Levorphanol Use: Past, Present and Future

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Levorphanol Use: Past, Present and Future

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Running Title: Levorphanol Use: Past, Present and Future

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Abstract

Levorphanol is a potent opioid analgesic that was first approved for use in the United States in 1953. Levorphanol is approved for use in moderate to severe pain where an opioid analgesic is appropriate. Levorphanol has a wide range of activities including mu opioid agonism, delta agonism, kappa1 and kappa3 receptor agonism, N-methyl-D-aspartate receptor antagonism, and reuptake inhibition of both norepinephrine and serotonin. This multimodal profile might prove effective for pain syndromes that are refractory to other opioid analgesics, such as central and neuropathic pain and opioid induced hyperalgesia. Levorphanol is well suited as a first line opioid and can also be used during opioid rotation. It has no known effect on the cardiac QT interval or drug-drug interactions involving hepatic cytochrome P450s enzymes. In these regards, levorphanol may offer a superior safety profile over methadone and other long-acting opioids. Despite its prospective value of multiple mechanisms of action and the potential for treating various types of pain, levorphanol use has been largely supplanted by other recently approved opioids. Its waning use over the years has caused it to be referred to as the “Forgotten Opioid” and resulted in what some consider its underutilization. In fact, levorphanol is relatively unfamiliar to most prescribers. The purpose of this review is to inform practitioners about the attributes of this opioid and reintroduce it to clinicians as an option for treating moderate to severe pain when alternative treatment options are inadequate, not indicated, or contraindicated.

Keywords: levorphanol, opioid, mu opioid receptor, kappa opioid receptor, N-methyl-D-aspartate, NMDA, analgesic, opioid rotation
**Introduction**

Levorphanol has been referred to as “the forgotten opioid”.[1] It is a unique, potent, opioid agonist that has a longer half-life than most other opioids, with the possible exception of methadone, and is indicated for moderate to severe pain where an opioid analgesic is appropriate.[2, 3] What makes levorphanol unique is the array of activities it possesses including mu receptor agonism, delta agonism, kappa1 and kappa3 receptor agonism, N-methyl-D-aspartate (NMDA) receptor antagonist activity, and reuptake inhibition of both norepinephrine and serotonin.[4, 5] Although it has similarities to methadone, it also has significant differences that may make it a superior and safer option.[2, 6] Potential uses for levorphanol include the treatment of pain syndromes that are refractory to other opioids, pain in the elderly, neuropathic pain, opioid induced hyperalgesia, and for opioid rotation.[2, 6-8] Despite its utility as an analgesic, levorphanol is underutilized, relatively unknown and unfamiliar to many, if not most of today’s prescribers.[7] The purpose of this review is to help practitioners better understand the pharmacologic profile and utility of this opioid.

Levorphanol was first approved for use in the United States in the 1950’s when it was marketed under the trade name Levo-Dromoran.[2, 7] Levorphanol was first synthesized in 1949 as the racemic mixture called D,L-methorphinan.[9] The racemic compound was studied in over 1500 patients where its analgesic potency, long duration of action, minimal respiratory depression, and wide margin of safety were noted before it was determined that the levorotatory (L) enantiomer was a potent μ receptor agonist; and thus responsible for the analgesic properties of the racemic compound).[9] The dextrorotatory (D) enantiomer was devoid of analgesic properties but did possess NMDA antagonist and antitussive properties. The L-isomer of methorphinan (levorphanol) was then studied and developed as an analgesic, gaining United States FDA approval in 1953.[9] Used primarily for chronic and cancer pain, prescribing by clinicians progressively declined in the 1980s and 1990s when long-acting forms of morphine, oxycodone and fentanyl were introduced.[2] Interest in levorphanol was revived by a study by Rowbotham and colleagues that examined the effects of high- and low-dose levorphanol in patients with neuropathic pain.[10] Recent reviews have
highlighted levorphanol's potential uses in the elderly, in the treatment of neuropathic pain and potentially as a better option than methadone.[6, 7, 9, 11]

Levomethorphan is a methylated prodrug which undergoes hepatic demethylation converting it to the more active form, levorphanol. Interestingly, the D-isomer (or mirror image) of levorphanol's prodrug, levomethorphan, is the well-known over-the-counter (OTC) cough suppressant dextromethorphan (DM) as pictured in Figure 1. DM retains antitussive properties at OTC doses and has NMDA blockade and mild opioid analgesic properties at higher doses.[12, 13]

**Structure and Chemistry of Levorphanol**
Levorphanol, whose chemical name is levo-3-hydroxyl-N-methylmorphinan, is a dehydroxylated phenanthrene opioid. Its chemical structure is similar to morphine, but is missing the 4,5 epoxy bridge, the 7,8 double bond and the 6-hydroxyl group (Figure 1). It is marketed as the dihydrate of the tartrate salt.

