

Treatment of Chronic Pain with Methadone or Levorphanol

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As an internist, palliative medicine consultant, and fourth-generation pharmacist, I have treated severe chronic pain in over 250 patients since 2001. Based on my experiences, it is now apparent to me that any practitioner treating patients with chronic pain must appreciate why chronic pain is woefully undertreated by physicians in this country, and why chronic pain is more complex and much harder to treat than acute pain. I began my pain practice by treating patients in hospice; I then began treating patients who required palliative care but declined hospice; then patients with nonmalignant complex pain (failed back and neck operations; polyarthropathies; fibromyalgia; and neuropathies resulting from diabetes, shingles, regional complex pain syndromes, or trauma). The majority of these patients were treated in their homes or in an outpatient clinic.

I believe that, if physicians and pharmacists could experience as unpleasant as the thought is—the depression, anxiety, frustration, and anger that patients experience from unrelieved chronic pain, and the resentment the patient feels when treated for what most physicians consider to be a symptom rather than a chronic disease, perhaps they could better understand the patients' urgencies, needs, and resentment at being treated as second-class citizens. The barriers that have influenced many physicians and pharmacists to avoid prescribing or dispensing opioids in the treatment of pain are well known:

Lack of education: In many colleges and universities, pain is considered an "orphan" subject, and the major specialties have not yet expanded their curricula to include courses in pain management. Without this education, students cannot gain the experience they need to successfully treat patients with chronic pain.

Fear of addiction: This is exaggerated in patients who have never been substance abusers. The risk of addiction in this population is estimated to be approximately 1% to 3%. Most patients comply with their physician's instructions. Those patients who are noncompliant are more prone to addiction. I tend to believe that

my patients are compliant until it is obvious that they are no longer compliant.

Scrutiny by state medical boards and by the US Drug Enforcement Agency (DEA): In the past, state medical boards and the DEA had a problem supporting the use of opioids. However, the Federation of State Medical Boards and the DEA now support the use of opioids for legitimate chronic pain as long as there is adequate documentation in the patient's medical record. **Supposed danger of using opioids in the dying to relieve pain and dyspnea:** This danger is not supported by the current medical

literature. The judicious use of opioids can provide compassionate pain relief and comfort for many patients without hastening death.

I am indebted to Dr. Daniel Brookoff for his article on chronic pain, which helped me appreciate the complexity of chronic pain resulting from activation of the N-methyl-D-aspartate (NMDA) receptor in the dorsal horn of the spinal cord.' When glutamate released by persistent pain stimuli from an injury overwhelms the normal pain receptor in the spinal cord, the normally inactive NMDA "awakens" and causes a cascade of changes affecting the entire central nervous system. These changes include the following:

1. Windup, an increased intensity and volume of pain impulses to the brain
2. Activation of neurokinin 3. Release of substance P
4. Bizarre spread of pain into areas of the body distant from the original injury
5. Growth of new nerve fibers from the dorsal nerve root into an area of the spinal cord where the conventional opioids and endorphins have no receptors to act on (Note: This change is specific to nerve injury)

The fifth change explains why those agents are poorly effective in relieving neuropathic pain. Thus, it appears that activating the NMDA receptor complicates and perpetuates pain, and that blocking the receptor can be an effective treatment. Methadone and levorphanol block the NMDA receptor sufficiently to be surprisingly effective, especially for neuropathic pain.

Treating Chronic Pain with Conventional Opioids

Chronic pain that requires treatment with opioids is commonly described as pain that is present for weeks, months, or years, and that lasts at least 12 hours per day at an intensity of at least 5 on a 10-point pain scale. Patients presenting for treatment usually have had inadequate response to conventional treatment modalities, including operations, interventional procedures, and the short- and long-acting forms of the major conventional opioids morphine, oxycodone, and fentanyl.

After a thorough history and physical examination of the patient, the practitioner attempts to control pain by (1) selecting a shortacting opioid and dosing it every 3 to 4 hours orally around the clock (not every 6 hours); (2) assessing pain relief every 1 to 2 days and titrating the dose as needed; (3) prescribing an equivalent dose of a long-acting similar opioid every 12 hours when pain is controlled; and (4) reassessing, using the short-acting drug for breakthrough pain. If this approach is ineffective and the patient continues to suffer, a careful trial of methadone or levorphanol is warranted.

Treating Chronic Pain with Methadone

Methadone is and has been a pain drug since the 1940s. Most physicians can prescribe methadone for pain and most pharmacists can dispense it. Methadone is available as generic 5-, 10-, and 40-mg

tablets, 10-mg/mL injection, 1-mg/mL oral solution, 40-mg dispersible tablets, and a 10-mg/mL oral concentrate. It ALSO can be compounded in as various concentrations as an oral solution, suppository, or transdermal gel. The cost is very low, usually less than \$20 a month.

Methadone is at least as potent as morphine with no metabolites to cause toxic side effects, can be used in patients with renal or liver insufficiency, and is less constipating than conventional opioids. Tolerance is less likely to develop during long-term use, and there is no significant "rush" or craving effect as with conventional drugs. Disadvantages of prescribing methadone include (1) the stigma of methadone being a potentially abusable substance; (2) its long half-life; (3) the potential for oversedation; and (4) theoretical interactions with other drugs. Side effects can include drowsiness and nausea. If methadone is providing good pain relief, I prescribe methylphenidate or modafinil to counter mild sedation. There have been no serious adverse events due to methadone in my patients, excepting pneumonitis (in one instance) due to a caregiver error. I find less need for the adjuvants when prescribing methadone or levorphanol.

Of over 200 patients for whom I have prescribed methadone, half experienced pain relief superior to that afforded by any prior treatment with no (or minimal) side effects; one quarter experienced fair relief; and one quarter experienced poor relief or side effects.

For patients who have severe pain despite taking large amounts of conventional opioids, the key to converting to methadone is to use a ratio table (Table 1). Add up all the opioids taken in 24 hours and convert to morphine using a standard equi-analgesic table, expressed as morphine-equivalent x 24 hours. The larger the morphine dose, the less methadone is needed. When the dose of morphine in 24 hours is 90 mg, 1 mg of methadone is equal to 4 mg of morphine, a ratio of 4:1.

Table 1. Conversion Ratio Table to Convert Morphine to Methadone

Dose of Oral Morphine (mg)/24 Hours	Ratio
<30	2:1
30 to 99	4:1
100 to 299	8:1
300 to 499	12:1
500 to 999	15:1
>1000	20:1

'Source: The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

Methadone is both an NMDA-receptor blocker and a mu-opioid agonist. The conventional opioids like morphine have no effect on the NMDA receptor.

Treating Chronic pain with Levorphanol

There has been a revival of interest in levorphanol, an excellent opioid, in the treatment of chronic pain. In 30 of my patients treated with levorphanol, 60% experienced significant pain relief; 20% experienced fair pain relief; and 20% experienced no improvement. Sedation was usually mild, and nausea infrequent. Cost and potency are similar to those of hydromorphone. A generic 2-mg tablet can

be dosed every 6 hours, 1 to 2 mg to start. An oral concentrate and a parenteral solution can be compounded.

Conclusion

I hope that this anecdotal report of the value of methadone and levorphanol will stimulate randomized controlled trials to compare these NMDA-blocking opioids to conventional opioids in the treatment of chronic pain.

Reference

1. Brookoff D. Chronic pain: 2. The case for opioids. Hosp Pract 2000; 35(9): 69-84.

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