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## Letter to the Editor

# Chronic Pain: Levorphanol, Methadone, and the *N*-Methyl-D-Aspartate Receptor

Dear Editor:

Not every clinician is in a position to undertake controlled trials to advance the science and practice of medicine. Even researchers in academic institutions are subject to problems with funding the cost of studies. End-of-life care, which is increasingly provided in the home, is beset with ethical and logistical problems regarding the use of evidence-based principles to study patients. Physicians practicing in home hospice settings are in a much different environment than those who work in hospitals and teaching institutions, and studies in those locations may not be comparable.

If a concept, new or old, is attractive to a physician because it may improve the care of patients and if a controlled trial is not possible, an uncontrolled observational case series may provide data that stimulate others to perform necessary research. This communication reports and expands on Brookoff's concepts that (1) chronic pain, particularly neuropathic and severe complex pain, is largely (though not exclusively) the result of activation, by excess glutamate, of the *N*-methyl-D-aspartate (NMDA) receptor in the dorsal horn of the spinal cord and that (2) blocking the activation of the NMDA receptor significantly reduces chronic pain.

There are currently three clinically effective agents for treating chronic pain that block the NMDA receptor: levorphanol, the forgotten opioid; methadone, the stigmatized opioid; and the anesthetic, ketamine. Our experience has led us to suggest that when chronic complex or neuropathic pain fails to respond to other opioids and/or adjuvants (gabapentin, pregabalin, duloxetine tricyclics), a trial with levorphanol, methadone, or ketamine may prove effective. In our largely home-based hospice program, we prescribe ketamine only in a compounded transdermal cream to relieve moderate localized pain.

From 2001 through 2008, I served as a medical director for a small, not-for-profit hospice in Covington, Louisiana, where I provided symptom management to 2148 hospice patients. During that time I also served as a palliative care medical consultant to 261 nonhospice patients in an outpatient clinic at a local hospital. Most of the palliative care pain patients had experienced severe nonmalignant chronic pain, which was the aftermath of diseases (fibromyalgia, spinal stenosis, degenerative arthritides), accidents, or failed operations of the back, neck, or extremities, for months or years. Many had undergone prior interventional pain procedures without lasting benefit.

Of the 2409 patients in our care during that 8-year period, 375 (roughly every sixth patient) were treated with methadone. Of those patients, 186 had an excellent response: on a 10-point scale, their pain was reduced from a score ranging from 7 to 10 to a score of zero to 3. Fair relief occurred in 94

patients, whose pain score was reduced to a score of 4 to 5. The overall response rate to treatment with methadone approached 75%. The pain relief provided by levorphanol was quite similar to that from methadone. Of the 73 patients who received levorphanol, 35 had an excellent response and 14 experienced fair relief. The overall response rate to levorphanol was 70%.

Levorphanol is a  $\mu$ - and  $\kappa$ -receptor agonist and an NMDA receptor antagonist. With respect to effectiveness and adverse-effect profile, it is much like hydromorphone but offers these important advantages: Levorphanol relieves neuropathic pain, and 1 dose is effective for 6, 8, or 12 hours as opposed to the 3 to 4 hours of relief afforded by hydromorphone. It has been our experience that when levorphanol is used, adjuvants are not needed, and there are no QTc issues with levorphanol. Until parenteral levorphanol becomes available again, that drug will be prescribed primarily for use in outpatient and home settings. Conversion from other opioids to levorphanol (Table 1) is similar to the conversion from other opioids to methadone (Table 2).

Methadone is a  $\mu$ -receptor agonist and an NMDA receptor antagonist. In our hospice, it has been used as a first-line drug, second only to morphine, for 5 years. Our hospice nurses prefer to administer methadone because it provides quick and effective pain relief, causes less sedation and constipation, and eliminates the need for adjuvants (so the concern about drug-drug interactions lessens). It has not been necessary to hospitalize patients to institute treatment with methadone, and there have been no serious problems with methadone-related oversedation, other than a patient with cancer who became oversedated due to caregiver error and was briefly hospitalized to treat pneumonia. Because we believe that QTc prolongation is related to methadone doses much higher than those we use, we avoid methadone only in selected cardiac patients. Conversion from other opioids to methadone has also been simplified (Table 2). The problems reported in the literature regarding the conversion of treatment from methadone to another opioid do not occur when methadone is converted to levorphanol, and in our experience, conversion from levorphanol to methadone has thus far been free of problems (Table 3).

Although our observational case series was uncontrolled and performed in a home-based hospice environment, its results showed that in patients whose severe chronic pain has a neuropathic component, levorphanol and methadone exert an analgesic activity superior to that of other opioids and adjuvants. We suggest that levorphanol is a valuable drug in the armamentarium of experienced palliative care physicians, and we look forward to controlled, evidence-based, government-funded studies that compare the effects of levorphanol

◀T1  
◀T2

◀T3

TABLE 1. CONVERTING TREATMENT WITH OPIOIDS TO LEVORPHANOL THERAPY

1. Convert all opioids taken in 24 hours to their oral morphine equivalents.			
2. Use the ratios below to convert treatment with morphine to levorphanol.			
Morphine equivalent daily oral dose:			
<100 mg morphine	ratio of morphine to levorphanol		12:1
100–299 mg morphine	"	"	15:1
300–599 mg morphine	"	"	20:1
600–799 mg morphine	"	"	25:1
800–999 mg morphine	"	"	No data
>1000 mg morphine	"	"	No data

TABLE 2. CONVERTING TREATMENT WITH OPIOIDS TO METHADONE THERAPY

1. Convert all opioids to the morphine equivalent daily oral dose.			
2. Use the ratios below to convert to methadone:			
< 30 mg morphine	ratio of morphine to methadone		3:1
30–99 mg morphine	"	"	5:1
100–299 mg morphine	"	"	8:1
300–499 mg morphine	"	"	12:1
500–999 mg morphine	"	"	15:1
>1000 mg morphine	"	"	20:1

TABLE 3. CONVERTING TREATMENT WITH LEVORPHANOL TO METHADONE THERAPY OR FROM METHADONE TO LEVORPHANOL THERAPY

1. Two milligrams of levorphanol orally = 5 mg of methadone orally. Levorphanol 2 mg every 8 hours roughly equals a dose of methadone 5 mg orally every 8 hours. The ratio for converting from methadone to levorphanol is 2:1, to allow for cross-tolerance.
2. Converting from methadone treatment to therapy with other opioids is difficult for patients, who often experience pain escalation and increased symptoms. Converting treatment from methadone to levorphanol has been associated with no adverse effects.

and methadone with those of other major opioids and adjuvants in the treatment of severe chronic pain.

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AU1: Provide update if available.