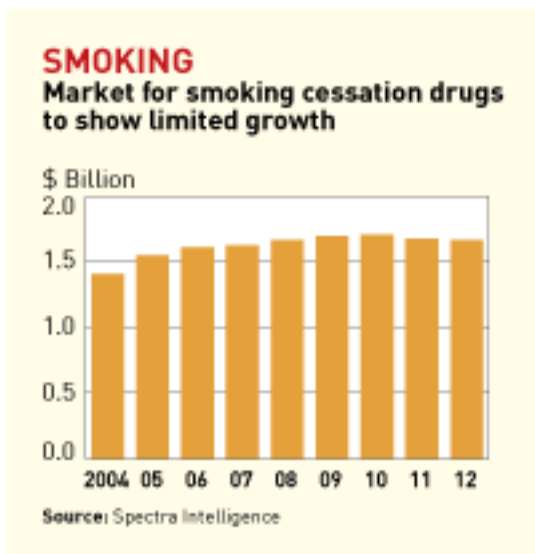


The discovery of varenicline involved screening, optimizing, and testing compounds inspired by the

plant alkaloid (-)-cytisine ([C&EN, June 6, 2005, page 36](#)). Cytisine has been used to treat nicotine dependence in Eastern Europe for more than 40 years (*Arch. Inter. Med.* **2006**, *166*, 1553). "We were very gratified to see that varenicline worked in the clinical setting as we hoped it would based on the preclinical work," Jefson adds. It turns out, he explains, that varenicline is a very high-affinity, high-selectivity nicotinic receptor partial agonist specific for the $\alpha_4\beta_2$ subtype.

Chantix was tested on a few thousand patients in a series of clinical trials. Results of several of these were published in the *Journal of the American Medical Association (JAMA)* in early July and in the *Archives of Internal Medicine* in August. In general, Chantix showed both short- and long-term effectiveness, being as much as four times as effective as placebo and twice as effective as Zyban. After one year without further treatment, about one in five patients who had received Chantix were not smoking.

Most smokers, even those using a therapy, don't manage to quit, and for those who do, the relapse rate is extremely high: Less than 10% stay abstinent for more than one year. Pfizer has developed a behavioral support plan, called GETQUIT, that it is offering at no charge with Chantix to increase the odds. The company anticipates initially offering the new drug through respiratory care specialists. A patient takes 1 mg twice daily for an initial period of 12 weeks and, if they succeed in quitting, for another 12 weeks to increase the likelihood of long-term abstinence.



Pharmaceutical industry analysts estimate that Chantix could boost the market for nicotine addiction therapies by \$400 million to \$500 million per year. "We saw an opportunity that was interesting scientifically and medically and where there was commercial opportunity for the right product," Jefson remarks. "Smoking's impact internationally on health is very dramatic, the prevalence is very high, and it's a very motivated patient population, which isn't the same across all substance abuse situations."

Response to the studies and to the drug's approval generally has been positive, with the events being called a step forward for smoking cessation therapy. Issues raised, nonetheless, were the side effects,

generally nausea in as many as 30% of people; nontrivial dropout rates, which are reportedly typical in smoking cessation trials; and the generalizability to real-world patient situations, as is true of many clinical studies. In an accompanying *JAMA* editorial, University of Tennessee health scientists call varenicline a "definite promise, but no panacea" (*J. Am. Med. Assoc.* **2006**, 296, 94).

They acknowledge that varenicline is associated with higher smoking cessation rates and represents a new class of drug that offers clinicians a pharmacological alternative with a mode of action different from that of NRTs or bupropion. But they also note that "clearly, quitting smoking, even with pharmacological and behavioral assistance, is extremely difficult. Patients currently cannot and probably never will simply be able to 'take a pill' that will make them stop smoking."

This isn't stopping other drug developers from trying. [Sanofi-Aventis](#)' rimonabant, which blocks the cannabinoid CB₁ receptor, is considered a promising candidate. Although the company recently received positive responses from regulators for the drug, trade-named Acomplia, as a weight management treatment, neither U.S. nor European regulators have given it the go-ahead for smoking cessation. It is also being investigated as a treatment for alcohol dependence.

In addition to other cannabinoid CB₁ receptor antagonists, compounds under study include the anticonvulsant topiramate, opioid antagonist naltrexone, and antidepressant fluoxetine, as well as a nicotinic partial agonist, dianicline, by Sanofi-Aventis and a glycine antagonist for preventing relapse by GSK. [Addex Pharmaceuticals](#) has been testing a dopamine D₁ receptor antagonist, but its current clinical status is unclear.

San Diego-based [Somaxon Pharmaceuticals](#) has completed a Phase II clinical study of oral nalmefene, an opioid receptor antagonist already used intravenously for reversing the effects of opioids after anesthesia or overdose. It has licensed the compound from Biotie Therapies in Finland for smoking cessation and impulse control disorders, such as pathological gambling.

[Yaupon Therapeutics](#), created in 2002 by two University of Kentucky professors and pharmaceutical industry executive Robert Alonso, is studying nornicotine, a tobacco alkaloid structurally similar to nicotine except it lacks one methyl group. "Nornicotine is very different from nicotine in terms of its pharmacology and pharmacokinetics," says [Peter Crooks](#), Yaupon's chief scientific officer and pharmaceutical sciences professor at the University of Kentucky. Although it would work like an NRT, the drug acts on receptor subtypes different from those that respond to nicotine to partially stimulate dopamine release and has a longer half-life and better side-effect profile.

"We've determined that one particular optical isomer of nornicotine appears to be most effective as a potential smoking cessation agent," Crooks adds. "And we've managed over the past year to come up with a very nice chemical method to inexpensively produce the desired pure enantiomer." The company is conducting toxicity tests and has received a National Institutes of Health grant that should allow it to begin Phase I clinical testing early next year.

