term habituation or to the different levels of activation required to excite short-term memory traces (*16*).

The short recovery cycle of P_3 may also be characteristic of other endogenous components associated with human information processing (*17*). If so, studies of refractory properties may provide a basic criterion for linking ERP components to specific perceptual and cognitive processes.

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References and Notes

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6. Tones and low-level (30-dB sound level) masking noise were presented binaurally through earphones. All stimuli were delivered under the control of a tape-recorded sequence of trigger pulses, so that each subject received an identical pattern of stimulation.
7. Two different groups of subjects were run in the near-threshold condition. Subjects in group 1 (three female and two male, ages 18 to 25) each participated in two successive test periods (600 trials). The EEG data from these subjects were amplified by chopper-stabilized d-c amplifiers (bandpass 0 to 40 Hz), and averaged and quantified by computer (PDP 11/45). Subjects in group 2 (five female and three male, ages 18 to 34) participated in a single test period. Their EEG's were amplified by low-frequency-sensitive a-c amplifiers (bandpass, 0.15 to 150 Hz), averaged on a signal averager and quantified from *x-y* plots with a ruler. In the suprathreshold experiment, five subjects (all female, 19 to 32 years old) reported the number of tones presented on each trial, as in the near-threshold experiment; stimulus delivery was controlled by the same tape-recorded sequence of trigger pulses. Procedures for data recording, analysis, and quantification were identical to those for group 1 subjects.
8. The P_3 was measured with respect to a baseline connecting the mean voltage during the 200 msec before stimulus delivery with the mean voltage from 450 to 600 msec after the stimulus. This baseline was chosen to minimize the possible influence of slow potential shifts on P_3 amplitude. Other measures (including prestimulus baseline-peak and P_3 area) provided results consistent with those reported here.
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11. Recovery cycle calculations for near-threshold P_3's were complicated by the fact that P_3's to unpreceded tones at S_a were slightly smaller (20 to 25 percent) than P_3's to unpreceded tones at other positions [$F(1,16) = 5.914$, $P < .05$]. Hence, while near-threshold P_3's following 300-msec ISI's were as large as those at S_a, they were slightly smaller than P_3's following unpreceded stimuli at the $S_{b_{300}}$ and S_c positions [$F(1,16) = 5.49$, $P < .05$ combined over S_b and S_c positions]. However, near-threshold P_3's to tones preceded by 900 msec ISI's were not only much larger than those at S_a, but were also larger than those following unpreceded stimuli at other positions ($P < .05$ for all comparisons). Although unpreceded suprathreshold P_3's did not differ in amplitude as a function of position, suprathreshold P_3 recovery cycles were complicated by the possible influence of the quantification procedure on the small P_3 component. In particular, with 300-msec ISI's the sloping baseline included portions of the preceding P_2-P_3 complex. Hence, at these intervals, the baseline may have been shifted positively, thereby reducing the measured suprathreshold P_3 amplitudes. Thus, the data in Fig. 2 may underestimate the extent of suprathreshold P_3 recovery at 300-msec ISI's.
12. For near-threshold P_3's, this latency difference averaged 26 msec [$F(1,16) = 13.57$, $P < .01$]; for suprathreshold P_3's, it was 20 msec [$F(1,16) = 4.49$, $P < .05$].
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Buprenorphine Suppresses Heroin Use by Heroin Addicts

Abstract. *Heroin-dependent men were given buprenorphine (a partial opiate agonist-antagonist) or a placebo under double-blind conditions on a clinical research ward where they could acquire heroin (21 to 40.5 milligrams per day, intravenously). Buprenorphine significantly ($P < .001$) suppressed the self-administration of heroin over 10 days. Control subjects took between 93 and 100 percent of the available heroin. The effects of buprenorphine were dose-dependent; a dose of 8 milligrams per day reduced heroin use by 69 to 98 percent; a dose of 4 milligrams per day reduced heroin use by 45 percent. Termination of buprenorphine maintenance did not result in opiate withdrawal signs or symptoms. The subjects liked buprenorphine and indicated that it was preferable to methadone or naltrexone. Buprenorphine should be a safe and effective new pharmacotherapy for heroin dependence.*

