nature neuroscience



# Taking addiction research into the clinic

As the focus articles in this issue demonstrate, our understanding of the neurobiology of addiction has progressed substantially over the last decade, largely through studies in rodents. However, despite having some of the best animal models in neuroscience, researchers have been less successful in translating this knowledge into effective therapies. To solve this problem, we need to remove the roadblocks to development and testing of new treatments.

Some medications are available. For alcoholism, the opioid receptor antagonist naltrexone and a newer drug, acamprosate, are approved in the US and Europe. (Acamprosate affects GABA and glutamate receptors, but its mechanism of action is not fully understood.) Each drug moderately reduces the amount and frequency of drinking in clinical trials, and combination therapy with both drugs seems to be more effective than either alone. For cocaine addiction, modafinil (an atypical stimulant that is approved for other uses) seems to increase abstinence during treatment[1]. For heroin addicts, the μ-opioid receptor partial agonist buprenorphine is available in Europe and the US. Buprenorphine is as effective as methadone (a full agonist that is tightly regulated), and has no abuse potential or overdose liability. However, in the US, federal regulations prohibit physicians from treating more than 30 patients. Such restrictions are common for treatments that target addiction to illegal drugs, and they unfairly reduce the availability of help for patients who need it most.

Other therapies affect not only drug addiction, but also the response to natural rewards, such as food. This is a potentially serious problem for drug design, as the brain circuits that respond to natural rewards partially overlap with those that respond to addictive drugs. For example, topiramate, an anticonvulsant that acts at AMPA/kainate glutamate receptors, is used for alcoholism and cocaine addiction, but it is also effective against binge eating, suggesting that it may affect responses to food. Rimonabant is a cannabinoid receptor 1 antagonist that reduces the expression of several addictions in animal models, and is now in clinical trials in humans. However, the compound is also in clinical trials as a treatment for obesity, and seems to promote modest weight loss, so it too is likely to affect eating behavior.

Preliminary results from clinical trials suggest that other approaches may be promising. Vaccines against cocaine[2] or nicotine seem to reduce drug intake in patients who produce enough antibodies, which then intercept the drug before it reaches receptors in the brain. N-acetylcysteine (a food supplement available over the counter) reduces cocaine addiction without affecting the response to food in rats, and is now being tested in people.

Some animal models of addiction mimic the diagnostic characteristics of the human disorder very closely, but unfortunately they are too complicated for use in large-scale drug screening. For example, in one model of drug seeking and relapse, rats are trained first to press a lever for access to a drug, and then to work for an intermediate cue that predicts the drug's future availability (as money might do for human addicts). If this behavior fails to produce the drug, the animal eventually will stop pressing the lever, but later exposure to stress, the addictive drug, or cues associated with the drug can cause the drug-seeking behavior to start again, mimicking relapse in human addicts. This entire assay takes 10 to 12 weeks.

Such models are time-consuming and expensive, so investigators typically begin screening for drug-induced neural changes with simpler tests. Promising hypotheses can then be studied with more complex behaviors. The disadvantage of this approach is that it does not allow the identification of neural adaptations that are specific to compulsive drug seeking and relapse—and such neural changes might be the most directly relevant to addiction treatment. For example, drug self-administration by rodents produces distinct effects in the brain that are not seen when the same amount of drug is simply injected by researchers.

Beyond the practical problems involved in identifying targets, pharmaceutical companies lack incentives to develop medicines for addiction. Treating addiction to illegal drugs raises legal issues, and the common view of addiction as a character defect rather than a neurobiological disorder[3] creates a public relations problem. In addition, the addicts who most need treatment are least likely to have jobs or medical insurance. Insurance companies often restrict the availability of treatment, even for the many alcoholics and nicotine addicts who have coverage.

For these reasons, pharmaceutical companies are often reluctant to undertake full-scale development of new drugs, or even to release the compounds that they already have for testing in addiction. Instead clinical trials for addiction typically involve drugs that are already approved for other uses, which reduces the costs of bringing them to market. In contrast, most drug targets proposed by basic researchers have not been tested properly in the clinic, either because drugs to target these mechanisms do not exist or because the companies that own the compounds have not made them available to researchers.

What can be done to improve the situation? Governments and charitable foundations could provide better incentives for drug development, such as promising to purchase a certain amount of any effective drug that is developed, or they could purchase candidate compounds from pharmaceutical companies for testing in their own trials. Doctors and insurance companies should begin to think of drug addiction as a chronic disease that must be treated over the long term, despite difficulties with patient compliance, like schizophrenia or hypertension. Behavioral choices contribute to many health problems—diet and exercise to heart disease, for example, or smoking to lung cancer—but we do not refuse these patients medical attention because they are culpable for their illness. A similar attitude toward addicted people would go a long way toward improving their care.

1. Dackis, C.A., Kampman, K.M., Lynch, K.G., Pettinati, H.M. & O'Brien, C.P. *Neuropsychopharmacology* **30**, 205–211 (2005).
2. Martell, B.A., Mitchell, E., Poling, J., Gonsai, K. & Kosten, T.R. *Biol. Psychiatry* **58**, 158–164 (2005).
3. Dackis, C. & O'Brien, C. *Nat. Neurosci.* **8**, 1431–1436 (2005).