Tackling the problem differently are a few companies developing nicotine vaccines. Nicotine is a small molecule that easily passes to the brain undetected by the immune system. The vaccines typically combine a nicotine derivative and protein carrier to stimulate the immune system to produce nicotine antibodies. The antibodies soak up nicotine in the bloodstream, prevent it from reaching receptors in the brain, and thereby block its effect. While this eliminates the pleasurable reward, as well as nicotine's addictive reinforcing effects, a vaccine isn't expected to ease withdrawal.

[Nabi Biopharmaceuticals](#) has been working with NIDA to develop and test NicVax, which consists of a nicotine-like molecule conjugated to recombinant exotoxin protein A from *Pseudomonas aeruginosa*. Preclinical studies have shown that the blocking effect works, while Phase I studies found the vaccine to be highly immunogenic and safe. The company has completed two Phase II trials on different formulations and began a Phase IIb, placebo-controlled study at nine sites in May. The study includes behavioral support and is designed to demonstrate proof-of-concept and determine optimal doses.

Even in Phase II trials not designed to show efficacy, smokers taking the highest dose of NicVax achieved a 33-40% quit rate versus 9% for placebo with mild to moderate side effects and none of the typical withdrawal symptoms, explains Thomas E. Rathjen, Nabi's vice president for investor relations. Nabi attributes the latter effect to a very small amount of nicotine still getting to the brain and moderating withdrawal while not eliciting a pleasurable response.

Unlike medications that a patient can stop taking, a vaccine "takes the control of the therapy away from the patient," Rathjen points out. After four or five shots over about three months, sufficient antibody levels develop and persist for 12 or more months. The 12-month mark seems to be critical, he adds, because if smokers get that far smoke-free, they have a 70-75% chance of remaining so. And although patients may smoke, the antibodies can't be overcome with any reasonable amount of relapse smoking. Boosters are also a possibility for continued treatment.

If all goes well, Nabi anticipates it could start Phase III studies in the second half of 2007. The company has been discussing appropriate end points for late-stage trials with regulators, Rathjen says, and already manufactures the vaccine at commercial scale in its Boca Raton, Fla., facility. Plans are to look for a pharmaceutical partner to market the vaccine through primary care physicians. In March, FDA granted NicVax fast-track approval status, designed to facilitate the development and expedite review of products for unmet medical needs.

Similarly, Switzerland-based [Cytos Biotechnology](#) is developing Cyt002-NicQb, consisting of nicotine attached to a viruslike particle called Qb. The company says its vaccine is safe, well-tolerated, and highly immunogenic. In a Phase II dose-ranging study, the company saw a 42% long-term abstinence rate among a subgroup of patients with high antibody levels compared with 21% for the placebo group. Since lower antibody levels weren't effective, Cytos has been optimizing the formulation and dosage to achieve high levels in as many patients as possible in future studies.

Meanwhile, [Celtic Pharmaceutical Holdings](#), an investment firm that acquired [Xenova](#) in September

2005, launched a Phase II placebo-controlled, multicenter trial of Xenova's nicotine vaccine, TA-Nic, in the U.K. in May and will begin a Phase IIa/IIb study in the U.S. this fall, says Patrick C. O'Connor, Celtic's managing director of clinical development. TA-Nic uses a nicotine derivative coupled to a recombinant nontoxic B subunit of cholera toxin. It has been shown to be immunogenic and safe in Phase I trials and gave indications of increased quit rates.

"The real downfall for a lot of people is not actually stopping, even though they go through an acute withdrawal phase; it's when they subsequently take the first cigarette and it feels so good," O'Connor says. The idea is that by raising antibody levels slowly, people will get less pleasure out of smoking and be able to quit. "But then, if they do relapse, they won't get that huge reinforcement from the first cigarette, because the antibodies would mop up the nicotine and not allow it to get into the brain," he says.

"There is a major gap in the market for something more effective, and the scale of the problems related to smoking is so huge that anything remotely useful in helping people to quit and stay quit is clearly going to find a place," says Michael Earl, Celtic's managing director for commercialization. "But I don't think there will be a magic bullet that solves everybody's problems." He anticipates further development will explore how vaccines, counseling, and other pharmacotherapies work alone or together for patient management.



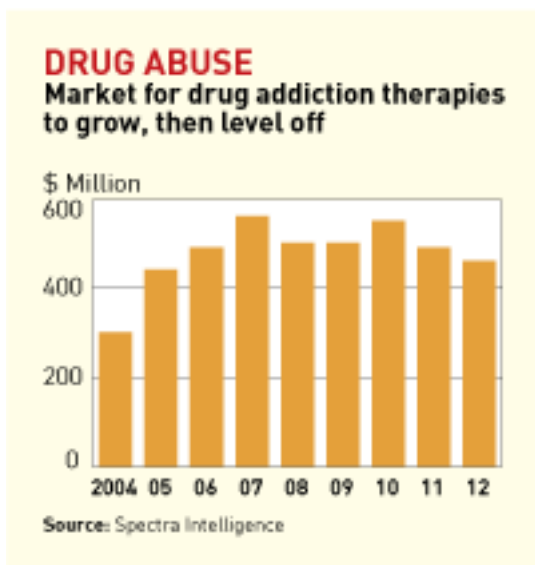
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DRUG ADDICTION. New doors may be opening as well for pharmacotherapies to treat addictions to other drugs, such as heroin, cocaine, and methamphetamine. For more than 30 years, methadone maintenance therapy has been the leading treatment method. Methadone is a long-acting, synthetic opiate administered orally to prevent withdrawal, block the effects of illicit opioid use, and diminish craving. Patients stabilized on this sustained-agonist therapy can function normally. [Mallinckrodt Pharmaceutical](#) is the leading bulk producer of the generic drug.