Buprenorphine is a new oripavine derivative (*1*) with 25 to 40 times the analgesic potency of morphine and an equivalent duration of action (*2*). The subjective effects of buprenorphine also resemble those of morphine, and former heroin addicts report that they like morphine and buprenorphine equally well (*3*). In addition to its morphinelike agonistic properties, buprenorphine is also an opiate antagonist that effectively antagonizes high doses of morphine for 24 to 36 hours (*3*). Since buprenorphine is a partial opiate agonist-antagonist, it combines in one drug the characteristics of two of the leading pharmacotherapies for heroin addiction. It is equivalent to the antagonist naltrexone in potency and duration of narcotic blockade (*4*), and its opiate agonist properties resemble those of methadone in terms of reported positive subjective effects. However, termination of maintenance with high doses of buprenorphine does not result in the severe and protracted withdrawal signs and symptoms (*3*) that occur when methadone treatment is ended. A mild, almost negligible withdrawal syndrome was detected about 2 weeks after abrupt cessation of maintenance on buprenorphine (*3*).

Table 1. Sequence and duration of experimental conditions.

Drug condition		Duration (days)
Buprenorphine	Placebo	
Baseline (drug-free)	Baseline (drug-free)	5
Buprenorphine (0.5 to 8 mg/day)	Placebo	14
Buprenorphine and heroin	Placebo and heroin	10
Buprenorphine detoxification (7 to 1 mg/day)	Methadone detoxification (25 to 5 mg/day)	5
Baseline (drug-free)	Baseline (drug-free)	3
Naltrexone (10 to 50 mg/day)	Naltrexone (10 to 50 mg/day)	3

Since buprenorphine has some desirable properties as an opiate agonist, does not induce physical dependence, and antagonizes the effects of other opiate agonists, it could be an effective pharmacotherapy for heroin addiction. This report describes the effect of buprenorphine (or placebo) maintenance on self-administration of heroin by male opiate addicts studied on a clinical research ward under double-blind conditions. Ten volunteers 24 to 32 years of age (mean, 28.6 years) and with a 1- to 19-year history of heroin use (mean, 10.4 years) gave informed consent for their participation in these studies. Each subject had been treated for heroin addiction in conventional programs but had failed to maintain abstinence from opiates. Each volunteer was in good physical health, as determined by appropriate medical, psy-

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Table 2. Effects of buprenorphine and placebo on intravenous heroin self-administration by heroin addicts. Amounts are in milligrams per day.

Subject	Day										Available heroin actually used (%)
	1	2	3	4	5	6	7	8	9	10	
						Placebo					
1	21	21	21	21	21	40.5	40.5	40.5	40.5	40.5	100
2	21	21	21	21	21	40.5	40.5	40.5	40.5	40.5	100
3	21	21	21	21	21	40.5	40.5	40.5	40.5	40.5	100
4*	21	21	21	21	21	40.5	40.5	40.5	40.5	40.5	100
5*	21	21	21	21	21	40.5	40.5	40.5	40.5	40.5	100
6*	21	21	21	14	21	40.5	27	40.5	40.5	40.5	93
7*	21	14	21	21	7	40.5	40.5	40.5	40.5	40.5	93
						Buprenorphine (4 mg/day subcutaneously)					
5*	14	7	7	7	0	40.5	13.5	27	27	27	55
						Buprenorphine (8 mg/day subcutaneously)					
4*	14	0	0	0	14	27	0	0	13.5	27	31
6*	14	0	0	0	0	0	0	0	0	0	5
7*	14	0	0	0	7	27	0	0	0	0	16
8	0	0	0	0	0	0	0	0	13.5	0	4
9	0	0	0	0	0	13.5	0	0	0	0	4
10	0	0	0	0	7	0	0	0	0	0	2

*This subject was studied under both buprenorphine and placebo conditions in successive 40-day studies run in a counterbalanced order.

chiatric, and laboratory screening examinations. Each of four subjects served as his own control in two consecutive 40-day inpatient studies in which buprenorphine or a placebo was given in a counterbalanced order. Six other subjects were given either buprenorphine ($N = 3$) or a placebo ($N = 3$) in a single double-blind study (*5*).

