

# Buprenorphine alone or in combination with naloxone reduced the use of and craving for opiates in opiate addiction

Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med.* 2003;349:949-58.

## QUESTION

Is buprenorphine alone or in combination with naloxone more effective than placebo for reducing the use of opiates and the craving for opiates in opiate-addicted outpatients?

## DESIGN

Randomized {allocation concealed\*}†, blinded (clinicians, patients, and monitoring committee),\* placebo-controlled trial with 4-week follow-up.

## SETTING

8 clinical sites in the United States.

## PATIENTS

326 patients defined as opiate dependent who were 18 to 59 years of age (mean age 37.5, 65% men) and were seeking opiate-substitution pharmacotherapy. Exclusion criteria included pregnancy or lactation, any medical condition that made participation medically hazardous, and aspartate or alanine aminotransferase levels > 3 times the upper limit of normal. Follow-up was 99%.

## INTERVENTION

110 patients were allocated to daily, office-based combination treatment with 16-mg sublingual buprenorphine plus 4-mg nalox-

one for 4 weeks; buprenorphine was administered alone on day 1 (8 mg) and day 2 (16 mg) to minimize the risk for naloxone-induced opiate withdrawal. 106 patients were allocated to buprenorphine alone; 8 mg on day 1, and 16 mg thereafter. 110 patients were allocated to placebo. All patients received counseling about HIV infection and ≤1 h/wk of individualized counseling.

## MAIN OUTCOME MEASURES

The percentage of opiate-negative urine samples and patients' self-reported craving for opiates. Secondary outcomes included patients' and clinicians' impressions of overall status since enrollment and previous visit; percentage of urine samples that were negative for amphetamines, barbiturates, benzodiazepines, cocaine, and methadone; and adverse events.

## MAIN RESULTS

Analysis was by intention to treat. Patients who received buprenorphine alone or in

combination with naloxone had more opiate-negative urine samples than did those who received placebo (Table) and had fewer cravings for opiates ( $P < 0.001$ ). Furthermore, patients in the buprenorphine alone or combination groups had greater improvement in overall health and well-being than did those in the placebo group ( $P < 0.001$ ). Groups did not differ for any other outcomes or adverse events.

## CONCLUSION

In opiate-addicted patients, buprenorphine alone or in combination with naloxone reduced the use of opiates and the craving for opiates.

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*For correspondence: Dr. P.J. Fudala, VA Medical Center, Philadelphia, PA, USA.* ■

\*See Glossary.

†Information provided by author.

## Buprenorphine alone or combined with naloxone vs placebo for opiate addiction at 4 weeks‡

Outcome	Comparisons	Least squares mean	P value
Proportion of opiate-negative urine samples	Buprenorphine alone vs placebo	20.7% vs 5.8%	< 0.001
	Buprenorphine plus naloxone vs placebo	17.8% vs 5.8%	< 0.001

‡Least squares mean calculated from analysis of variance (ANOVA).

## COMMENTARY

Fudala and colleagues have provided impressive evidence supporting the safety, acceptability, and efficacy of buprenorphine in managing opioid dependence in an office setting. The study showed an 82% retention rate for the 4-week intervention period, despite requiring daily visits for patients to receive their medication. Patients who received buprenorphine had a 4-fold higher rate of drug-negative urine test results than those who received placebo.

Despite these encouraging results, implementation of new buprenorphine therapies by primary care providers, or even addiction medicine physicians, will first require the removal of 5 substantial barriers. First, providers must believe that they have a problem with their current management of opioid-dependent patients before they are likely to adopt new practices.

Second, opioid addiction must be systematically identified before it can be treated. Physicians must know which patients in their practice panels are opioid dependent. Similarly, patients need to understand that their primary care physicians are access points for addiction treatment before they will come forward to seek help.

Third, providers must become knowledgeable about the pharmacologic properties of buprenorphine, be certified to use it, and feel competent to build therapeutic relationships with these patients.

Fourth, patients will need adequate resources to pay for the medication. The cost of buprenorphine or naloxone (16 mg/d or 4 mg/d, respectively) in this study was about U.S. \$230 per month. The cost of a comparable methadone dosage (60 mg/d) is U.S. \$3 per month. This cost differential is a high price to pay to gain freedom from the regulatory constraints of methadone programs.

Fifth, under current regulations in the United States, providers are limited to treat no more than 30 patients at any 1 time. For large group practices, this number is unrealistically low. Based on the U.S. Office of National Drug Control Policy estimate for heroin dependence, a group practice such as mine (serving 300 000 adults) should have 1500 heroin-dependent members (0.5%). The 30-patient limit for our group would permit serving only 2% of these patients at any 1 time.

Allan W. Graham, MD  
Kaiser Permanente of Colorado  
Denver, Colorado, USA