"There are probably about 250,000 people on methadone," NIDA's Vocci says. "But there's an estimated 1 million heroin addicts in the U.S. and anywhere between 1.5 million and 4 million people who have a problem with prescription opiates." The system, he believes, is constrained by limited public funding and access to treatment clinics. Europe, meanwhile, has an estimated 1.1 million intravenous drug users, 70% of whom are said to be untreated.

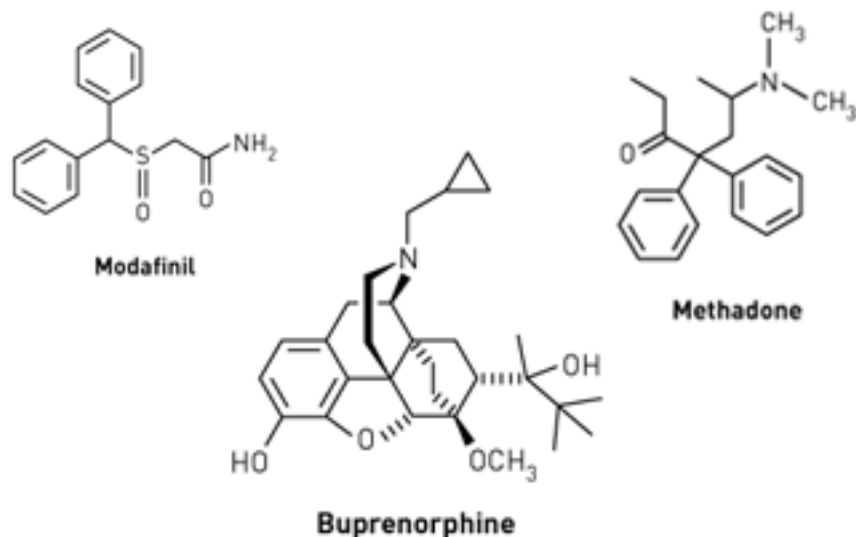
For about 10 years starting in 1993, methadone wasn't alone; levo-alpha-acetylmethadol was available, but then Roxane Laboratories ceased making it following reports of severe adverse events. Naltrexone, a synthetic opiate antagonist originally marketed by DuPont as Trexan in 1984 but is now off-patent, can be used after a patient undergoes opiate detoxification. It blocks the effects of self-administered opiates, so it can prevent relapse. It also is used to reverse acute opiate overdose. Other drugs used for detoxification and withdrawal are clonidine and lofexidine.

Without effective counseling or monitoring, patient compliance with addiction therapies can be a problem. To improve compliance, several companies are creating new formulations. [DrugAbuse Sciences](#) (DAS), based in Paris, has a sustained-release form of naltrexone for once-monthly injection. The company has it in Phase II clinical trials for opioid dependence and in Phase III for alcohol dependence. DAS and [Titan Pharmaceuticals](#) both are developing sustained-release buprenorphine. Titan expects to begin a Phase II clinical trial of its six-month version soon, while DAS anticipates starting a Phase I trial by 2007 for its once-per-month form.



Approved in the U.S. in 2002, buprenorphine was the first new treatment to arrive in more than a decade. Like methadone, it is a substitution therapy with the potential for abuse, although it has weaker opiate effects. It blocks cravings and can prevent withdrawal. In different regional markets, [Schering-Plough](#) and [Reckitt Benckiser](#) sell an oral form as Subutex and an oral combination of buprenorphine and naloxone as [Suboxone](#).

Opioids attach to opioid receptors in the brain, spinal cord, and gastrointestinal tract and block the transmission of pain and cause neurotransmitter release in the brain's reward center. Buprenorphine acts as a partial agonist at the μ -opioid receptor and an antagonist at the κ -opioid receptor subtypes. The structurally similar compounds naloxone, nalmefene, and naltrexone have antagonistic effects at various μ -, δ -, and κ -opioid receptors (*Chemistry Today* **2006**, 24, 54) and thereby block the neurochemical reward and reinforcement system.



The combination of drugs in Suboxone is designed to minimize misuse. Naloxone is ineffective when taken orally, but it attenuates buprenorphine's agonist effect when Suboxone is abused by injection. According to an article in the July 22 issue of the *Lancet*, Subutex smuggled in from Europe—it was first approved in France in 1996—has become a major drug of abuse in Russia. In late July, European regulators recommended marketing approval for Suboxone.

In Europe, the prescription of opioids by doctors for treating addictions is less restricted than it is in the U.S. When the U.S. Congress passed the Drug Addiction Treatment Act (DATA) in 2000, it brought about a major change for patients in that treatment could take place in the privacy of a doctor's office rather than a rehabilitation clinic. The act allows certified physicians to prescribe certain controlled substances approved by FDA for the treatment of addictions.

Subutex and Suboxone are currently the only drugs qualified under DATA. A recent study reported in the *New England Journal of Medicine* (**2006**, 355, 365) found that office-based treatment combining Suboxone and brief counseling was effective in substantially reducing drug use in about 40-50% of patients.

No drugs have been approved for cocaine addiction, despite it being a large problem, although a significant number of candidates have been and continue to be tested (*Eur. J. Pharmacol.* **2005**, 526, 101). For several years, NIDA has aggressively pursued this area and, more recently, methamphetamine abuse, Vocci says.

In 1990, NIDA set up its Medications Development Division to address the need for such pharmacotherapies. Its approach has been to support and coordinate the testing of marketed medications, whose properties suggest they might be effective, as a rapid and less expensive route to new treatments, as well as the discovery and investigation of new compounds. About 65 existing medications have been tested and more than 3,000 compounds identified and evaluated.

Disulfiram, one of the few existing pharmacotherapies for alcohol dependence, has given the most consistent and reproducible results in cocaine studies, Vocci says. It works as an aversion therapy, because its interaction with alcohol produces undesirable physical effects. In cocaine users, disulfiram produces an unpleasant sense of hyperstimulation, likely attributable to enhanced dopamine activity. Cocaine is believed to act as a dopamine-reuptake inhibitor, and disulfiram inhibits dopamine β -hydroxylase, which metabolizes dopamine.

