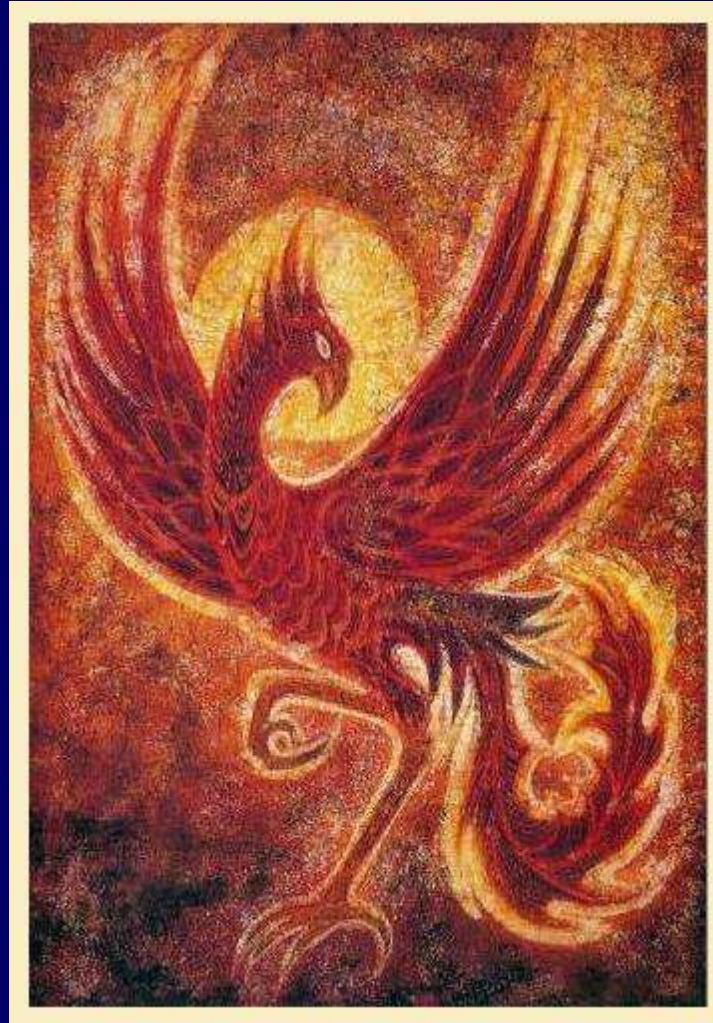


“PHOENIX ARISING
FROM THE ASHES”



Levorphanol: Clinical Use in Palliative Care and Hospice

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Objectives

- 1) Become aware of the rationale and use of the “forgotten” opioid levorphanol as an alternative to methadone for the treatment of intractable chronic pain
- 2) Learn of recent case reports using levorphanol as a first or second choice for pain in hospice and palliative care patients

Objectives

- 3) Compare the advantages and disadvantages of levorphanol to the other major opioids, including methadone
- 4) Consider the use of randomized controlled trials of levorphanol to provide evidence of its value in treating chronic pain

Rediscovery of Levorphanol

- Of the 6 major opioids, levorphanol is the least known and least used clinically.
- An excellent opioid marketed since 1958 as Levo Dromoran, levorphanol fell into disuse in the 1980s, when long-acting forms of morphine, oxycodone, and fentanyl dominated the chronic pain market.
- The failure of those drugs to effectively relieve neuropathic pain has stimulated interest in drugs with N-methyl-D-aspartate (NMDA)-receptor blocking activity.

Recent Signposts in the Literature

- In July and September 2000, a 2-part series (1,2) by Daniel Brookoff, MD, in *Hospital Practice* examined the role of NMDA receptors in the spinal cord in producing and perpetuating chronic pain as a disease rather than a symptom.
- In that article, levorphanol and methadone were described as having NMDA-receptor blocking activity in the spinal cord in addition to being mu opioid agonists.
- 1. Brookoff D. Chronic pain: 1. A new disease? *Hosp Pract* (Minneap). 2000 Jul 15;35(7):45-52, 59.
- 2. Brookoff D. Chronic pain: 2. The case for opioids. *Hosp Pract* (Minneap). 2000 Sep 15;35(9):69-72, 75-6, 81-4.

