# Levorphanol: An Optimal Choice for Opioid Rotation

The forgotten opioid may be a “new” treatment for chronic pain syndromes that are refractory to other opioids, as well as a favored alternative to methadone, as it has a lower potential for drug-drug interactions, and has no reports of QT interval prolongation.

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Levorphanol, termed “the forgotten opioid,” is a potent opioid analgesic available for the treatment of moderate to severe pain. It was first approved in 1953, and it has a wide range of ascending and descending pain pathway receptor-mediated pharmacological activities, including mu, delta, and kappa (kappa 1 and 3) opioid agonism; *N*-methyl-D-aspartate (NMDA) antagonism; and reuptake inhibition of both norepinephrine and serotonin.[1]

Levorphanol’s multimodal profile is unique amongst the class, and may make it an optimal agent both for initial use, as well as for opioid rotation. Levorphanol may address pain that is refractory to other opioid analgesics, such as central and neuropathic pain syndromes, and may also play a role in addressing opioid-induced hyperalgesia (OIH) [3].[2] This review will discuss some of the benefits of levorphanol over other opioids and its potential use in difficult-to-treat pain syndromes.


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## Pharmacokinetics of Levorphanol

Levorphanol (levo-3-hydroxy-N-methylmorphinan) is a dehydroxylated phenanthrene opioid with a chemical structure similar to morphine. In 1983, the pharmacokinetic (PK) profile of levorphanol was studied in 13 chronic pain patients age 20 to 60 years following intravenous (IV), intramuscular (IM), and

oral administration.[2] Levorphanol was found to be readily absorbed orally, is 40% protein bound, and has a longer half-life (11 to 16 hours) and duration of analgesia (6 to 15 hours) than most opioids. Levorphanol undergoes rapid hepatic conversion to an inactive glucuronide,[3] which reaches concentrations 5 to 10 times that of levorphanol, and is eliminated relatively slowly by renal excretion. Data suggest that the glucuronide metabolite is slowly reconverted to free levorphanol, thereby establishing equilibrium between the active drug and the inactive glucuronide metabolite.[2,4] The large pool of the slowly excreted glucuronide may serve as a substrate for regenerating free levorphanol, leading to its longer half-life.

Levorphanol is not metabolized by cytochrome P450 (CYP) enzymes or dependent on p-glycoprotein in the gut for absorption, thus eliminating the potential for genetic variations in metabolism, as well as a greater potential for drug-drug and drug-food interactions via those 2 mechanisms. Other opioids that do not require CYP metabolism include hydromorphone, morphine, oxymorphone, and tapentadol—but all of these are metabolized by Phase 2-type reactions, primarily glucuronidation.[5] (See *Common CYP450 Pharmacokinetic Opioid-Drug Interactions: What Clinicians Need To Know* [5].)

## Adverse Events

The prescribing information list adverse events and warnings for levorphanol that are similar to other mu opioid analgesics, and include nausea, vomiting, altered mood and mentation, pruritus, flushing, difficulties in urination, constipation, and biliary spasm.[6] No unusual toxicities or effects of levorphanol on the QT interval have been reported in clinical trials. Since levorphanol requires hepatic metabolism to the glucuronated form for elimination, caution should be used when administering levorphanol to patients with severe hepatic dysfunction.

## Clinical Utility

Due to its pharmacologic profile, levorphanol has shown to be useful in multitude of pain states, such as chronic pain syndromes—where both nociceptive and neuropathic pathways are involved—and OIH. Glazebrook reported on 200 chronic pain patients treated with levorphanol and successful analgesia was produced in 79.5% of the cases.[7]

Levorphanol blocks NMDA receptor activity. Because prolonged and repeated activation of the NMDA receptors by glutamate is characteristic of neuropathic pain [6],[8] this would suggest that levorphanol could be an effective treatment for neuropathic pain. In a prospective trial, 81 subjects with neuropathic pain were randomized to either a low-dose (2.7 mg/d) or high-dose (8.9 mg/d) regimen of levorphanol. The results of the study indicated that in the high-dose group, pain was reduced by 36%, and 66% of patients achieved moderate or better pain relief.[9] Although the published evidence is very limited on the efficacy of opiates in neuropathic pain, we also use opiates for patients with severe neuropathic pain along with non-neuropathic analgesics.