"There are about half a dozen other drugs that have given us positive signals in reducing cocaine use in double-blind, placebo-controlled trials," Vocci says. "We are in the process of doing confirmatory evaluations." The drugs include topiramate, modafinil, tiagabine, propranolol, ondansetron, naltrexone, and a combination of disulfiram and naltrexone. Many are existing CNS drugs that act on similar targets affected by drugs of abuse, or are useful in clinical populations where other conditions, such as depression, occur along with drug abuse.

For example, some antiepileptic drugs have multiple mechanisms of action and, in addition to controlling seizures, can reduce obsessive or compulsive thoughts that may be connected to treating drug craving, Vocci explains. Similarly, the anticonvulsant topiramate, sold by Johnson & Johnson as [Topamax](#), causes weight loss and may affect other appetitive mechanisms.

Topiramate indirectly influences dopamine levels by activating γ -aminobutyric acid (GABA), an inhibitory neurotransmitter, and blocking glutamate, an excitatory neurotransmitter. According to NIDA, small-scale clinical studies have shown it helps cocaine-addicted individuals remain drug-free for three or more weeks—possibly enough time, when combined with behavior therapy, to offer a good chance for long-term cessation.

Modafinil, a drug that promotes wakefulness and is sold by [Cephalon](#) as [Provigil](#), enhances glutamate levels. Animal studies have shown that repeated exposure to cocaine depletes glutamate in areas of the brain related to the development of addiction. And an increase in glutamate levels blocks cocaine self-administration in rats. University of Pennsylvania researchers have already reported positive clinical trial results, and results from a major trial are expected later this year, Vocci says.

Tiagabine, an anticonvulsant sold by Cephalon as [Gabitril](#), is also being tested. The drug is a selective GABA reuptake inhibitor that increases GABA levels by selectively binding to GAT-1, the predominant GABA uptake transporter. If the company's products are found to work, Cephalon CEO Frank Baldino Jr. says it would be a "big step forward for drug abuse therapy" and one the company would support if it sees decent market opportunities.

[Catalyst Pharmaceutical Partners](#) (CPP) of Coral Gables, Fla., is developing vigabatrin for cocaine and other drug addictions. Vigabatrin, a γ -vinyl derivative of GABA, works by inhibiting the enzyme that breaks down GABA. The company licensed the compound from Brookhaven National Laboratory, which had conducted about a decade of addiction-related research. Sanofi-Aventis markets the drug as

Sabril for epilepsy outside the U.S. CPP has completed two clinical trials in Mexico and has the go-ahead from FDA to begin a Phase I trial in the U.S.

There's clearly much more to treating addiction than simply blocking reward systems. Areas for discovery include finding existing or new compounds that modulate appetitive systems in the brain, Vocci says. Such systems, and the dopamine system is one of these, alert human beings to internal and external stimuli and shape behavior over time. "The stimuli of greatest importance are probably conditioned cues, mood and affect changes, drug priming, and stress," he explains. "So we are looking at medications that can block these processes."

A formerly dependent individual responds more strongly to an initial intake of a drug or alcohol than does a nondependent individual and thus is primed for further consumption. Animal and clinical studies have shown that dependent individuals also interpret stress almost as if it were a low drug dose that activates their dopamine systems. And stress, combined with a conditioned cue or trigger, can lead to relapse.

Drugs that might block priming include dopamine D₃ receptor antagonists, D₃ receptor partial agonists, cannabinoid antagonists, and narcotic antagonists, Vocci says, whereas antistress compounds include CRF antagonists, vasopressin 1B antagonists, orexin antagonists, and certain glutamate antagonists. "There are a host of approaches, and some companies are working with us right now at the preclinical and clinical pharmacology levels, and we're looking at moving into clinical studies."

Another approach is aimed at drugs that affect cognition. "Five or 10 years ago, I would have said these are a great idea, but we don't know much about drugs that would affect cognition in a way we want," Vocci comments. Now, drugs are emerging that can enhance cognition, increase attention, stop persistently recurring thoughts, increase inhibitory responses to stimuli, or decrease impulsiveness and risk-taking behaviors. Addressing these traits, which may be genetic or acquired through repeated drug abuse, is believed to be relevant to mitigating addictive behaviors, he says.

"When someone decides drug use is going to be an organizing principle of their life, they are addicted, and what you need to do is to alter their cognition in order to alter their behavior," Vocci explains. "There are cognitive behavioral therapies, and they may work in some of the population. But it's the others for whom we're looking for medications, because they are the ones that relapse and continue to use drugs."

As in nicotine addiction, vaccines are also in development. Celtic has in development a cocaine vaccine called TA-CD that consists of a cocaine derivative conjugated to a cholera-toxin protein. The company reported preliminary results this summer from two Phase II studies supported in part by NIDA. After the body develops antibodies, the rate at which cocaine can pass into the brain is blunted as long as the antibodies are present.

Studies performed at Columbia University nicely showed a reduction in cocaine's binding to dopamine

transponders, O'Connor says. "If you get a reduction greater than about 45%, you actually blunt the euphoric effect." In clinical trials, patients with high antibody levels and reports of strongly diminished pleasure actually reduced their cocaine use, rather than trying to increase it to overcome the vaccine.

Whereas people addicted to nicotine may be able to remain abstinent after 12 weeks of treatment, the therapeutic window may be two to three years or longer for cocaine.

"We are discussing with NIDA—and planning to with FDA—the whole issue of what is a successful treatment for a patient addicted to cocaine," O'Connor says. "Obviously, the optimum goal would be that everyone would quit, but that may not be attainable, and what may be of real interest is that patients reduce their use of cocaine and become more productive members of society." Celtic anticipates having TA-CD in Phase III trials by late 2007.