Phoenix Arising from the Ashes

- Marketed as a conventional opioid (a mu opioid receptor agonist), levorphanol was almost forgotten clinically until 2003.
- A landmark trial (1) by Michael Rowbotham, MD and colleagues that compared low-dose and high-dose levorphanol showed the dose-related efficacy of that drug in relieving chronic neuropathic pain.
- An editorial (2) by Kathleen Foley, MD, regarding the article by Rowbotham and colleagues supported their conclusion that levorphanol could relieve neuropathic pain.
- 1. Rowbotham MC et al. Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med. 2003 Mar 27; 348(13): 1223-32.
- 2. Foey KM. Opioids and neuropathic pain N Eng J Med 2003 Mar 27; 348(13): 1279-81

Phoenix, continued

- The article by Rowbotham and colleagues was selected as one of the five most important articles of 2003 by Daniel Fischberg, MD, in his annual review of the palliative care literature at the 2004 convention of the American Academy of Hospice and Palliative Medicine.

Recent Signposts in the Literature, continued

- In recent articles (1,2), Eric Prommer, MD discussed the value of NMDA-receptor blockers in relieving severe complex pain and in retarding the development of tolerance to opioid drugs. He also discussed the pharmacology and adverse effects of levorphanol compared to that of morphine and methadone.
- 1. Prommer E. Rotating methadone to other opioids: a lesson in the mechanisms of opioid tolerance and opioid-induced pain. *J Palliat Med.* 2006 Apr;9(2):488-93.
- 2. Prommer, E. Levorphanol Revisited. *J Palliat Med* 2007, Nov,10(6):1228-9
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Clinical Experience with Levorphanol



Personal Clinical Experience: Levorphanol 2001-2005

- Patients under our care: Hospice 1508
Palliative care 244
- Pts. prescribed Levorphanol: Hospice 11
Palliative care 20
- Excellent response (0-3 on pain scale)= 14
- Fair response (4-6 “ “ “)= 9
- No or poor response = 8
- McNulty,J, Can Levorphanol be Used like Methadone for Intractable Refractory Pain,J Palliat Med. 2007(April) 10(2); 293-6

Levorphanol Use: 2006-2007

Patients under our care: Hospice: 504

Palliative care: 27

Patients prescribed levorphanol: Hospice: 24

Palliative care: 8

Excellent relief: $19 + 5 = 24$

Fair relief: $2 + 1 = 3$

Poor or no relief: $3 + 2 = 5$

Case 1: Fibrosarcoma of Face

- Ford, 81 yr male: Desmoid tumor of left nasolabial fold was excised 2002, with minor recurrence x 2.
- Pain and swelling left cheek 6/07; large mass in maxillary sinus. Bx = fibrosarcoma, low grade, eroding ant sinus wall and inferior orbit.
- Radiation Rx x 2; no benefit by 2/08

Case 1: Ford

- Not surgical candidate: coronary disease.
- Pain, trigeminal distribution, lancinating and aching, 8-9. No relief from hydrocodone, oxycodone, morphine.
- Methadone eased pain to 4-5; too drowsy.
- Levorphanol begun 12/07, gradually titrated to 6 mg po q 6 hr. Pain score 1-3 after 8/09.
- No functional impairment or side-effects.

Case 2: Renal Cell CA

- Lester, 74 yr male; L. Nephrectomy 2005 for renal cell CA. Did well postop.
- Radiation RX 12/06 for mets to L1 spine, abd lymph nodes. Post. radiation: pain, nausea, vomiting. Admitted to hospice 1//07
- Sx abated until 4/07: back pain again
- Hydrocodone/APAP 5 mg helps until 8/07

Case 2: Lester

- Back and abdominal pain increasing 8/07
- Levorphanol 2 mg po q 12 hr effective; Karnofsky score 90
- Levorphanol 2 mg po q 8 hr needed 3/4/08
- Since 3/11/08 Levorphanol 2 mg po q 6 hr; hydrocodone/APAP 7.5 mg hs.
- Pain score 2-3; Karnofsky score 70
- Died comfortably 12/08.

