

Methadone Is Complex Choice for Managing Pain

BY KERRI WACHTER
Senior Writer

TAMPA — Methadone is an excellent choice for pain management when the prescribing complexities are understood, said two experts at the annual meeting of the American Academy of Hospice and Palliative Medicine and the Hospice and Palliative Nurses Association.

"While it's probably the best opioid analgesic out there, it's also probably the most dangerous," said Dr. Jane E. Loitman, who is the medical director for the palliative care service at Barnes-Jewish Hospital in St. Louis.

Methadone, a synthetic opioid that is available in the United States as a racemic mixture of two isomers, has several advantages over other opioid analgesics.

"Methadone is the only opioid that acts as an NMDA [N-methyl-D-aspartate] receptor antagonist as well as acting as a mu-[opioid] agonist," said Dr. Gail Gazelle of Harvard Medical School, Boston. Other opioids work only as mu-opioid agonists. "Methadone also acts as a mu agonist but has this unique property, unlike all of the other opioids, that blocks NMDA receptors." This action on NMDA receptors makes methadone an excellent choice for the treatment of neuropathic pain. And methadone does not appear to carry the same risk of respiratory depression as other opioids because of NMDA-receptor blockade, Dr. Gazelle said. There is also some evidence that because of the NMDA-receptor antagonism property, methadone has an antitussive action.

In addition, NMDA activity "may mean that it reduces some of the cross-tolerance that we see with patients being converted from another opioid to methadone," she said. Because NMDA antagonism is one of the mechanisms to prevent tolerance and inhibit neuronal excitation, "methadone may be the drug of choice as an opioid analgesic for someone who has hyperalgesia," Dr. Loitman said.

Methadone typically has very little euphoric effect, which can be advantageous when there is a concern about diversion. Methadone has no known active metabolites and blocks serotonin/norepinephrine uptake. Another "important advantage of methadone is that it is the only opioid that is fecally excreted. So it's an excellent med-

ication to use for patients with known chronic renal insufficiency," she said.

Methadone also has fewer of the neuroexcitatory side effects of opioids, such as myoclonus and delirium, and may be associated with a lower incidence of constipation than other opioids. The drug can be given orally, rectally, sublingually, intravenously, subcutaneously, and transdermally. It has a very high potency when used after another opioid, and its oral bioavailability is very high (85%), compared with roughly 35% for morphine.

"If you have a DEA license to prescribe other schedule II medications, you can prescribe methadone," Dr. Loitman said. No special license is required, and one doesn't need to be a pain specialist to prescribe this drug. But "before you start someone on methadone, you need to understand the pharmacology, the side effects, the advantages and disadvantages, the myths, and who you're prescribing it for," she said.

Despite methadone's attractiveness for the treatment of pain, it's a complicated drug to prescribe. Methadone is difficult to dose and equianalgesia is a particular problem, because the analgesic and biologic half-lives don't match. While the biologic half-life of methadone can range from 18 to almost 100 hours (average, about 24 hours), the analgesic half-life ranges from 6 to 12 hours. "So the steady state of methadone—because of its long half-life—can take a while to reach," Dr. Gazelle said. Reaching a steady state takes about five biologic half-lives, she said.

Methadone also has a risk of cumulative toxicity because of its long and unpredictable biologic half-life, and it's necessary to titrate this drug more slowly than other opioids. Because methadone is lipophilic, it can be difficult to titrate the drug in elderly patients, who have a greater percentage of adipose tissue.

Another complication is that methadone is metabolized through the cytochrome P450 system, which is induced by a number of other drugs, including phenytoin and rifampin. Larger doses of methadone might be needed when a patient is also on one of these drugs. "It's almost impossible to get therapeutic levels of methadone in patients on rifampin," Dr. Gazelle said. Other medications, including azole antifungal agents and macrolide antibi-

otics, might inhibit the cytochrome P450 system and require decreased doses of methadone. Therefore, it is important to review all of the drugs that a patient is on before prescribing methadone.

In 2006, the Food and Drug Administration issued a public health advisory for methadone, in part because of reports of QTc interval prolongation and serious arrhythmia (torsades de pointes) that had been observed during treatment with methadone. Most of these cases involved patients in pain who were receiving large, multiple daily doses.

"I don't think there is any standard of care that has developed. I think that we probably need to be cognizant of the fact that methadone may prolong the QTc interval," Dr. Gazelle said. She advises thinking about what the goals of care are for individual patients and discussing with them the potential cardiac risks.