"There are 300,000 to 400,000 people actively seeking help with their cocaine addiction in the U.S., but that probably only scratches the surface of whom you could access with an effective outpatient therapy," Celtic's Earl says. Estimates place the number closer to 10 million together in the U.S. and Western Europe where, he says, it is a rapidly growing problem and high on government and law enforcement agendas. "Our expectation is that when an effective product becomes available the uptake will be pretty rapid," Earl says.

Celtic has arrangements for manufacturing the vaccine and envisions finding a larger company to commercialize it. "At the appropriate time, we will auction our programs to an appropriate universe of big pharma companies positioned to make the best of them in the marketplace," says Stephen Evans-Freke, Celtic's managing general partner. He expects interest will be high, since the "major pharmaceutical companies have only very recently woken up to the scale of the medical need and therefore the commercial opportunity in treating drug addiction."

Other medications being tested for cocaine and for methamphetamine addictions include selegiline, used to treat Parkinson's disease; baclofen, used for muscle spasms; and ondansetron, which prevents nausea during chemotherapy. Methamphetamine has an even greater effect on dopaminergic systems than cocaine, and there are reportedly an estimated 350,000 heavy users in the U.S. alone. The smoking-cessation medication bupropion has recently been found to reduce drug use and craving in low-to-moderate methamphetamine users, or those who use the drug fewer than 18 days per month, Vocci says.

[InterveXion Therapeutics](#) in Little Rock, Ark., has received a \$3 million grant from NIDA that is helping the firm prepare for clinical testing of monoclonal antibody (mAb) treatments. "We expect to meet with FDA just after the first of the year and hopefully start clinical trials as soon as next June," says President and CEO R. Barry Holtz. The company's first candidate for testing, InterveXin-PCP, targets phencyclidine (PCP) abuse and is to be followed soon after by InterveXin-METH for treating methamphetamine abuse.

Initially, Holtz explains, the company will investigate the treatment of acute cases using passive or

nonimmunogenic mAbs to bind with high affinity to, and thereby neutralize, the drug of abuse. The technology came out of the laboratory of [S. Michael Owens](#), professor of pharmacology and toxicology at the [University of Arkansas for Medical Sciences](#) and director of the UAMS Center for Alcohol & Drug Abuse. He also serves as InterveXion's chief scientific officer.

"It's important to detoxify patients proactively in the emergency room," Holtz says, "because, for example, the problem with methamphetamine is that it binds permanently to receptors in the brain and destroys them. So there is no recovery." Long term, methamphetamine use alters activity in the dopamine systems associated with motor control and verbal learning, as well as affecting areas of the brain connected to emotion and memory.

After several years of preclinical work, the company is producing the antibodies in an alfalfa-based system with the help of [Medicago](#) in Quebec. "In the long run, this should reduce costs quite a bit," Holtz explains, especially in methamphetamine cases where patients often have very high levels of the drug in their bodies and large amounts of antibody will be needed. Because of the long half-life of the mAbs, the therapy will also be used to help recovering addicts overcome their dependence and to prevent or reduce adverse effects in chronic users.

Meanwhile, DAS has advanced anti-cocaine and anti-methamphetamine antibodies as far as preclinical development. It has put these products on hold, however, as it works on other products. One of these is DAS-431, a dopamine D₁ receptor agonist licensed from [Abbott Laboratories](#) in 2000. Abbott tested the compound in Phase IIa studies for cocaine addiction and saw positive results, according to DAS, which expects to begin Phase IIb studies in 2007.

Yaupon Therapeutics, meanwhile, has funding from NIDA and anticipates starting Phase II studies of the dopamine-modulating agent lobeline for treating methamphetamine addiction in early 2007. Preclinical studies have found lobeline to be effective in animal models and that it also protects dopamine-producing neurons. Like Yaupon's other drug candidates, lobeline is a plant alkaloid; the compound comes from the Indian tobacco plant and has been known for centuries.

"It was defined as a nicotinic receptor agonist in most of the old literature," explains University of Kentucky professor of pharmaceutical sciences and Yaupon founder [Linda Dwoskin](#). "From our data, however, we figured out that in the central nervous system it's actually acting as a nicotinic receptor antagonist." She notes that lobeline's use as a smoking cessation agent had been studied decades earlier without definitive results.

"We've also looked at interactions with dopaminergic systems and found that lobeline is a potent inhibitor of the vesicular monoamine transporter 2, which is the protein that stores dopamine in vesicles for release," Dwoskin adds. As such, it functions to antagonize the effects of amphetamine stimulants and prevents the amphetamine-induced release of dopamine. It does so by binding noncompetitively at an allosteric site, and because of this mechanism, its effect can't be overridden by increased intake of the drug of abuse.

Phase I work was carried out through a clinical trials agreement with NIDA. "They have helped us tremendously in getting this compound into the clinic," Crooks says. "It's a partnership that has really provided a lot of basic support that normally you wouldn't expect to have when commercializing a product on your own." Crooks and Dwoskin's work has continued in the synthesis and development of lobeline analogs to both test the target mechanism and find more selective and novel inhibitors.

"The mechanisms of drug abuse and treatment are complex, and I don't know that we are going to be able to find any one medication that works," Vocci says. "Most of the time in CNS pharmacology, it seems like the 'dirty' drugs with multiple mechanisms work best." Then, once effective pharmacotherapies are found, the task is to reduce side effects. "For example, newer selective serotonin reuptake inhibitor antidepressants don't work any better than the old tricyclics, but they do have fewer risks," he adds. And, in treating drug abuse, as for other disorders, combinations of medications may play a role.

The market for narcotic addiction therapies is about \$440 million and is not expected to grow between now and 2012, on the basis of current therapeutics, reports Spectra Intelligence. The entrance of any one new medication, especially one that creates a new market sector around cocaine dependency, could be a significant boost. If approved, for example, products with the potential of \$300 million to \$400 million in annual sales include TA-CD and long-acting buprenorphine.