Case 3: Papillary CA Thyroid: Mets to Lung, Spine, Brain

- Ann, 49 yr housewife: Rt pleural pain 1/07
- Lung Bx: papillary adeno-CA thyroid. No thyroid mass; 2 micro-foci found after thyroidectomy. No response to I-125x2 7/07
- Failed experimental Rx at MD Anderson.
- Methadone controlled pain initially; stopped with experimental Rx. Levorphanol begun.

Case 3: Ann

- No response to levorphanol at 12 mg q 6 hr.
- By 1/08 mets to T10-11, both lungs, neck
- Radiation Tx to spine, then to brain mets 3/08. Admitted to Hospice 5/08.
- Methadone gradually increased to 120 mg q 6 hr po over 1 month for good control.
- Dying: methadone 20 mg/hr by SQ pump

Case 4: Intercostal Neuropathy

- Cary, 60 yr business consultant: 8/07 Bx. rt. pleural mass (laparoscopic) was benign.
- Pain, burning (2-5); lancinating (8) rt. lateral rib cage for 5 weeks. No relief with hydrocodone/APAP, drowsy. Unable to travel.
- He preferred trial with levorphanol rather than gabapentin.

Case 4: Cary

- Levorphanol 2 mg tab po q 8 hr: excellent control of pain except for brisk walking
- Levorphanol increased to 3 mg q 8 hr; able to travel to Europe comfortably.
- Nerve blocks x 2: no help; Cymbalta and pregabalin: confusion, dysphoria. Disc'd.
- Since 2/08 he remains on levorphanol 4 mg po q 12 hr and is fully functional.

Case 5: Ulnar Neuropathy

- Mike: Forty-six-year-old male attorney who suffered ulnar nerve injury that affected the left hand and forearm during 4-hour coronary bypass operation.
- Lancing, burning pain (best pain level, 5; worst pain level, 9 on a 0-10 point pain scale); weak interosseous muscle function.
- After 12 weeks: constant pain and poor relief with hydrocodone and gabapentin. Infected leg vein wound treated with Rifampin.
- Medical history: type 1 diabetes (only fair control)
- Referred for consultation 3 months postop.

Case 5: Mike

- Treatment: levorphanol 2-mg tablet: ½ tablet (1 mg) every 6 hours for 2 days: pain slightly less.
- With 2-mg first dose, lancinating pain subsided to level 0-1 on pain scale and has not recurred. Mild burning pain was present with levorphanol 2 mg every 8 hours.
- Burning pain responded to levorphanol 3 mg every 8 hours; patient then underwent surgery for nerve entrapment 1 month later.
- Excellent pain relief on levorphanol 4 mg every 12 hours for over 1 year.

Pharmacology of Levorphanol:

Pharmacodynamics

- Levorphanol (levo-3-hydroxy-N-methyl morphinan) is an opioid agonist to mu, kappa, and delta opioid receptors; an NMDA-receptor blocker; and a monoamine reuptake inhibitor.
- Levorphanol is the levo-enantiomer of dextrorphan, a potent blocker of NMDA.
- The inhibition of monoamine reuptake induced by levorphanol is similar to that induced by methadone and tricyclic antidepressants.

Pharmacodynamics

- Levorphanol reduces blood pressure by reducing sympathetic tone, an effect reversed by naloxone.
- Levorphanol appears to prevent arrhythmia.
- Levorphanol increases biliary pressure.
- The intrinsic efficacy of levorphanol is equal to that of morphine and is half that of fentanyl or methadone.
- Genetically determined factors appeared to be important in the analgesic response to levorphanol in a murine model (1).

