The study by Batterham et al. also shows that infusion of PYY decreases fasting concentrations of the orexigenic peptide ghrelin. Ghrelin is a 28-amino-acid, acylated peptide secreted by oxyntic cells in the stomach fundus. Ghrelin acts on growth hormone secretagogue receptors to increase the release of growth hormone from the pituitary. Recently, the putative roles of ghrelin in energy homeostasis and, in particular, premeal hunger and meal initiation have been identified. Circulating ghrelin concentrations increase preprandially and decrease postprandially. Ghrelin increases food intake through the stimulation of ghrelin receptors on hypothalamic neuropeptide Y–expressing neurons and agouti-related protein–expressing neurons. Although PYY infusion reduces the concentrations of ghrelin in lean and obese subjects who are fasting and diminishes the preprandial rise in ghrelin in lean subjects, the extent to which suppression of ghrelin secretion contributes to a PYY-mediated reduction in food intake is unclear.

If ghrelin signals hunger and PYY signals satiety, can these hormones be manipulated therapeutically? Gene-knockout studies in mice reveal that one cannot easily fool the homeostatic mechanisms that maintain body fat: experimental knockouts of the ghrelin gene, AgRP, and the neuropeptide Y gene (Npy) and a double knockout of AgRP and Npy are not associated with any obvious effects on energy metabolism or food intake. In contrast, inactivating mutations of POMC, the genes that encode leptin and the leptin receptor, and MC4R produce profoundly obese phenotypes in mice as well as in humans. It appears that orexigenic pathways are so critical to survival that the absence of one peptide is compensated for by the actions of others. Studies of gut hormones after weight loss induced by dieting or surgery have provided some clues to potential pharmacologic therapies. Weight loss by caloric restriction is associated with an increase in hunger and circulating concentrations of ghrelin. After gastric bypass surgery, hunger diminishes, circulating concentrations of ghrelin decrease, and circulating concentrations of PYY increase. Hormonal changes after bypass surgery may therefore play a part in the suppression of hunger and the long-term maintenance of reduced body weight.

Although single intraperitoneal injections of PYY decrease food intake for up to seven days in rats, the results of a single infusion in humans cannot be extrapolated to predict long-term outcomes. The use of PYY may prevent counterregulatory mechanisms from overriding the stimulation of anorexigenic pathways. However, the development of antibodies or tachyphylaxis through receptor down-regulation may limit the efficacy of prolonged PYY administration. It is unlikely that any one molecule or derivative will provide a magic bullet to induce and maintain weight loss. Successful pharmacologic treatment for obesity may be possible only by simultaneously targeting the interlocking, redundant systems that drive food intake and act to resist the loss of body fat.

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address the medical needs of those with opioid-use problems. But there is a wide gap between those who need treatment and the programs that are available to treat them. There are only about 1200 regulated opioid-treatment programs nationwide, and six states have no such programs.

On October 17, 2000, the Drug Addiction Treatment Act of 2000 was signed into law in the United States. This act allows Schedule III, IV, or V narcotic medications that have been approved by the Food and Drug Administration (FDA) for the treatment of narcotic-use disorders to be administered for either medically supervised tapering (detoxification) or long-term maintenance. On October 8, 2002, the FDA approved the use of buprenorphine (see Figure) and of buprenorphine in combination with naloxone — both Schedule III drugs — for either detoxification or maintenance. The purpose of the combination is to reduce the chance of drug diversion, since naloxone precipitates withdrawal symptoms if the combination tablet is misused and injected intravenously. The Drug Addiction Treatment Act and these FDA approvals create an opportunity for practicing physicians to provide critical assistance to patients. Buprenorphine is already used in France and in Australia in physicians’ offices. A benefit of office-based treatment is that it allows patients to obtain help without having to travel great distances or be put on a waiting list.