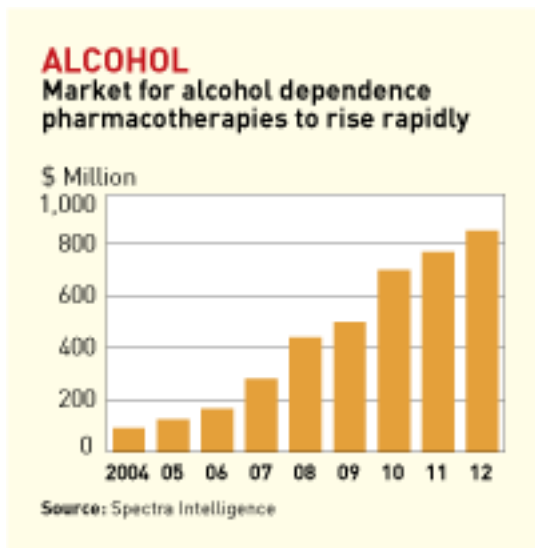
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ALCOHOLISM. In contrast to the market for narcotic addiction therapies, Spectra Intelligence says the alcohol addiction medication market was just \$125 million in 2005, but forecasts it to grow more than sixfold to \$840 million by 2012. The small size today is despite a total potential market of 30 million or more people in the U.S., Europe, and Japan. Growth will come largely from the very recent launches of [Vivitrol](#), developed by [Alkermes](#) and marketed by Cephalon, and of [Campral](#), which has been gaining ground since FDA approved [Forest Laboratories'](#) version in 2004.

For about 45 years, the aversive agent disulfiram, sold by [Odyssey Pharmaceuticals](#) as Antabuse, was the only treatment. Today, some researchers consider it ineffective at best and often dangerous, as well as antiquated since it doesn't target known neurochemical mechanisms in alcohol addiction. Instead, it works by inhibiting aldehyde dehydrogenase, an enzyme that converts acetaldehyde to acetic acid,

which leads to a buildup of acetaldehyde in the body. After taking disulfiram and then consuming alcohol, a person experiences nausea, flushing, headaches, and chest pains. The drug also can have more severe adverse effects, including death. Many patients simply stop taking it.

In 1994, an oral form of the opioid antagonist naltrexone, renamed ReVia, was approved by FDA for treating alcoholism; it is now sold as a generic drug under many different names. The drug's safety profile is good at lower doses, although it can cause liver failure at excessive doses and thus bears a warning on its label, which some in the field say has limited its use. It generally has been considered moderately effective in reducing drinking and cravings.



Alcohol dependence, with relapse rates of more than 75% after one year, and other addictions often require extended treatment and retreatment. Patient compliance is a serious issue with oral medications, according to David R. Gastfriend, Alkermes' vice president of medical affairs. "About 30 years ago, NIH issued a call for help to develop technologies for extended-release preparations," he says. With seed money from NIAAA and NIDA, Alkermes spent about six years developing Vivitrol, which was approved in April.

Vivitrol is naltrexone embedded in polymer microspheres for once-monthly intramuscular injection. Clinical studies have demonstrated that patients like the new formulation and can tolerate it and that its safety profile is good, he says. Results also show that Vivitrol helped decrease heavy drinking and prolong abstinence. In addition, the priming effect, which causes acute craving, is reduced. In clinical studies, patients used Vivitrol for at least six months, but in practice, a patient and physician will determine the duration of treatment.

FDA has approved Vivitrol for patients who have initiated abstinence, a group in which the drug has been found to work best and one consisting of individuals who essentially have chosen to address their dependence. It also is to be used in combination with psychosocial treatment. Although being abstinent or even entering treatment may be a hurdle, Gastfriend says, "the real message is that this is a potentially life-threatening disease, it's a medical condition, and it has to be taken seriously, and this is a

serious medicine.

"We know that out of the 8 million or 9 million people in America with alcohol dependence, maybe 100,000 get medication, which is essentially nobody," he says, although about 2 million per year seek treatment. "Since 1935, at the outset of the Alcoholics Anonymous movement, we've had one major approach to treating alcohol dependence, and that is talking. And we have taken that, it seems, about as far as we are going to get with it," he says. He believes medications will be a crucial part of future treatment.

Although there are many different, rigorous approaches to behavioral or psychosocial therapy that all seem to do equally well, he says, "none of them stabilizes the chemical or neurological origins of this disease in the brain" as naltrexone is believed to do. "It's only through the science of neurotransmitter receptors that we are able to add another conceptual approach to stabilize the circuitry of reward systems in the limbic areas of the brain and address cognitive learning processes in the cortex for recovery."

Most physicians have approached addiction by prescribing abstinence, since they didn't favor "substituting dependence on one drug for another," Cephalon's Baldino remarks. "There's been a dearth of products and very low success rate for the abstinence route, and with a drug like Vivitrol, you really can improve today's standard of care." Cephalon intends to introduce Vivitrol first through addiction specialists to gain experience with them, then expand it to others, such as psychiatrists focusing on addiction, and eventually to primary care physicians.

"Primary care physicians will be an important audience because patients may be more likely to discuss their problems with them," he says. A recent clinical study, "Combining Medications and Behavioral Interventions for Alcoholism," or COMBINE, "really underscores the value of the combination of pharmacotherapy and psychosocial support," he says, and should help physicians realize that there is more they can do for patients. NIAAA recently issued guidelines supporting the combination of therapies.

Cephalon will offer a program called VIP³, or Vivitrol Information for Patients, Physicians & Providers, to integrate support services for all three groups as part of its commercialization strategy. Three years ago, it would have been extremely difficult to get doctors to consider using a pharmacotherapy, Baldino says, "but we're happy to have a new drug to launch into today's environment" that is more receptive to pharmacotherapy. In 2005, Cephalon signed a \$490 million deal with Alkermes to market the drug.