Davis MP, Glare P, Hardy J, eds. *Opioids in Cancer Pain*: New York, NY: Oxford University Press, 2005; 199-205.

Pharmacokinetics of Levorphanol

- Triexponential kinetics; terminal half-life of 11 hours.
- First-pass hepatic clearance is approximately 50%.
- Drug concentrations peak 30 minutes after parenteral injection and 1 hour after an oral dose.
- Conjugated levorphanol appears rapidly as morphanol glucuronide, the blood level of which is 5 to 10 times greater than that of levorphanol at steady state.

The metabolism of levorphanol does not occur through type 1 cytochromes.

Conjugated levorphanol, which is formed by the liver, is found in stool. It may be reabsorbed and may increase the terminal half-life of levorphanol.

- Whether conjugated levorphanol exerts an analgesic effect is unknown.
- Levorphanol is poorly absorbed sublingually.
- The plasma protein binding of levorphanol is similar to that of morphine or oxycodone.

- The half-life of levorphanol is long because of its large volume of distribution and low clearance rate.
- Levorphanol demonstrates good penetration into the cerebrospinal fluid.
- The correlation between plasma drug levels of levorphanol and analgesia varies greatly among individual patients.
- A minimum plasma concentration of 10 ng/mL of levorphanol was required for pain relief in a small study (1) involving cancer patients.
- 1. Dixon R et al. Levorphanol: pharmacokinetics and steady-state plasma concentrations in patients with pain. Res Commun Chem Pathol Pharmacol. 1983 Jul;41(1):3-17.

Drug Interactions and Toxicity

- Few data involving levorphanol are available.
- Levorphanol demonstrates the potential for interaction at glucuronidation enzyme sites and thus a theoretical (but unproven) interaction with nonsteroidal anti-inflammatory drugs (NSAIDs), valproic acid, lorazepam, and rifampin.
- Pentobarbital sedation is greatly increased by levorphanol; concomitant sedative use should be carefully monitored.

- Levorphanol is pharmaceutically incompatible with aminophylline, amobarbital, heparin, methicillin, pentobarbital, phenobarbital, phenytoin, secobarbital, sodium bicarbonate, and thiopental.
- The adverse effects of levorphanol, which do not differ from those produced by other opioids, include pruritus, dry mouth, sweating, sedation, euphoria, mental cloudiness, personality changes, weakness, confusion, constipation, and dizziness.

Levorphanol Advantages over Morphine, Oxycodone, Fentanyl, Hydromorphone

- Acts on multiple receptor sites, including NMDA receptor
- Relieves neuropathic pain
- Long half-life; administered every 6-8 hours
- Less development of tolerance
- Can rotate to levorphanol when methadone no longer effective
- No serious adverse effects

Levorphanol Advantages over Methadone

- Predictable half-life
- Less drug interactions; no C450 activity
- No effect on ECG QT interval
- No stigma

Levorphanol: Disadvantages

- No recent promotion or marketing
- No parenteral form currently available
- Little evidence-based documentation in the literature of its efficacy in the treatment of neuropathic or chronic complex pain
- Safety profile needs more data
- Dosing interval is shorter than that of long-acting fentanyl, morphine, or oxycodone
- More expensive than methadone

Change to Levorphanol or Methadone:

- When pain control provided by other major opioids is ineffective or causes adverse effects.
- When modalities (anticonvulsants, tricyclics, conventional opioids) used to treat neuropathic pain are ineffective.
- When cost is a factor.

Routes of Administration and Dosage

- Levorphanol can be administered orally or parenterally, either subcutaneously or intravenously. It is poorly absorbed when given sublingually.
- There are no data on the effects of spinal dosing.
- Initial doses in the opioid-naïve patient:
 - Parenterally, 1-2 mg every 6-8 hours; or orally, 1-2 mg every 6-8 hours.
 - Total daily doses should not exceed 3-8 mg parenterally or 6-12 mg orally.

