
Authors and Disclosures

Journalist

Caroline Helwick

From Medscape Medical News For Prescription Opioid Dependence, Relapses Associated With Shorter Treatment Course



Caroline Helwick

May 24, 2010 (New Orleans, Louisiana) — In persons dependent on prescription opioids, tapering with buprenorphine during a 9-month period, whether initially or after a period of substantial improvement, led to nearly universal relapse in the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study, presented here at the American Psychiatric Association 2010 Annual Meeting.

"There has been virtually no research on the treatment of persons dependent on prescription opioids, in spite of the major increase in prescription opioid abuse and in the numbers of persons entering treatment for addiction to prescription opioids," said Roger D. Weiss, MD, professor of psychiatry at Harvard Medical School, Boston, and chief of the Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, Massachusetts.

The study, which is the largest treatment study ever conducted for prescription opioid dependence (POD), sought to answer several questions regarding the optimal length of pharmacotherapy, the value of intense counseling, and the role of chronic pain.

Specifically, the study asked whether adding individual drug counseling to buprenorphine-naloxone (a semisynthetic opioid and a partial agonist) plus standard medical management improves outcomes, what duration of buprenorphine is best for these patients, and whether presence or absence of current chronic pain influences outcomes.

"The trial was designed to help the physician manage patients who are dependent on opioids and want off the drugs but refuse treatment in a drug abuse treatment program," Dr. Weiss said.

The study enrolled 653 persons with POD and offered them standard medical management, which included buprenorphine (usually 12 - 16 mg maximum, adjusted for addiction, not pain), an initial 1-hour visit, and weekly 20-minute sessions with a physician who counseled the patients and monitored for drug adverse effects. Half the group remained in this standard medical management (SMM) group and half received enhanced medical management (EMM), which included twice-weekly 60-minute individualized drug counseling focusing on interpersonal issues, coping with triggers and high-risk situations, homework, and so forth.

Under a somewhat complicated schema, patients were evaluated after periods of individualized buprenorphine tapering and maintenance and were assessed for abstinence from opioids at various times.

Study Population

All patients had a *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*, diagnosis of opioid dependence and had used opioids for at least 20 of the last 30 days. Other substance abuse disorders were allowed, with the exception of active heroin use or history of injecting heroin. All patients expressed an interest in stopping opioids.

The population was made up of 60% men, was 91% white, had a mean age of 33 years, was likely to be cigarette smokers (71%), and had been using opioids for an average of 4.5 years. Most patients had received some college education and were employed full-time. There were no significant differences at baseline between the SMM and EMM groups.

A number of patients reported current chronic pain (42%), and some were taking opioids for this condition. Although current polypharmacy was uncommon, many patients reported a lifetime history of heroin use (23%), alcohol abuse (60%) or dependence (27%), cannabis abuse (47%) or dependence (15%), and cocaine abuse (32%) or dependence (18%). Stimulant and sedative use were less common.

Opioids used within 30 days included sustained-release oxycodone (35%), hydrocodone (32%), immediate-release oxycodone (19%), methadone (6%), and others (8%).

Thirty percent of subjects had received some previous treatment for opioid dependency, primarily "self help" (59%), inpatient/residential treatment (42%), outpatient counseling (40%), and methadone maintenance (31%).

"For most subjects, this was the first treatment for opioid dependence," said Dr. Weiss.

Treatment and Maintenance

Treatment success was defined as 4 or fewer days of opioid use per month, no positive urine screens for opioids for 2 consecutive weeks, no other formal substance abuse treatment, and no injection of opioids.

Phase 1 included 1 month of tapering and 2 months of stabilization. At the end of this time, few patients were successfully treated, and enhanced management did not influence the results, Dr. Weiss reported.

In the SMM group, only 7% met the criteria for success, as did just 6% of the EMM group ($P = .45$). "Nearly all patients relapsed after a 4-week taper," Dr. Weiss said.

Patients who relapsed were asked to enter phase 2, at which time 360 patients were again randomly assigned to SMM or EMM and received 3 months of buprenorphine stabilization, then had treatment tapered for 1 month, with a 2-month follow-up.

At the end of the stabilization (at week 12), substantial improvement was noted for 52% of the EMM group and 47% of the SMM group, though again there was no additional benefit to enhanced management ($P = .3$). Substantial improvement was defined as abstinence for 3 or more of the final 4 weeks of buprenorphine stabilization (urine-confirmed self-report).

However, by the end of the stabilization period, many patients had relapsed again, Dr. Weiss reported.

"We went from an average success rate of 49% to 26% at week 16," he said. At week 24 (8 weeks posttaper), only 9% of patients remained successfully treated.

"At the end of the study, we were back into phase 1 territory," he said. "Seven of 8 patients doing well on buprenorphine maintenance had relapsed."

Predictors of Outcome

The only predictor outcome was ever-use of heroin. At week 12, improvement was noted for 37% of those reporting lifetime heroin use compared with 54% of those without such a history ($P = .003$); at week 24, this was 5% and 10%, respectively ($P = .13$). "Having dabbled in heroin was a bad prognostic sign," Dr. Weiss observed.

The presence of chronic pain did not influence outcomes. Patients with chronic pain were equally likely to enter phase 2 (indicating early treatment failure) and were equally likely to be substantially improved at week 12 of phase 2 (53% vs 47% for those without chronic pain).

Chronic pain tended to be lumbar/sacral (65%) and classified as only moderate (median 4.4 on 10-point scale) but was of long duration, as more than half the patients had suffered from it for at least 4 years, he said.

"Interestingly, we found that in many cases the patient's pain got better," he added. More than half the subjects reported at least a moderate reduction of pain from baseline ($\geq 30\%$), and one third had a substantial improvement ($\geq 50\%$).

Nevertheless, Dr. Weiss said one cannot assume that buprenorphine itself improved the pain, as there was no control group, "but it is an intriguing possibility," he commented.

Sean Mackey, MD, PhD, associate professor of anesthesia and chief of the Division of Pain Management at Stanford University, Palo Alto, California, who delivered an overview of the treatment of pain in patients with addiction at the session, commented on the current study for *Medscape Psychiatry*.

He was particularly interested in the finding that persons with a history of heroin use had worse outcomes. "Could it be that prior exposure to heroin fundamentally alters the neurobiology in this group such that they need higher doses of buprenorphine to prevent relapse?" he asked.

Dr. Mackey maintained that the study is important because it asked a clinically relevant question: "Does putting people on a short period of buprenorphine maintenance combined with counseling lead to reductions in relapse? It's a great idea, and a wonderful hypothesis, because if it does work then this would be a huge win. We would not have to use extended maintenance. Unfortunately, it did not work, but the study needed to be done."

He further noted that the standard management group was likely getting better care in this study than is delivered in usual practice, which may have diluted potential differences.

Dr. Weiss has reported receiving research support from Eli Lilly. Dr. Mackey has disclosed no relevant financial relationships.

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