There are several opioid/methadone conversion protocols, including the U.K. Hospice model (Pain Rev. 1998;5:51-8), the Milan model (J. Clin. Oncol. 1998;16:3216-21), the Edmonton model (Cancer 1996;78:852-7), the German model (Am. J. Hosp. Palliat. Care 2001;18:200-2), and the Royal Perth Hospital model (Med. J. Aust. 2000;173:536-40).

For physicians with adequate experience prescribing methadone, the drug should be considered under the following circumstances:

- ▶ When starting a patient on a long-acting opioid.
- ▶ For patients already on very high doses of a long-acting opioid.
- ▶ When side effects from current pain medications are unacceptable.
- ▶ When a patient has inadequate pain control.
- ▶ For the treatment of neuropathic pain.
- ▶ For patients with current or recurrent substance abuse problems.
- ▶ When there is concern about drug diversion.

Despite the complexity of proper use, with methadone "we can really change a patient's level of suffering, in ways that we sometimes can't with other opioids," Dr. Gazelle observed.

Neither Dr. Loitman nor Dr. Gazelle had any relevant financial relationships to disclose. ■

Ten Minutes a Day Walking on Treadmill Eases Mood, Pain

BY FRAN LOWRY
Orlando Bureau

ORLANDO — A physical conditioning program that consisted of just 10 minutes a day of walking on a treadmill at a moderate pace for 3 weeks significantly improved measures of pain perception, aerobic capacity, depression, and anxiety, in chronic pain patients, according to the findings of a small, uncontrolled study.

"A frequent comorbid condition of chronic pain is profound physical deconditioning that results from inactivity. People are in too much pain to exercise or be even moderately physically active," Amy M. Burleson, Psy.D., of the Cleveland Clinic, said in an interview.

"This inactivity often leads to depression and other mood disorders, and we know that these can exacerbate pain, so we were very pleased to see how effective this very moderate amount of exercise was in improving not only the cardiovascular fitness of our study sample, but also their mood and their pain," she continued.

After rehabilitation programs were completed, improvements of pain, depression, and anxiety have been well doc-

umented. However, the immediate effects of brief exercise on these factors were unknown.

The investigation's 28 patients were admitted to the Cleveland Clinic's chronic pain rehabilitation program for a variety of chronic pain conditions, including low back pain, neuropathy, fibromyalgia, and migraine. They also had a psychiatric diagnosis, which included depression, anxiety, or a combination of both. Their mean age was 43 years and 53% were female, said Dr. Burleson, who presented the results at the annual meeting of the American Academy of Pain Medicine.

"The Cleveland Clinic's chronic pain program is an interdisciplinary program incorporating psychiatry, nursing, psychology, physical therapy, and addiction therapy. This is very important because treatment of chronic pain requires the expertise of multiple specialties," Dr. Burleson said.

The exercise component consisted of a daily 10-minute walk on a treadmill. Patients began with the treadmill speed set at 1.0 mile per hour. The pace was increased by 0.5 mile per hour every 2 minutes, so that patients reached a final speed

of 3.0 miles per hour, a pace that most people could manage, Dr. Burleson said.

After the 3-week program, the brief duration of daily exercise was associated with significant improvements in exercise-induced cardiac acceleration, as measured by a change in the median heart rate from 31 beats per minute to 22 beats per minute.

Patients also reported significantly less depression, anxiety, and perceived exertion. Acute antidepressant and anxiolytic effects were seen after 10 minutes of walking, as depression dropped from 6.36 to 4.86 and anxiety dropped from 5.86 to 4.07 on a 10-point Likert scale. These improvements continued to be seen at the 3-week mark.

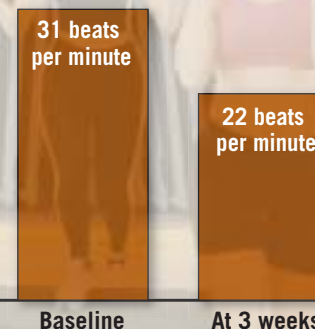
Patients reported that it took less effort to do their treadmill walks after the 3-week program. The median exertion score on the Likert scale went from 6 to 4.

Patients' perception of pain also diminished, with Likert scale scores falling from 7.32 at baseline to 2.75 at 3 weeks.

"This research suggests that relatively modest exercise leads to improved mood and physical capacity, which has further implications for mortality risk," she com-

mented. "Further, it suggests that brief exercise is a safe, cost-free, nonpharmacologic strategy for immediately reducing depression and anxiety. So if we can get our chronic pain patients moving, even for short periods, it appears we can really help them feel better, both physically and mentally." ■

Median Heart Rate Reduced With Daily Exercise In Chronic Pain Patients



Note: Study of 28 patients who walked 10 minutes a day on a treadmill.
Source: Dr. Burleson