

Methadone Used for Pain Linked to Sleep Apnea

The sleep-disordered breathing seen in baby boomers being treated for chronic pain is severe.

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Dr. Amanda A. Beck and her colleagues were puzzled by some of their patients at the University of New Mexico's Sleep Disorders Center in Albuquerque. The patients took methadone, but they did not have histories of drug abuse. They were middle-class baby boomers under treatment for chronic pain, and their nighttime breathing problems were severe.



They needed a variable positive airway pressure device, the VPAP Adapt, recently approved for the treatment of central sleep apnea, mixed sleep apnea, and periodic breathing. "We are getting this very complicated sleep-disordered breathing, which used not to be in our lexicon," Dr. Beck, director of adult services, said at a university-sponsored psychiatric symposium, where she described her center's experience as a red flag for methadone prescribers.

Concern about accidental deaths from methadone use is long-standing. Reports linking methadone to sleep-disordered breathing are a recent and, as yet, poorly understood phenomenon. Dr. Beck said her group and other sleep centers are documenting cases of sleep-disordered breathing in methadone patients, now estimated at one per week in her clinic.

The Food and Drug Administration has responded to concern over methadone related deaths and complications with an advisory. (See related story, p. 2.)

Several studies of the complication have been published, but most accounts are anecdotal. Some reports focus on patients on methadone maintenance, while others address the growing number of people taking opioids for chronic pain. (See box.)

Emerging Evidence

In 2003, physicians at the Intermountain Sleep Disorders Center in Salt Lake City described ataxic breathing, central apnea, sustained hypoxemia, and other abnormalities in three patients on long-term opioid therapy for pain (Chest 2003;123:632-9).

That article spurred Dr. Lynn R. Webster to order sleep studies on patients prescribed opioid therapies at the Lifetree Pain Clinic in Salt Lake City. Dr. Webster, medical director of the clinic and its affiliated research center, presented polysomnography data on 152 patients at the American Academy of Pain meeting in February 2006.

Three-fourths of the patients had an abnormal apnea-hypopnea index, including 42% with obstructive sleep apnea, 12% with central sleep apnea, and 21% with mixed obstructive and central sleep apnea. One-third of the patients had been prescribed methadone and long-acting opioids; 4% took only methadone, according to the abstract.

In another study that Dr. Webster presented at the same meeting, he compared polysomnography data on 73 opioid-naive primary care patients who had been referred for sleep studies with data on 139 asymptomatic chronic pain patients taking opioids. In both groups, 36% of the patients had severe sleep apnea.

Obstructive sleep apnea was more common in the primary care patients at 89%, vs. 77% of cases in the pain group. Central sleep apnea, a more severe condition, occurred more in the pain patients: 32%, vs. 6% of the primary care cases.

As a result of his ongoing research, Dr. Webster has become a campaigner for more conservative use of methadone. "No one was aware this was a problem. Most pain practices would not ordinarily order sleep studies," he said in an interview with this newspaper.

Dr. Webster emphasized that he is not opposed to methadone use for pain management. "But patients and physicians need to understand it is not like other opioids."

Recent reports have also associated methadone with poor sleep quality in addiction patients at maintenance programs.

A U.S. study reported that 84% of 225 patients were "poor" sleepers with Pittsburgh Sleep Quality Index scores of 6 or higher (J. Subst. Abuse Treat. 2004;26:175-80).

Israeli researchers found that 75% of 102 patients were poor sleepers (Drug Alcohol Depend. 2006;82:103-10).

Searching for Mechanisms

Looking for sleep-disordered breathing (SDB), an Australian group reported that 30% of 50 stable methadone maintenance patients had central sleep apnea.

Blood methadone level was significantly associated with severity but was only a minor contributing factor, explaining just 12% of the variability. The authors speculated that central sleep apnea in the population "may be multifactorial in nature and related to abnormalities of the central controller and central and peripheral metabolic control mechanisms" (Chest 2005;128:1348-56).

Abnormalities in both waking hypoxic and hypercapnic ventilatory responses in the methadone patients would lead to this instability, Dr. Harry Teichtahl, who is director of respiratory and sleep disorders medicine at Western Health in

Victoria, said in an interview.