In addition, activation of NMDA receptors by glutamate has a central role in the development of OIH,[10] and NMDA antagonists like ketamine have been used to treat or reduce the development of OIH. Thus, levorphanol is worthy of further investigation for its use in treating OIH and other disease states where both nociceptive and neuropathic pathways are involved.

## Dosage and Administration

The only commercially available preparation is levorphanol tartrate [7], 2 mg tablets, manufactured by Sentynl Therapeutics in Solana Beach, California.[6] The usual recommended starting oral dose is 2 mg repeated in 6-, 8- (most common), or 12-hour intervals, depending on patient age and comorbidities, as needed for pain relief; not exceeding a total daily dose of 6 to 12 mg in 24 hours in non-opioid-tolerant patients.[6] (See Figure 1 for conversion ratios recommended by McNulty).[3] The dose may be increased to

3 mg (1.5 2 mg tablets) or higher and repeated every 6 to 8 hours, or less frequently, if necessary.

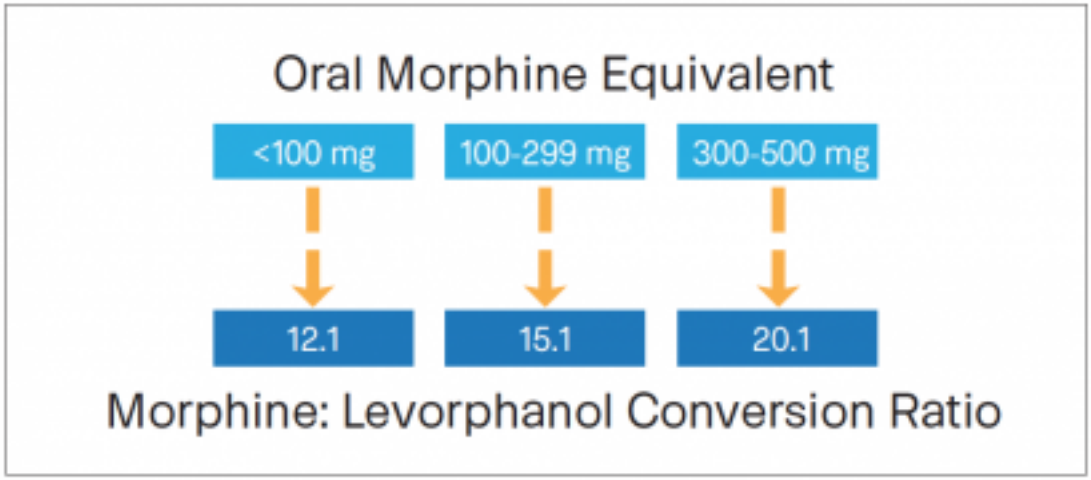


Figure 1. Conversions to levorphanol from morphine.

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Levorphanol has a half-life of 11 to 16 hours,[2] and it accumulates with repeat dosing, reaching steady state in about 3 days (5 half-lives); therefore, adequate timing should be permitted between dose adjustments. Since levorphanol is 4 to 8 times more potent than morphine, when switching to levorphanol, the recommended starting daily dose is 1/15 to 1/12 of the daily morphine dose, which includes a reduction for incomplete cross-tolerance. As with any opioid, the dose should be individualized for the patient, taking into consideration factors such as age and comorbidities.