"Large pharmaceutical companies historically have not gone into small emerging markets, which fortunately is good for smaller companies like us," he says. "The current alcohol dependence market is not an attractive market, and there are only a couple of players here." He believes, however, that if Vivitrol does well, it will spark the interest of other pharmaceutical companies, bring more investment in R&D, and eventually give patients more choices.

Meanwhile, Finnish biotech company [Biotie Therapies](#) is testing an oral form of nalmefene for alcohol dependence and for impulse disorders. "Opiate receptor antagonism has a solid base in treating dependence disorders," Biotie CEO Timo Veromaa says, "and nalmefene has a better bioavailability than naltrexone, is longer lasting, and does not have the liver toxicity issues." Side effects are those common to the overall class of opiate antagonists, he adds.

The company has been working for several years to show the drug's efficacy in reducing heavy drinking, rather than achieving or maintaining abstinence. "We have taken a completely new look at this and devised a clinical development program from the opposite viewpoint," Veromaa explains, since he says results for abstinence-oriented therapies have largely been extremely poor and relapse rates very high.

Unlike other therapies, Biotie's nalmefene has been designed to be used on demand. "Patients are advised to take one tablet per day as needed, when drinking is imminent—and these people know when they are going to drink," Veromaa says. "Because nalmefene takes away the craving, it leads to the ability to resist urges to drink excessively." In one large, late-stage clinical trial, nalmefene reduced heavy drinking by almost 50%.

"We have completed two Phase III clinical studies and are now going into the registration phase in Europe for alcohol dependence," Veromaa says. Approval is anticipated first in the U.K. in 2007, followed by other European countries in 2008. Biotie will manufacture the drug. It has signed on [Britannia Pharmaceuticals](#) as a marketing partner for the U.K. and Ireland and is finding others in other markets outside the U.S. Somaxon Pharmaceuticals has licensed North American rights to nalmefene but is not yet pursuing it for alcohol dependence.

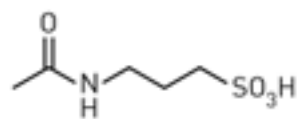
Forest Laboratories' business model is to look for products in areas of unmet medical need, where the mechanisms are unique, or where there may be some distinct safety or efficacy advantage, explains Jeffrey M. Jonas, Forest executive vice president and medical officer. The company licensed Campral from [Merck KGaA](#) in Europe and has been marketing it in the U.S. since 2004. How the drug works in alcohol dependence is not well understood, but it is thought to modulate glutamatergic activity, possibly reducing glutamate levels and alcohol withdrawal symptoms.

"It's believed that alcoholics develop compensatory mechanisms in the brain because of chronic alcohol use, and when alcohol is removed, they develop cravings due to changes in the neurochemistry," Jonas says, "and somehow Campral stabilizes the neurochemistry." The drug, given as two 333-mg tablets twice daily, is to be used along with psychosocial therapy in patients who have been abstinent. Jonas says that taking a medication routinely may actually be positive for patients "for whom having a reconfirmation of treatment is important in acknowledging their illness."

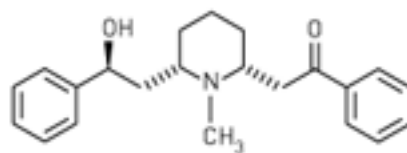
Results from clinical trials suggest that after as long as a year patients that had used Campral were about two or three times more likely to achieve complete abstinence than those on placebo, Jonas

explains, "and we think that's a meaningful effect." In contrast to pharmacotherapies and clinical trials targeting a reduction in drinking, Jonas says, "we have to believe that the ability to sustain abstinence is probably the gold standard for treating alcoholism."

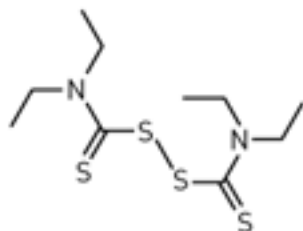
The results of the COMBINE study, published in the May 3 issue of *JAMA*, have sparked a great deal of discussion. NIAAA launched the 1,400-patient multicenter study in 2001 to identify the most effective treatments for alcohol dependence. In addition to naltrexone, the study included acamprosate and a combination of the two drugs, all given along with medical management or behavioral support. Acamprosate had been widely studied and used in Europe since 1989, where the vast majority of clinical studies have shown it helps individuals maintain abstinence, before being approved on the basis of these data in the U.S.



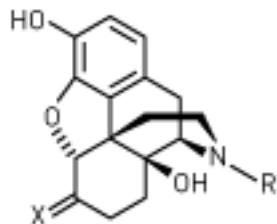
Acamprosate



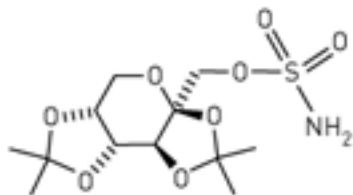
Lobeline



Disulfiram



Naltrexone (X = O, R = cyclopropylmethyl)
 Naloxone (X = O, R = allyl)
 Nalmefene (X = CH₂, R = cyclopropylmethyl)



Topiramate

Although treatment using naltrexone performed slightly better than placebo in the study, acamprosate alone or in combination with naltrexone, did not—much to many people's surprise (*J. Am. Med. Assoc.* **2006**, 295, 2075). The trial has raised differing views about study design, including questions around population differences in determining efficacy and applicability to real-world settings. Maybe most important, it highlights the challenge in finding effective treatments.

"Alcoholism is a difficult illness to treat," Jonas says. "It is a very complicated mix of psychological drives and physiologic drives." This often makes it difficult for medications to show an effect, which makes treatment for this kind of disorder daunting and, in turn, makes the impact of these drugs somewhat less dramatic. Further complicating matters, patients also often have a gamut of psychosocial problems and coexisting conditions, such as depression and anxiety.