How to Dose Levorphanol

- Levorphanol will usually be a second or third-line choice for complex chronic or neuropathic pain.
- Add up all the opioids prescribed for the patient in the previous 24 hrs
- Convert each of the opioids to their 24 hr oral morphine equivalent (OME), using the tables on slides 33 and 34.

Equianalgesic Dose Conversion

- The conversion ratio of oral to parenteral levorphanol is 2:1.
- The ratio of oral morphine to parenteral morphine is 3:1.
- The ratio of oral morphine to oral levorphanol varies inversely with the amount of morphine (see table on slide 34), similar to the ratios used in converting treatment with other opioids to treatment with methadone.

Converting from Morphine to Levorphanol

- Use the table on slide 35 to convert the 24 hr oral morphine equivalent amount to the 24 hr oral levorphanol dose for the patient.
- That amount usually is dosed orally every 8 hr to begin. 6 hr doses are often needed for severe pain. 12 hr doses are more often used in the elderly and when renal function is impaired.

Example: Adult, breast Ca, mets to lung, bone

- Rx ineffective: Oxycotin 80mg q 8 hr; Percocet 10mg four doses/24hr for breakthrough pain.
- 1) convert all opioids to po Morphine: total oxycodone=280mg
- 2) 1mg oxy is approx. 1mg MS,so oral morphine 24hr equivalent (OME) is 280mg
- Convert to Levorphanol (from table)= 15:1
- 280mg MS divided by 15= 18.7mg Lev/24h
- Can dose 6mg po q 8h or 3mg iv or sq q 8h

Equianalgesic Conversion Tables

Equianalgesic Doses if Morphine = 10 mg p.o.

- Hydromorphone = 2 mg- 2.5 mg (I use 2 mg)
- Oxycodone = 5-10 mg (I use 10 mg)
- Hydrocodone = 15 mg
- Codeine = 60 mg
- Ultram(tramadol) = 50 mg
- Demerol(merperidine) = 50 mg
- Fentanyl(duragesic) = see slide 33
- Levorphanol = see slide 34

Fentanyl: converting to and from Morphine

12.5 mcg/hr Transderm patch = 25 mg
oral Morphine per 24 hr.

25 mcg/hr Transderm.patch = 50 mg
oral Morphine per 24 hr.

50 mcg/hr Transderm.patch = 100 mg
oral Morphine per 24 hr.

75 mcg/hr Transderm.patch = 150 mg
oral Morphine per 24 hr.

100 mcg/hr Transderm.patch = 200mg
oral Morphine per 24 hr.

CONVERTING TREATMENT: from oral
MORPHINE to oral LEVORPHANOL
Morphine (MS)/24 h to Levorphanol (LEV)/24 h

- MS < 100 mg 12:1 (12 mg MS:1 mg LEV)
- MS 101-300 mg 15:1 (15 mg MS:1 mg LEV)
- MS 301-600 mg 20:1 (20 mg MS: 1 mg LEV)
- MS 601-800 mg 25:1 (25 mg MS: 1 mg LEV)
- MS 801-1000 mg No data
- MS > 1000 mg No data

Converting Methadone to Levorphanol

- Reverting from methadone back to another major opioid in a chronic pain patient is usually a more complicated and protracted process.
- Anecdotal experience suggests that converting from methadone to levorphanol is less problematic.

Methadone to Levorphanol

- For conversion to levorphanol, using the ratio of methadone to levorphanol of 5:2 has been successful in a small number of conversions.
- A ratio of 3:1 or 4:1 is suggested to allow for cross-tolerance in patients. When the methadone amount is large, using a 3 day conversion is suggested.

Next Steps: Evidence-Based Studies

- Controlled clinical studies
 - Levorphanol treatment for chronic neuropathic pain
 - Levorphanol as first-line treatment for cancer pain
 - Levorphanol as treatment for severe nonmalignant chronic pain
- Head-to-head comparative studies with other major opioids
- Basic research
- Consider National Institutes of Health (NIH) grant support

Summary

- The standard of care for the treatment of chronic pain is changing as we learn more about the ways in which chronic pain develops and is perpetuated.
- The role of NMDA-receptor activation in this process appears very important.
- As an NMDA-receptor blocking opioid, levorphanol has potential as a first-line or second-line agent for treating chronic pain, especially neuropathic pain.