Recent evidence suggests that the use of dose conversion ratios published in equianalgesic tables may lead to fatal or near-fatal opioid dosing by underestimating the potency of the new opioid.[11] Therefore, clinicians should use the most conservative estimates, and then decrease the estimates by 25% to 50% (exceptions: methadone, see below). After this initial dose reduction, a second dose adjustment is made [9] to "best tailor the starting dose to the individual's presentation, including pain severity, medical factors, and psychosocial characteristics."[12] Once the patient has been successfully started on the new opioid, the dose can be titrated for efficacy.

## Discussion

Levorphanol's pharmacological profile makes it a viable alternative to methadone [10],[13] and it may be a safer choice in patients with comorbidities such as arrhythmias, or taking specific medications. Both methadone and levorphanol have multimodal pharmacological effects, but levorphanol is a more potent mu opioid, has stronger delta and kappa opioid activities, as well as a NMDA antagonist. In 2009, methadone represented less than 2% of all opioid prescriptions but greater than 30% of opioid-related deaths.[14] Levorphanol has no reported effects on QT interval, and lower risk of drug-drug interaction because it is not metabolized by CYP enzymes. In contrast to methadone, which is known to have a highly variable PK profile and metabolic characteristics that lead to the risk of drug accumulation, levorphanol has a predictable PK profile and a shorter half-life.

In addition to being well-suited as a first-line opioid, levorphanol also fits well in opioid rotation, especially for pain refractory to treatment with other opioids and situations where other opioids cannot be used because of potential drug-drug interactions or drug-food interactions.

## Case Example

A 42-year-old male presented to our clinic with neck and low back pain that began 3 years ago. At the time of presentation, he was taking oxycodone, gabapentin, and duloxetine [doses not provided]—with only partial relief of pain. His past medical history was significant for multilevel degenerative disc disease in the lumbar and cervical areas. He underwent multilevel cervical fusion and a series of epidural injections with temporary relief of symptoms.

Over the next few months, we switched his medications to oxymorphone, tapentadol, and fentanyl, but again he had only partial relief of his symptoms. The patient was not able to tolerate this new regimen because of gastrointestinal or central nervous system adverse events. We then switched him to hydromorphone and titrated the dose up to 24 mg (8 mg tid). He had minimal relief of pain, but was complaining of severe constipation.

At this point we decided to try levorphanol. He was started on 2 mg tid (total daily dose of 6 mg), which he tolerated well, and we have slowly titrated him to 4 mg tid (total daily dose of 12 mg). He reported that this dose gave him the best pain relief. As of time of this publication, the patient is tolerating the regimen well and has good pain relief.

## Conclusion

Although levorphanol is an effective treatment for pain, many clinicians remain unfamiliar with its use. Levorphanol is an agonist at the mu, delta, kappa 1 and kappa 3 opioid receptors; agonist of NMDA receptor; and inhibits the reuptake of both serotonin and norepinephrine. This multimodal profile is unique amongst the opioids and may make levorphanol an optimal single-agent opioid analgesic. Levorphanol has a longer half-life (11 to 16 hours) than many opioids and therefore is best suited for treating chronic pain; an interval of approximately 72 hours should pass to allow the patient to achieve steady-state before being assessed for a dose adjustment. Because levorphanol is not metabolized by CYP enzymes and is not dependent on p-glycoprotein for absorption, there is less potential for the adverse drug-drug and drug-food reactions observed with many opioids. This profile also lends strong support for a place for levorphanol in opioid rotation, especially for pain that has proven refractory to treatment with other opioids, such as complex pain syndromes with neuropathic and nociceptive components, as well as OIH. Further investigations of the clinical utility of levorphanol, especially in the areas of chronic complex pain, OIH, and as a substitute for methadone, are warranted.

Clinicians should recognize that while prescription opioids can be part of effective pain management plan, they have serious risks. Prescribers should be fully aware of the boxed label warning for extended-release long-acting opiates. Newer guidelines recommend maximizing the use of other effective treatments available for chronic pain, such as nonopioid medications along with physical and behavioral therapies while monitoring patients closely.

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