Methadone Dose Higher With Chronic Pain

BY DEEANNA FRANKLIN
Associate Editor

Patients on methadone maintenance often have chronic pain, and those with more intense pain receive higher doses of methadone, said Einat Peles, Ph.D., and colleagues at Tel-Aviv Elias Sourasky Medical Center.

The researchers nonselectively enrolled 170 consecutive drug-abuse patients and found that 94 (55%) had experienced chronic pain (J. Pain 2005;113:340-6).

The mean duration of methadone maintenance treatment (MMT) was equivalent for the chronic pain and non–chronic pain groups. The patients completed a cross-sectional survey on chronic pain, and all met addiction criteria similar to the DSM-IV criteria for dependence on multiadministrations of heroin for at least 1 year.

Dr. Peles and her colleagues defined chronic pain as lasting 6 months or longer, and chronic severe pain was defined as pain of moderate to very severe intensity. Urine samples taken 1 month before the study and during the first month of treatment were analyzed for cocaine metabolites, opiates, benzodiazepines, cannabis, amphetamines, and methadone, and "the threshold for positive urine for benzodiazepines was higher than the therapeutic range," they said.

There was no significant difference between the two groups in terms of Axes I and II: Axis I disorders were seen in 54% of chronic pain patients and 47% of non–chronic pain patients, while Axis II disorders were seen in 72% and 71%, respectively.

Pain was present before admission in 63.8% of the patients, and after MMT in 36.2%. However, duration of MMT was not related to pain duration or severity.

MMT dose was associated with pain severity and pain duration. The mean methadone dose was 147.1 mg/day for the 76 non–chronic pain patients, 134.6 mg/day for 12 patients with mild chronic pain, 159.8 mg/day for 38 patients with moderately severe pain, 175.5 mg/day for the 22 patients with severe pain, and 176.7 mg/day for the 22 patients with very severe pain.

The 26 patients with chronic pain for over 10 years got the highest methadone doses (182.1 mg/day). The 59 patients with pain for 1-10 years received 160.9 mg/day; doses of 134.2 mg/day went to patients with pain of less than 1 year. The researchers noted, however, "that methadone treatment was not initiated or directed toward pain relief."

According to Dr. Peles and her associates, "it is probable that such high dosages of methadone may also be beneficial for pain, regardless of the primary indication for the treatment and the regimen of administration, which differed from that indicated for pain (i.e., once daily and not every few hours)."

Some MMT patients were given take-home dosages for the week, and against clinic directions, may have split their high doses, which might have reduced pain, the researchers speculated. Patients may also have misinterpreted pain as a withdrawal symptom, which may have led to requests for increased doses. Patients taking higher doses also may have built up a tolerance to the methadone.

Current positive urine test for benzodiazepines, and positive antibody to hepatitis C, correlated with significantly higher methadone doses. Benzodiazepine abuse may start as a form of self-medication to relieve pain, but the investigators suggested that it might also be that abuse of these drugs is a cause of "repeated rather than chronic pain."

"We cannot conclude from these analyses whether or not pain was a cause or a consequence of the drug abuse," said Dr. Peles and her associates. ■

Smoking Cessation Drug Could Be Major Advance

BY BRUCE JANCIN
Denver Bureau

ORLANDO, FLA. — Varenicline, a first-of-its-kind selective nicotinic receptor partial agonist, has racked up unprecedented smoking-cessation success rates in a pair of phase II clinical trials, Cheryl A. Oncken, M.D., reported at the annual meeting of the American College of Cardiology.

Based on these extremely encouraging albeit short-term results, multiple year-long phase III trials are underway using varenicline at 1.0 mg twice daily, a Pfizer spokesman told this newspaper.

The two phase II placebo-controlled studies totaled 1,253 smokers. In one 6-week study, 48% of participants assigned to 1.0 mg of varenicline twice daily quit smoking for a 28-day period as determined by review of daily smoking diaries, compared with 37% on 1.0 mg/day of the drug, 33% on 150 mg of bupropion twice daily, 29% on 0.3 mg/day of varenicline, and 17% on placebo, said Dr. Oncken of the University of Connecticut, Farmington.

In the other study, which lasted 12 weeks, 51% of patients on 1.0 mg of varenicline twice daily abstained from smoking during weeks 9-12 as confirmed by carbon monoxide testing. This was also the case for 45% of those randomized to 0.5 mg of the drug twice daily and for 12% of the placebo group. The adjusted odds ratios for abstinence were 6.1 and 7.8 for 0.5 and 1.0 mg of varenicline twice daily, respectively, compared with placebo.