In this issue of the Journal, Fudala et al. (pages 949–958) describe the results of a multicenter, randomized, placebo-controlled trial involving opioid-addicted persons who were assigned to office-based treatment with buprenorphine alone, buprenorphine in combination with naloxone, or placebo for four weeks. They also describe the results of a larger, open-label study of treatment with buprenorphine and naloxone for up to 52 weeks. In the double-blind phase, subjects received their medication in the clinic during the week and were given take-home medications for the weekend. During the open-label phase, medications were administered at the clinic daily for 2 weeks, after which up to a 10-day supply of medication could be provided at the discretion of the investigators. Thus, neither phase of the study truly mimicked current standards for office-based treatment of opioid dependence, which allow physicians to prescribe buprenorphine for periods of up to 30 days. Nevertheless, the study showed that it is possible to administer buprenorphine or a combination of buprenorphine and naloxone in an office-based setting with good results. Both regimens were well tolerated, and both reduced the craving for opioids and the use of opioids. The open-label follow-up phase confirmed the safety and efficacy of the buprenorphine–naloxone combination.

In the double-blind phase, although the percentage of opioid-negative urine samples was significantly higher with either active treatment than with placebo, fewer than a quarter of the urine samples in each of the active-treatment groups were free of opioids. Although these results may seem unimpressive, the percentage of opioid-negative speci-
Buprenorphine can be prescribed to persons who are abusing heroin and to those who are abusing prescribed opioid analgesics. Its use can help prevent fatal overdoses and, by reducing the practice of sharing needles, decrease the spread of the human immunodeficiency virus and hepatitis B and C viruses.

The Drug Addiction Treatment Act requires that the physician undergo eight hours of training in the use of buprenorphine for either detoxification or maintenance and that the training be provided by designated organizations through either face-to-face or online courses. Physicians in certain categories (e.g., those who are certified in addiction medicine by the American Board of Medical Specialties, the American Osteopathic Association, or the American Society of Addiction Medicine) are exempt from the training requirement. All physicians who wish to prescribe buprenorphine for detoxification or maintenance must obtain from the federal government a waiver of the requirement to comply with the Controlled Substances Act and must treat no more than 30 patients with buprenorphine at one time. Since physicians have to complete continuing-education requirements to maintain their licenses, eight hours of additional training should not be a major inconvenience. The application for the waiver may be submitted by mail, fax, or e-mail or on the Web.

Data from the American Medical Association show that more than 473,000 physicians provide general ambulatory care. Many of these physicians are logical recruits for expanding access to care for those who have opioid-use disorders. As of July 11, 2003, however, the Substance Abuse and Mental Health Services Administration had received only 1981 waiver notifications from physicians. Many more physicians need to provide office-based treatment if the promise offered by the availability of buprenorphine is to be achieved. What are the barriers?

Although there is now a large body of data that shows that drug addiction has a neurobiologic basis (as reviewed by Camí and Farré in this issue of the Journal [pages 975–986]), the question is whether the legacy of Webb v. United States can be overcome. One barrier to the prescription of buprenorphine for the treatment of opioid-use disorders is the reluctance of many physicians to treat patients with opioid-use disorders. Another impediment to office-based treatment may be the inadequate reimbursement for these services. There are wide variations in coverage among insurers, including Medicaid. Thus, out-of-pocket payments may be prevalent. The estimated daily cost of the medication currently ranges between $5 and $10. The cost of physicians’ services and ancillary services will be prohibitive for some patients. Finally, physicians must have the ability to refer patients for appropriate counseling.

To increase physicians’ acceptance of office-based treatment, the Substance Abuse and Mental Health Services Administration is working with several professional medical organizations to support training in the use of buprenorphine for the treatment of opioid-use disorders. Information about buprenorphine is available at http://buprenorphine.samhsa.gov (or 866-287-2728).

Fudala et al. clearly show that buprenorphine and buprenorphine in combination with naloxone can be administered safely and effectively to reduce the use of opioids. Although office-based therapy may not be suitable for all persons with opioid-use disorders, it does offer patients and physicians a viable option. The challenge now is to encourage as many physicians as possible to undergo training in the appropriate use of these agents and to administer them comfortably as part of their practice.