The sequence and duration of each experimental condition is shown in Table 1. After a baseline period during which no drugs were given, increasingly large doses of a placebo or buprenorphine were given to assess the effects of the drug and to evaluate its safety at high doses. An initial dose of buprenorphine (0.5 mg/day subcutaneously) was gradually increased by increments of 0.5 mg until a final, maintenance dose (8 mg/day) was reached over 14 days. The subjects were maintained on this dose of buprenorphine (or placebo) for 10 days, during which heroin was made available. Subjects could work at a simple operant task to earn heroin during the last 2 days of the buprenorphine baseline period and the 10 days during which heroin was available, or to earn money throughout the study. They could earn $1.50 or one injection of heroin in approximately 90 minutes of sustained operant performance on an FI 1-second schedule of reinforcement, in which only the first response after 1 second has elapsed is recorded as an effective response. Details of this operant paradigm have been reported previously (*6*).

Since medical and ethical considerations preclude spontaneous self-administration of unlimited quantities of heroin, subjects were allowed only three doses of heroin each day (once every 8 hours). The efficacy of buprenorphine was examined at both low and high doses of heroin. Subjects could earn heroin (up to 21 mg/day) during the first 5 days of its availability, and more (up to 40.5 mg/day) during the second 5 days. The heroin, provided by the National Institute of Drug Abuse, was 98 to 99 percent pure. Subjects administered themselves sterile heroin intravenously under medical supervision. After the period of heroin availability, the buprenorphine dosage was gradually reduced over 5 days. The subjects given placebo, who used heroin, were offered the long-acting antagonist naltrexone and were told that naltrexone would be available after discharge.

The first few doses of buprenorphine (0.5 to 1.5 mg/day subcutaneously) produced transient morphinelike side effects, including nausea, occasional vomiting, some initial sedation and anxiety, and mild to moderate constipation. Tolerance to most of these effects developed within 3 to 4 days; constipation usually decreased within 19 to 21 days. Mild hypotension was occasionally observed. One subject (No. 5) developed persistent hypotension, and was maintained at half the standard 8-mg dose of buprenorphine (4 mg/day). Buprenorphine caused pupillary constriction, a typical effect of opiate agonists, for as long as 24 hours after an 8-mg dose.

All subjects reported that buprenorphine had opiatelike effects. In contrast to the "rush" or rapid "high" that follows the intravenous administration of heroin, a generalized feeling of contentment was reported. These findings are consistent with previous reports of morphinelike euphoria after short- and long-term administration of buprenorphine (*3*). Subjects reported a preference for maintenance on buprenorphine over maintenance on methadone or naltrexone, and asked that they be contacted when buprenorphine becomes available for outpatient treatment.

The effect of buprenorphine and placebo maintenance on daily heroin intake is shown in Table 2. Five of the subjects given the placebo took all the available heroin every day; two took all the available heroin on 8 of the 10 days. In contrast, the seven subjects maintained on buprenorphine took significantly less heroin than the subjects given the placebo ($P < .001$). Buprenorphine suppressed the self-administration of heroin 69 to 98 percent.

On the first day of heroin availability, three of the subjects maintained on buprenorphine took two 7-mg doses of heroin; however, buprenorphine completely antagonized the short-term heroin effects. Each subject reported that he felt no sensation from the intravenous heroin injection. One subject (No. 6) did not take heroin again during buprenorphine maintenance. Two subjects (Nos. 4 and 7) sampled heroin occasionally, and each took two injections when the amount of heroin available each day was increased from 21 to 40.5 mg on day 6. Buprenorphine (8 mg/day) effectively antagonized the effects of 13.5 mg of heroin, and subject 7 did not use heroin subsequently. Although subject 4 used more heroin than any other subject maintained on the standard (8 mg/day) dose of buprenorphine, he used less than one-third of the amount available.

Three of the subjects (Nos. 8, 9, and 10) maintained on buprenorphine did not take any heroin during the first few days of heroin availability. (All subjects knew when they were given buprenorphine rather than the placebo because of the morphinelike angonistic effects of the former.) Subjects 8, 9, and 10 each took a single dose of heroin on one occasion, but the effects were antagonized by buprenorphine. These subjects did not take heroin subsequently.