The most common varenicline-related side effect was transient mild to moderate nausea. Tolerability compared favorably with placebo in both studies. It also compared favorably with bupropion—a drug with a Food and Drug Administration indication for smoking cessation—in the one comparative trial where it was used, with discontinuation due to adverse events occurring in 11% of patients in the high-dose varenicline group and 16% of those on bupropion. No varenicline-related safety issues arose during monitoring of laboratory tests and ECGs.

Nicotine dependence in smokers is mediated via the neuronal $\alpha 4\,\beta 2$ nicotinic receptor. Varenicline is believed to act by blocking nicotine binding to the receptor during smoking, thereby interfering with smoking's extremely potent reinforcement and reward effects. Moreover, partial activation of the $\alpha 4\,\beta 2$ receptor by varenicline during abstinence has been hypothesized to relieve nicotine craving and withdrawal symptoms, Dr. Oncken explained.

Her studies were sponsored by Pfizer Global Research and Development. ■

Experimentation Before Age 11 Predicts Later Smoking Habits

BY DIANA MAHONEY
New England Bureau

BOSTON — Children who experiment with smoking even minimally before age 11 are more likely to take up smoking as teens than are their nonexposed peers, Jennifer Fidler reported at the annual meeting of the Society of Behavioral Medicine.

Because there is an apparent protracted period of dormant vulnerability—or "sleeper effect"—before social or environmental conditions trigger the onset of a stable smoking pattern, "interventions should target the prevention of first, short experimentation with smoking," she said.

Using data from the 5-year longitudinal Health and Behavior in Teenagers Study (HABITS) of 5,000 British adolescents, which included yearly assessments of smoking status, Ms. Fidler and her colleagues at University College London calculated the probability of becoming a smoker as a function of having tried smoking just once by age 11.

Early one-time triers were significantly more likely than those who had never smoked at age 11-12 to take up current smoking for the first time up to 3 years later. The study data showed that very few participants reported current smoking at age 11-12, "making this an ideal time to study smoking progression," she said.

After the investigators controlled for personal factors known to influence smoking—including ethnicity, socioeconomic deprivation, gender, family/peer smoking, and conduct problems—logistic regression analyses confirmed a statistically significant sleeper effect, Ms. Fidler said. The adjusted odds for taking up smoking at 1, 2, and 3 years following initial exposure relative to same-age nonexposed peers were 6.3, 2.9, and 2.1, respectively.

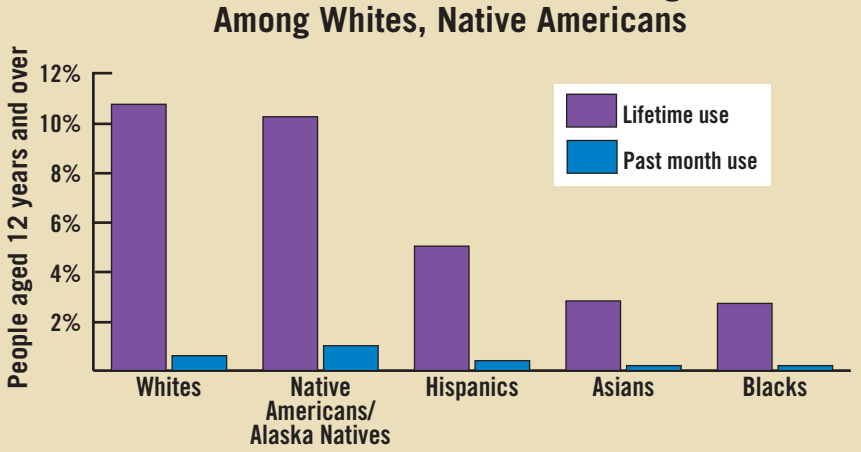
"Only after 4 years of nonsmoking following an initial try before age 11 was the difference between triers and nontriers not significant," she said.

Various behavioral and biophysical conditions may contribute to the sleeper effect, including the possibility "that early nicotine exposure alters neurologic reward pathways," Ms. Fidler said. "Or it may be that the first smoking experience breaks down such barriers to smoking as fear and insecurities about how to smoke, or that personality traits leading to the initial try may continue to stand individuals at an increased risk."

From a policy perspective, the findings suggest that community interventions should be aimed at preventing early experimentation with smoking to reduce the risk of smoking uptake, Ms. Fidler said. Additionally, interventions should target adolescents who report having tried smoking, albeit just once, because of their increased risk of later smoking. ■

DATA WATCH

Nonmedical Use of Stimulants Is Highest Among Whites, Native Americans



Note: In 2003, 20.8 million people aged 12 years and older had used prescription-type stimulants at least once in their lifetime.
Source: Substance Abuse and Mental Health Services Administration

RICHARD FRANKI, RESEARCH