More Cases



Case 6: Cancer of the Tongue

- Fifty-six-year-old man with cancer of the tongue; underwent radical resection of the soft palate and hemiglossectomy. Recurrence of this aggressive tumor to the oropharynx, sinus, and cheek caused severe chronic trigeminal and glossopharyngeal neuropathic pain.
- Long history of anxiety and panic attacks.

- Patient admitted to hospice 2/19/06. Pain at level 7-8 on a 10-point pain scale.
- Methadone oral concentration 20 mg/mL: 5 mg every 8-12 hours via percutaneous endoscopic gastrostomy (PEG) administration; not taken regularly due to anxiety.
- Levorphanol 2 mg every 6 hours; pain at level 5 on treatment day 5.
- Levorphanol increased to 12 mg/24 h; pain at level 5-6 on treatment day 19.
- Levorphanol 16 mg/24 h administered as patient's condition deteriorated; pain at level 3 on treatment day 22.
- Death occurred on day 47; treatment of terminal delirium required chlorpromazine; pain not apparent during last week of life.

Case 7: Diabetic Neuropathy

- Seventy-eight-year-old woman with type 1 diabetes, heart disease, and osteoarthritis. Patient was irritable and depressed; pain level, 8-9 on a 0-10 point pain scale.
- Gabapentin, conventional opioids ineffective in relieving pain; patient reported impaired ability to perform the activities of daily living. Consultation on 12/03.
- Methadone 2.5-5 mg reduced pain level to 4-5. Methadone discontinued after 14 days because it induced drowsiness.

Treatment: Case 7

- Levorphanol 2-3 mg every 6 hours plus oxycodone (OxyIR) 5 mg twice daily for breakthrough pain; pain level, 4-5.
- Pain bearable at level 3-4 for next 6 months.
- Cardiac and brain function then worsened; patient admitted to hospice home-care on 8/14/04.
- Levorphanol 2 mg every 6 hours; pain level, 3.
- Patient's condition progressively declined, died comfortably on 9/5/04.

Case 8: Cancer of the Ovary

- Sixty-six-year-old woman with recurrent cancer of the ovary after treatment for 6 years; large mass in the right lower abdomen and pelvis; visceral and lumbar plexus pain.
- Pain level, 7-10 on a 0-10 point pain scale despite treatment with a fentanyl patch 50 mcg/h every 72 hours and hydromorphone 8 mg every 4 hours (48 mg hydromorphone/24 h).
- To convert those opioids to their 24-hour oral morphine equivalent, using slides 33, 34 = 340 mg morphine/24 h.
- Patient admitted to hospice on 1/21/06.

Treatment: Case 8

- Treatment: Levorphanol 2 mg orally every 6 hours; pain reduced to level 3-4; hydrocodone-APAP 10/500 for breakthrough pain.
- Levorphanol increased to 4 mg every 6 hours on day 7 to maintain analgesia at pain level 3-4.
- Patient's condition slowly deteriorated; pain level, 2-3 except for hip decubitus pain.
- Morphine oral concentration, 20 mg/mL. Five milligrams of morphine added on day 72, every 2-4 hours as needed for breakthrough pain.
- Patient died peacefully on day 81.

Personal Clinical Experience with Levorphanol:2001-2005

- Patients with complex chronic neuropathic pain or mixed nociceptive-neuropathic pain treated with levorphanol in an outpatient palliative care setting (n = 31, including 10 hospice patients):
- Results (expressed on a 0-10 point pain scale)

Excellent relief (pain level, 0-3)	14 patients
Fair relief (pain level, 4-6)	9 patients
Poor or no relief	8 patients

1) McNulty, J. Can Levorphanol Be Used Like Methadone For Intractable Refractory Pain?
J Palliat Med. 2007(April) 10(2);293-6