bryos with mutations in *Oct4* or *Nanog*, two key pluripotency genes, fail after implantation, demonstrating that these genes are crucial for embryos to develop. Most cloned embryos fail in this way as well, said Jaenisch. "I would argue that all of those genes need to be active for the embryos to succeed," he said.

REPROGRAMMING THE GENOME

Jaenisch set out to see if he could activate such pluripotency genes in somatic cells and make the cells' nuclei behave like those of embryonic cells. Several of these genes, *Oct4*, *Nanog*, and *Sox2*, have been shown to be regulators of the expression of genes that are vital to maintaining pluripotency in embryonic stem cells (Rodda et al. *J Biol Chem*. 2005;280:24731-24737). "The question is, what happens when you induce these genes in somatic cells where they're not normally expressed?" Jaenisch said. "Is there alteration of cellular growth characteristics, and will it improve reprogramming?"

Jaenisch began to address this question by expressing *Oct4* in somatic cells in mice. Research has shown that *Oct4* expression keeps embryos in an immature state and prevents cells from differentiating into tissue-specific cells. When Jaenisch and his team caused the expression of this gene in somatic cells, they observed rapid induction of cell proliferation (which often occurs in cells that are undifferentiated) in the intestinal tract, an effect that was fully reversible when *Oct4* expression was switched off. In addition, when the gene was shut off, the cells expressed proteins indicative of differentiation. The results suggest that certain somatic cells remain able to respond to key embryonic signals that inhibit cellular differentiation (Hochedlinger et al. *Cell*. 2005;121:465-477).

To better understand the effects of these embryonic signals, researchers would like to identify the target genes of the Oct4, Nanog, and Sox2 proteins. Jaenisch and his colleagues have found that the Oct4, Nanog, and Sox2 proteins bind to and regulate some of the same genes, and they even collaborate to regulate each others' gene expression through what is known as autoregulatory loops. Grasping the intricacies of these relationships should provide scientists with new insights into embryonic cell regulation.

Jaenisch envisions that such research may provide a way around the impediments of nuclear cloning for generating embryonic stem cells customized to specific patients. If scientists can understand the differences between the molecular circuitry of stem cells and differentiated cells and learn how to reprogram gene expression in somatic cells, they might one day be able to achieve such feats as turning a skin cell into a neuron or beta cell without the use of human eggs. To do that, though, much more work needs to be done to reveal all of the key genes involved and the precise effects they have on cell growth and differentiation. □

Office-Based Treatment for Opioid Addiction Achieving Goals

Bridget M. Kuehn

ORLANDO, FLA—Many individuals with opioid addictions who might otherwise go untreated are seeking office-based buprenorphine treatment and many are having positive outcomes, according to emerging data on the 3-year-old treatment program. But challenges remain for patients seeking care and the physicians who treat them.

Office-based buprenorphine treatment represents a new paradigm for treating opioid addiction. While methadone treatment through clinics has proven effective for many with opioid addictions, the stigma associated with the clinics, constraints on their locations, and the logistics of getting to them for daily treatment have been obstacles for some individuals, explained Arlene Stanton, PhD, social science analyst at the Center for Substance Abuse Treatment at the Substance Abuse and Mental Health Services Administration (SAMHSA) in Washington, DC. Officials hoped that making buprenorphine available through qualified primary care physicians and addiction specialists would attract a new group of patients to treatment.

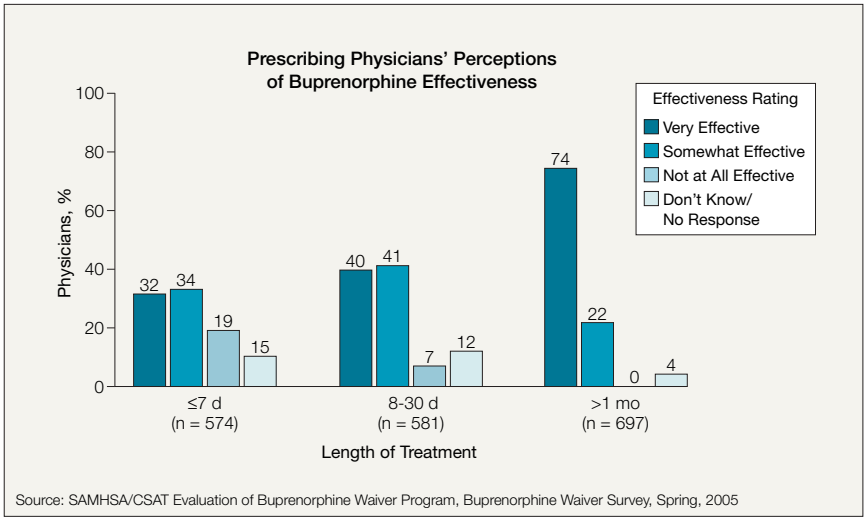
So far, it seems to be working.