It's not unusual to find that a drug may work in some trials and not in others, and the reason why isn't

always clear, says Raye Z. Litten, coleader of NIAAA's medications development team and COMBINE's government director. And all medications don't work in all patients. "We know, for example, that acamprosate and naltrexone don't work for everyone, but that doesn't mean they don't help some people," he says. The institute is still conducting an exploratory analysis of the COMBINE data to see whether they can identify who did and didn't respond.

"If you could predict the population a drug would work in, you would undoubtedly see a better effect and more consistent results," Litten says, "and be able to deliver medications in a more effective, more reliable, and safer manner." The need for personalized treatment is evident in alcohol dependence, according to NIAAA researchers whose work has helped determine that complex mechanisms underlie the disease, which likely is not a single disorder but many with common defining features.

"The disease phenotype is a product of the interaction of genes and the environment," says Markus Heilig, chief of the Laboratory of Clinical & Translational Studies at NIAAA. At one extreme, people have a genetic susceptibility, and progress is being made in identifying genetic variations. At the other, the disease is shaped by environmental factors. "What people fail to appreciate is that the major environmental factor is alcohol itself," he adds. Cycles of intoxication and withdrawal over a sufficiently long time trigger neuroadaptive changes.

Thus, in very simple terms, neurochemical imbalances that manifest as the same apparent dependence on alcohol can arise from either genetics or environment, or actually a combination of both sources. Neuroadaptive and genetically susceptible individuals, and others in between, react differently to alcohol, to factors such as stress, and to pharmacotherapies. Understanding and identifying these mechanisms and their manifestations has implications for both finding drugs and the patients in which they'll work and may even influence clinical trial design.

For example, a genetic variation found in the μ -opioid receptor enhances the pleasurable effects of alcohol, Heilig says. "And blocking that receptor would be expected to have more of an effect in people with that variation than in others." Pharmacogenetic data—namely, a predictive positive therapeutic response to naltrexone—have emerged to support this hypothesis, he adds. Similarly, a hallmark of some neuroadaptive alcoholics is a hyperglutamatergic state; acamprosate reverses the effect in alcohol-dependent animals but has no effect in those not adapted to alcohol.

"We have right now about six to seven preclinically very well-validated targets" that have fulfilled specific requirements, Heilig says. "They have to be compounds that either already have properties that are useful for clinical development or that we can hopefully optimize to that stage, and there needs to be a serious pharmaceutical company willing to support development." It can be difficult to find partners for off-patent drugs, even when the compounds hold promise or NIAAA assumes the development risk, because they offer no earning potential.

Nevertheless, interest on the part of pharmaceutical companies is increasing for a number of reasons, says Mark Egli, coleader of the NIAAA medications development team, including companies' need for

new products and the size of the potential market. They also are attracted to new animal models for evaluating compounds based on a significantly improved understanding of the mechanisms of alcohol dependence and addiction in general, he says. As proof of companies' growing interest, one can look back 10 years when no major company had any large-scale clinical trials under way in this area; since then there have been at least a dozen.

NIAAA itself has more than 50 clinical trials under way for alcohol dependence and related conditions. It has been exploring existing medications, such as topiramate, gabapentin, valproate, ondansetron, baclofen, aripiprazole, memantine, and rimonabant. It also has been investigating new compounds targeting opioid, serotonin, GABA, dopamine, glutamate, cannabinoid, CRF, adenosine, and neuropeptide Y receptors. Egli has coauthored two recent reviews on the subject with Heilig (*Pharmacol. Ther.* **2006**, *111*, 855) and with Litten and others (*Expert Opin. Emerging Drugs* **2005**, *10*, 323).

Clearly, when it comes to alcohol dependence, it's not all about dopamine. "Dopamine is a very important neurotransmitter that's involved in many aspects of behavior, and it got a lot of attention because of its role in reinforcement and reward," Egli says. "It's certainly part of the equation, but because alcohol affects so many systems in the body, and because there is no one single receptor to target, finding drugs that work may be more complex than for other addictions."

"Before naltrexone and acamprosate were approved, many people were saying we'd never get a drug through FDA because there was no receptor to target," Litten says. Both drugs are now approved in about 29 countries. "Maybe it's a small step in curing alcoholism, but it's certainly a big step for researchers," he says. It demonstrates both the progress in basic science over the past 10 to 15 years and the possibility for success in development and approval. Work is expected to continue on establishing targets, validating models, and finding genetic markers.

NIAAA is taking steps to address development issues. "We are finalizing the formation of an integrated medication development program here at the institute," Willenbring says. "For a long time, we have been funding extramural research, but now we are more systematically providing a certain set of services and strategies that we hope will serve as a complement to industry." The idea is to facilitate early-stage clinical development and proof-of-concept stages and not replicate industry's capabilities in either drug discovery or large-scale efficacy and safety trials.

NIAAA also is hoping to access libraries of compounds at pharmaceutical companies. "We're in dialogue with various pharmaceutical companies about compounds they have but aren't going to pursue, or they'll come to us because they believe something might be effective," Willenbring explains. The institute then might conduct preclinical research and even initial clinical trials with the hope of having something to hand back that a company will want to develop further.

Willenbring believes there will be considerable advances in pharmacotherapy. "There are so many potential targets, which is both good and bad news," he says. "It means there are a lot of opportunities,

but it also means we are unlikely to find a single medication that's going to make a really big difference because the disease is so complex." Instead, at least near term, successful treatment strategies will probably involve medications with multiple actions or multiple medications as doctors learn more about what is available, is effective, and works best for their patients.

In the past, addiction treatment has been handled largely by specialists rather than within general health care, but there aren't that many specialists, and awareness about pharmacological approaches has been limited. Marketing has also been lackluster, and thus there's been little market penetration. "One of the biggest problems we have is that the drugs are not being used because we don't have the infrastructure set up to provide treatment," Willenbring says. Although there are expectations for another six or more new addiction medications within the next 10 years, it will require change to make these treatment options available.

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