

**FAST FACTS AND CONCEPTS #240
LEVORPHANOL**

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Overview Levorphanol, a “forgotten” potent opioid agonist, has unique attributes (1). This *Fast Fact* summarizes its pharmacology and role in pain management.

Pharmacology Levorphanol is a unique opioid, with both similarities to and important differences from methadone (see *Fast Facts* #75, 86, 171 about methadone pharmacology).

- It is an agonist at the mu, kappa, and delta opioids receptors, an NMDA antagonist, and a monoamine reuptake inhibitor of norepinephrine and serotonin (10).
- Similar to methadone, levorphanol analgesic half-life is 6-8 hours, and its elimination half-life is longer than its analgesic duration of action (patients can still have significant tissue and serum levels of levorphanol even after its analgesic effect has waned). However, its elimination half-life of ~11 hours is more predictable than methadone’s (9). Accumulation and toxicity can occur if levorphanol’s dose is increased too quickly, without waiting for steady-state to occur (at ~5 elimination half-lives or 2-3 days).
- Drug concentrations peak 30 minutes after parenteral injection and 1 hour after oral doses.
- An oral dose undergoes approximately 50% first-pass clearance.
- Levorphanol is metabolized via conjugation to a 3-glucuronide in the liver; however, the cytochrome P450 system does not appear to be involved with levorphanol. Hence it may have less drug interactions than methadone. Like methadone, it has no known active metabolites. Side effects are similar to other opioids. There are no documented studies showing QT interval prolongation or Torsades de Pointes.

Clinical Uses Several properties of levorphanol make it of interest as an analgesic.

- Similar to methadone, levorphanol’s longer duration of action is not affected by crushing, and it can be safely administered down a gastrostomy tube.
- Levorphanol lacks the stigma associated with methadone and its use in addiction medicine.
- Levorphanol is a strong NMDA receptor antagonist which has generated interest in it as a treatment for neuropathic pain. Limited research has supported its role as an effective treatment for neuropathic pain, allodynia, and hyperalgesia (2,3,4,5). Rowbotham demonstrated a dose-response curve with oral levorphanol for patients with neuropathic pain; 9 mg daily was more effective than 3 mg (2). As with methadone, levorphanol has not been directly compared with other opioids or adjuvant analgesics for neuropathic pain.
- McNulty showed in a recent case series of 31 patients (including hospice patients and chronic non-malignant pain patients) that 74% of patients had improved pain relief when switching to levorphanol in the setting of inadequately controlled pain on other opioids (6).

Dosing Parenteral levorphanol is twice as potent as the oral formulation. Published oral morphine:oral levorphanol equianalgesic ratios range from 30:4 to 12:1 (4, 6). The most recent case series looking at switching from other opioids to levorphanol used a staggered morphine:levorphanol ratio (6), similar in concept to switching to methadone (see Table). Available data indicate these ratios are reasonably safe and effective. The medication is dosed every 6 – 12 hours depending on an individual patient’s duration of analgesia. Opioid naïve patients can start with 6 mg orally a day, divided. Levorphanol is available in 2 mg tablets and 2 mg/ml or 2 mg/10ml parenteral formulations.

Table. Conversions to Levorphanol (6).

Baseline 24 hour Oral Morphine Equivalent	Morphine:Levorphanol Ratio
<100 mg	12:1 (e.g. 60 mg PO morphine/24h = 5 mg PO levorphanol/24h)
100-299 mg	15:1

300-599 mg	20:1
600-799 mg	25:1
>800 mg	No data

Cost Levorphanol is relatively expensive. A 2 mg tablet is roughly 5-10 times more expensive than an equivalent dose tablet of methadone and 2 times more expensive than an equivalent dose of a sustained-release morphine tablet.

Conclusion Levorphanol is a unique opioid analgesic, has pharmacologic properties which may make it particularly suited for patients with neuropathic pain, and recent data suggesting it is a safe and effective opioid in patients having inadequate response to other opioids.

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