"We found office-based buprenorphine, even in its limited use to date, has been successful in fulfilling its promise to reach new patient populations," said Lynn E. Sullivan, MD, assistant professor of medicine at Yale University School of Medicine, New Haven, Conn. Sullivan and her colleagues published their cross-sectional, longitudinal analysis of a clinical trial of office-based buprenorphine treatment in the July issue of *Drug and Alcohol Dependence*.

These findings were supported by preliminary results from an evaluation conducted by SAMHSA of office-based buprenorphine treatment nationwide. Results from the three-pronged evaluation, which included surveys of addiction specialists, physicians prescribing buprenorphine, and data from patients receiving treatment, were presented at the annual meeting of the College on Problems of Drug Dependence in Orlando in June. Also presented at that meeting were results from the first 3 years of the 5 years of postmarketing surveillance (paid for by the medication's manufacturer, Reckitt-Benckiser Pharmaceutical Inc, Berkshire, England) that was mandated by the Food and Drug Administration when the drug was ap-

proved. Both the evaluation and surveillance show few reports of adverse events, minimal diversion, and overall positive reports of the drug's effectiveness.

Ultimately, these data will inform policy decisions regarding the program that makes office-based buprenorphine treatment possible. The Drug Addiction Treatment Act of 2000 established a waiver program that authorizes qualified physicians in a variety of health care settings to dispense and prescribe narcotics approved by the Food and Drug Administration for the treatment of opioid addiction. Buprenorphine, which received such approval in 2002, was the first medication to be distributed under the waiver program. A opioid partial agonist, the medication blocks cravings for opioids and, when used properly, prevents withdrawal. Physicians are required to attend at least 8 hours of training on buprenorphine therapy, although there are exemptions for some addiction treatment specialists. SAMHSA provides information about the buprenorphine waiver program on its Web site (http://buprenorphine.samhsa.gov/).



A survey of physicians treating patients with buprenorphine showed the vast majority of those who had treated patients for more than 30 days found the drug to be effective.

PATIENT PROFILE

Sullivan found that individuals enrolling in office-based buprenorphine treatment were more likely than those enrolling in methadone treatment to be male and to have full-time jobs, no history of previous methadone treatment, fewer years of opioid dependence, and lower rates of injection drug use (Sullivan et al. *Drug Alcohol Depend*. 2005;79:113-116). Among those enrolling in office-based treatment, those who were new to treatment were younger, more likely to be white, more likely to report current prescription opioid use, less likely to report a history of injection drug use, and less likely to test positive for hepatitis C. Individuals who were new to treatment also had a shorter mean history of opioid dependence.

"We may be catching them earlier in their drug dependence and that may allow us to treat them more successfully and allow them to avoid some of the serious consequences of long-term drug use," Sullivan said.

The SAMHSA evaluation, which collected information from 434 patients receiving treatment from a sample of more than 100 physicians, found a similar profile. The findings suggest that in late 2004 and early 2005, individuals treated with buprenorphine for addiction were more likely to be white, younger, employed, and better educated than individuals treated in publicly funded methadone treatment, as reported to the Treatment Episode Data Set in 2002. Only 9% of the patients entering buprenorphine treatment had been transitioned from methadone, 31% had never been treated for substance abuse before, and 60% had never been treated with medication for substance abuse.

According to the SAMHSA patient study, about two thirds of the buprenorphine patients were addicted to opioids other than heroin, particularly oxycodone and hydrocodone. These individuals may have been prescribed pain medication and may still be seeing a physician regularly, Stanton said. "[The waiver program] gives that physician the option of continuing to care for that person in all respects of their life, and keep them employed and functioning in society."

EFFECTIVENESS

There has been slow growth in the number of physicians who have received waivers and are prescribing buprenorphine. More than 4500 physicians had waivers in the first quarter of 2005, and according to a survey of waivered physicians conducted as part of SAMHSA's evaluation, 67% of them were prescribing the drug. A total of 104 640 patients have entered buprenorphine treatment so far.

"We were pleasantly surprised at the number of physicians who have used buprenorphine and found it somewhat effective or very effective," Stanton said.

Based on the results of the waivered physician survey, physicians treating patients for longer periods are more likely to report that the drug is effective, Stanton said. Seventy-four percent of surveyed physicians treating patients for more than 1 month reported that it was very effective compared with 32% of the physicians treating patients for 7 days or less. Reports of severe adverse reactions were remarkably low, with the surveyed physicians reporting that just 0.5% of their 47 664 patients had a severe adverse reaction. Withdrawal symptoms were by far the most common type of adverse reaction (103 of 217 patients reporting reactions experienced withdrawal).