One subject (No. 5) was maintained on a low dose of buprenorphine (4 mg/day) because of its hypotensive side effects. Although he used significantly less heroin during buprenorphine maintenance

than during placebo maintenance ($P < .02$), he used heroin almost every day. The degree to which buprenorphine suppresses the self-administration of heroin appears to be related to the maintenance dose of buprenorphine, since 4 mg/day produced a 45 percent suppression whereas 8 mg/day produced a 69 to 98 percent suppression. Since these data are based on a direct behavioral measure of heroin self-administration over 10 days, rather than on retrospective recall or an anticipatory self-report, it appears that buprenorphine maintenance effectively suppresses heroin use by heroin addicts.

After buprenorphine was discontinued, no subject complained of opiate withdrawal symptoms and no withdrawal signs were observed. After discharge from the clinical research ward, we maintained contact with most subjects. No subject reported any withdrawal signs or symptoms over a period of 30 days after the termination of buprenorphine maintenance. This indicates that buprenorphine, unlike methadone, does not induce a significant degree of physical dependence. The finding confirms previous observations of the effects of long-term buprenorphine administration to five former heroin addicts (*3*).

Buprenorphine appears to offer significant advantages over an antagonist such as naltrexone, which blocks opiate effects without concomitant agonistic actions. Moreover, buprenorphine suppresses heroin self-administration by addicts as effectively as naltrexone, which was studied under similar conditions on a clinical research ward (*7*). Outpatient acceptance of naltrexone has been disappointing despite its effectiveness as a long-acting narcotic antagonist. Each of our ten subjects discontinued naltrexone maintenance, and only one agreed to try outpatient naltrexone at the end of the study. Although naltrexone has been helpful to a few well-motivated patients, most fail to continue outpatient naltrexone maintenance (*4, 7*). Most heroin addicts appear to prefer methadone, which produces some positive mood changes.

The agonistic properties of 8 mg of buprenorphine are equivalent to those of 40 to 60 mg of methadone (*3*). Since methadone has been used illicitly (presumably for its mood-elevating effects), buprenorphine might also be subject to abuse. Our preliminary findings indicate that buprenorphine is reinforcing in a model in which monkeys administered themselves the drug. However, buprenorphine is safer than methadone in two ways: (i) it does not induce significant physical dependence and (ii) the possibility of overdose is remote due to its opiate antagonistic properties. Deaths attributed to methadone overdose are occasionally reported (*8*), and withdrawal from methadone is more protracted than withdrawal from morphine (*9*).

Promising as this new partial agonist-antagonist appears to be as a pharmacotherapy for heroin addiction, it is unlikely that there will ever be a simple chemical panacea for this complex and multiply determined behavior disorder. Despite the capacity of buprenorphine or any other drug to antagonize heroin effects and improve mood, there is always the possibility that the heroin addict may engage in other forms of addictive drug use. It is generally acknowledged that patients maintained on methadone often continue to use some heroin and various other licit and illicit drugs (*10*). Further research will be required to determine whether buprenorphine can be more effective in reducing illicit drug use. Despite those qualifications, our results, which are based on direct measurement of heroin use by addicts, lead us to believe that buprenorphine should be a safe and highly effective mode of pharmacotherapy for heroin addiction.

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References and Notes

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Amino Acid Acylation: A Mechanism of Nitrogen Excretion in Inborn Errors of Urea Synthesis

Abstract. *Treatment of a patient deficient in carbamyl phosphate synthetase with benzoate or phenylacetic acid resulted in an increase in urinary nitrogen, which could be accounted for by the respective amino acid acylation product, hippurate or phenylacetylglutamine. Benzoate treatment of four hyperammonemic comatose patients led to clinical improvement and a return of plasma ammonium levels toward normal.*

Previous therapeutic approaches to patients with urea cycle enzymopathies have been designed to reduce the requirements for urea synthesis by quantitative and qualitative manipulation of dietary protein, amino acids, or their nitrogen-free analogs. Success of these measures has been limited to increased survival time, with death usually occurring in the first year of life.

We recently suggested (*1*) a form of therapy of these diseases wherein two new pathways of waste nitrogen excretion may substitute for the defective urea pathway. That such alternative pathways exist was shown by Lewis (*2*), who demonstrated that in man, after oral administration of sodium benzoate, urinary hippurate nitrogen substituted for urinary urea nitrogen with little change in total urinary nitrogen excretion. Subsequently Sherwin and Shiple (*3*) showed that in man urinary phenylacetylglutamine nitrogen substituted for urinary

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