Instability in carbon dioxide ventilatory responses may be involved in SDB in asymptomatic patients, continued Dr. Teichtahl, of the University of Melbourne.

His study showed a high prevalence of central sleep apnea, he said, but the patients had no more obstructive sleep apnea than a normal control group did.

Risky Business

Last July, researchers from the CDC reported that increases in prescriptions for opioid analgesics paralleled and may have contributed to an annual 18% increase in unintentional drug-poisoning deaths from 1990 to 2002.

From 1999 to 2002, the number of death certificates listing methadone poisoning rose by 213%, according to Dr. Leonard J during this period, while sales through narcotics treatment programs rose only 43% (Pharmacoepidemiol. Drug Saf. 2006;15:618-27).

Methadone Prescribing on the Rise

Not without irony, Dr. Webster said physicians turned to methadone for treatment of pain in part because they believed it was safer than other opioids and less likely to bring regulatory sanctions. When OxyContin abuse became a public policy issue, they saw methadone as a drug with little street value or abuse potential.

"Physicians think it is safe because it has been used for addiction so many years," he said.

Health insurers also appear to have played a role. Methadone is the cheapest opioid by far. One estimate puts the monthly cost to pharmacists as \$8 for an oral dose of 5 mg taken three times a day, based on wholesale prices. In comparison, chronic pain therapy with generic sustained-release morphine would cost \$101.50; MS Contin, \$113.50; OxyContin, \$176.50; and Duragesic, \$154 (Am. Fam. Physician 2005; 71:1353-8).

Confronted with such steep price differences, some health plans reportedly have made methadone their drug of choice when an opioid is prescribed for pain. In many cases, Dr. Beck said, that is why methadone is being prescribed to older pain patients with co-

morbidities and other medications that can interact with methadone.

"It is really irresponsible of insurers and HMOs, of anyone who sets up a formulary that [designates] the most dangerous in its entire category as the first-line agent to be used. I think that is unconscionable," she said.

Formularies also are responsible for an increase in methadone prescribing by primary care physicians who are not familiar with its unique characteristics, according to Dr. Howard A. Heit, a chronic pain specialist certified in addiction medicine who practices in Fairfax, Va. "Are we forcing doctors to use a medication that they don't have the knowledge to use, which could be fraught with major complications, which will cost more in the long run?" he asked during an interview.

Dr. Heit served on a U.S. Substance Abuse and Mental Services Administration panel that reported in 2004 on nationwide increases in methadone-related deaths. The panel cited as a likely factor a fivefold increase from 1998 to 2002 in the volume of methadone distributed through pharmacies. The risk of apnea was not considered because it was not an issue at that time, he said.

Caffeine Associated With Improved Cognition in Apnea Patients

SALT LAKE CITY — Increased caffeine intake was associated with better cognitive functioning in patients with obstructive sleep apnea, according to the results of a small study.

In 42 patients with untreated obstructive sleep apnea, a statistically significant inverse relationship was found between caffeine intake and a global deficit

score that was derived from an aggregate measure of neuropsychological functioning, Dr. Daniel Norman reported at the annual meeting of the Associated Professional Sleep Societies.

The association persisted after controlling for body mass index and apnea-hypopnea index, said Dr. Norman of the University of California, San Diego.

Patients had a mean apnea-hypopnea index of 63 episodes per hour, indicating severe sleep apnea. The neuropsychological assessment battery included tests of speed of information processing, executive functioning, memory skills, verbal skills, and attention and working memory domains.

Caffeine intake was assessed using a detailed instrument that

has been shown to characterize usual caffeine consumption based on 24-hour recall.

Daily caffeine intake in cognitively impaired patients was one-sixth that of non-cognitively impaired patients (30 mg vs. 180 mg), Dr. Norman said. Previous findings that obstructive sleep apnea patients consume three times the caffeine of nonapneic indi-

viduals on a daily basis led to speculation that those with sleep apnea were self-medicating with caffeine to counteract daytime sleepiness. Caffeine has been shown to enhance cognition, and the findings of the current study suggest this is an additional effect experienced by those who use caffeine for that purpose.

—Sharon Worcester