Further Information

The Substance Abuse and Mental Health Services Administration provides educational materials on its Web site, available at http://buprenorphine.samhsa.gov/, for clinicians who currently treat or are interested in treating opioid-addicted patients with buprenorphine, as well as for patients seeking information about treatment. In addition to providing basic information about buprenorphine therapy, the site provides information about

- The buprenorphine physician waiver program.
- Where to receive training that meets the requirement for a waiver.
- An online mentoring program for prescribing physicians.
- A directory of physicians who are authorized to prescribe buprenorphine.
- Clinical guidelines for using buprenorphine for opioid addiction treatment.

Charles R. Schuster, PhD, who is conducting the postmarketing surveillance, said withdrawal was also the most common adverse event reported by the physicians he surveyed. He explained that if patients are given a dose of buprenorphine while they are still under the influence of opioids, the medication will precipitate withdrawal. "It's very important for physicians to allow patients to go into mild withdrawal before they are started on buprenorphine," he said.

Additional data on the drug's effectiveness from the SAMHSA evaluation are being analyzed and are expected to be presented in the fall.

WORD ON THE STREET

There have been relatively few reports of diversion and abuse of buprenorphine and the number of reports does not seem to be increasing as the number of treated patients increases, said Schuster, a former director of the National Institute on Drug Abuse who is now director of the Substance Abuse Research Division at Wayne State University, Detroit, Mich.

Most of the buprenorphine prescribed in office-based settings is an abuse-resistant formulation called Suboxone, which includes a small dose of the opioid-receptor antagonist naloxone. When taken sublingually, as prescribed, the naloxone is inactive but induces withdrawal if it is injected. The buprenorphine-only formulation, Subutex, is used in limited circumstances, such as hospital-based detoxification or in pregnant patients.

According to the postmarketing surveillance, ethnographers studying trends in illegal drug use have reported little street knowledge of buprenorphine and only a few or no reports of diversion in seven major metropolitan areas. Additionally, quarterly random surveys of waivered physicians have also indicated low rates of diversion, said Schuster. Each quarter, 15% to 30% of the physicians surveyed since late 2003 have reported knowledge of illegal sales of buprenorphine and 10% or less have reported knowledge of prescription shopping.

Follow-up interviews have revealed that when diversion occurs, it often involves individuals who are trying the drug therapeutically. In many cases, physicians learn of the diversion from would-be patients who say they have tried buprenorphine and would like to enter treatment. "They've gotten the drugs illegally from diverted sources, but they have not used it to get high," Schuster said. "They've used it because their friends have said, 'Hey, this stuff really works.'"

PHYSICIAN SUPPORT

Despite these promising findings, physicians are reporting some challenges.

In SAMHSA's surveys of waivered physicians, 39% of those who have not yet prescribed the medication cited such logistical difficulties as setting up the required recordkeeping protocols. Thirty percent cited too few referrals or appropriate patients and 23% cited patients' inability to pay.

About half of the physicians who were prescribing the drug said that patients' inability to pay was their biggest challenge, findings consistent with results from the postmarketing survey. Schuster explained that few third-party payers cover the drug and those that do may cover only short-term treatment.

"I'm concerned about a two-tiered system where Medicaid will support methadone so poorer people will be on methadone, and those with greater resources will be on buprenorphine," he said. Among other obstacles, 42% of physicians prescribing the drug cited patients' resistance to required substance abuse counseling and 35% cited treating concurrent nonopioid abuse.

Another important factor, surveyed physicians say, is the 30-patient limit imposed on prescribing physicians. As written, the 30-patient limit also applies to some multiphysician practices or group insurance plans, which means a plan with hundreds or thousands of physicians may only be able to treat 30 patients total. Thirty-two percent of the physicians surveyed by SAMHSA said the 30-patient limit decreased the number of patients treated and 45% of the physicians surveyed in postmarketing surveillance said this was an obstacle to care.

In an effort to support physicians treating opioid-addicted patients with buprenorphine, SAMHSA provides educational materials on its Web site (http://www.samhsa.gov) and offers an online mentoring program for prescribing physicians.

Perhaps the most compelling data from these surveys will come from personal accounts of physicians treating patients for opioid addiction. Said Caroline McLeod, PhD, project manager of the SAMHSA evaluation, "Hundreds of the physicians who have responded to our survey have said the medication has been an absolute lifesaver for many of their patients." □