Overall, the phenanthrenes are the most common class of opioids and are generally well tolerated. Although levophorphanol has many similarities to methadone pharmacologically, methadone is a diphenylheptane. It may be important for clinicians to understand the different molecular structures of opioids when considering opioid rotation for lack of efficacy or tolerability. (Figure 2).

**Receptor Binding and Other Activities of Levorphanol**
Levorphanol has a diverse set of affinities and activities that may contribute to its analgesic properties. The affinities and activities of levorphanol for the mu, delta, and kappa opioid receptors (including kappa1, and kappa3), NMDA receptor, serotonin (5-HT), and norepinephrine reuptake are shown in Table I. Levorphanol is a commercially available opioid with high affinity for all three opioid receptors.[14] Levorphanol’s binding affinity for the mu opioid receptor 0.42 nM, is greater than the affinity of morphine,1.24 nM .[5]. Within the kappa-opioid receptor family, levorphanol has high affinity for kappa1 and kappa3 (Kᵢ = 8.1 nM and 5.6 nM, respectively)[15], but very low affinity for
kappa2.[16] Murine studies provide evidence that $\kappa_3$ and not $\kappa_1$ is involved in the analgesic activity of levorphanol.[16] Levorphanol also has strong affinity (4.2 nM) for the delta-opioid receptor.[5]

The strength with which a drug binds to its receptor is termed its affinity. The degree to which a drug activates its receptors is termed its intrinsic activity. Affinity for a receptor and activation of the receptor are two different qualities of a drug. A drug can have high affinity for a receptor but not activate the receptor (e.g., an antagonist). Mu opioid agonists, partial agonists, and antagonists can vary in their affinity.

Care must be exercised in extrapolating affinities of opioids for their receptors to specific clinical benefits. Affinity at particular receptor does not guarantee that all downstream effects of that receptor will occur. Levorphanol is a full kappa agonist, yet it does not induce the phosphorylation of kappa receptors and their internalization that is triggered by other full kappa agonists.[18] Because levorphanol has strong affinity for a range of receptors, its clinical utility in areas where the activity of kappa receptors has been implicated should not be assumed. The potential clinical benefits of the observed affinity levorphanol for kappa receptors, however, is worthy of further investigation.

In addition to its opioid receptor affinities, levorphanol has affinity for and blocks the NMDA receptor[4] and inhibits both serotonin and norepinephrine reuptake.[5] Levorphanol’s affinity for the NMDA receptor (630 nM) is stronger than that of methadone (2600 nM) and similar to that for ketamine (800 nM).[5] Since levorphanol is considered a strong NMDA antagonist[6] and has inhibitory action on the uptake of norepinephrine in particular, it may be a suitable option for the treatment of neuropathic pain.[8, 10]

**Pharmacokinetics and Metabolism of Levorphanol**

The pharmacokinetics (PK) of levorphanol following IV, IM, and oral administration were studied in 13 chronic pain patients (9 cancer patients, 1 vertebral body fracture patient, 1 postsurgical pain patient, 1 Arnold-Chiari malformation patient, and 1 patient with
central pain syndrome).\[19\] Participants included men and women, ages 20-60 years, who were treated with a wide range of doses of levorphanol before the study. It was reported that some patients may have developed “some degree of tolerance” to levorphanol.\[19\]

Levorphanol rapidly appeared in the systemic circulation following oral dosing, reaching peak plasma concentrations approximately 1 hour post dosing (Figure 3B).\[19\] Although the oral bioavailability was not determined during PK studies\[19\], the oral to IV conversion ratio of 2:1 suggests that levorphanol is well absorbed when orally dosed.\[11\] Plasma concentrations decay in a triexponential manner following IV administration with a terminal half-life of 11 to 16 hr (Figure 3A).\[19\] The duration of analgesia has been reported to be 6-15 hr. Thus levorphanol is a fairly long-acting opioid whose serum concentration is expected to increase with repeat frequent dosing. Dixon et al. report that positive analgesic effects are associated with a plasma concentration of about 10 ng/mL.\[19\]

Levorphanol has been found to be 40 ± 2.6% protein bound.\[19\] It readily crosses the blood brain barrier, as the concentration of levorphanol in cerebral spinal fluid (CSF) is approximately 60% of that in plasma.\[19\] The CSF concentration approximately equals that of the non-protein bound drug in plasma.

Levorphanol is readily metabolized to levorphanol-3-glucuronide, which is reported to be inactive.\[3, 19\]. Metabolism by cytochrome P450 enzyme systems is not required for its elimination and levorphanol is not a known substrate of P-glycoprotein.\[7\] The glucuronide metabolite of levorphanol rapidly appears following dosing and reaches concentrations in plasma 5 to 10 times greater than levorphanol.\[19\] Even at the earliest time points following oral dosing, the concentration of the glucuronide was 3 to 4 times that of levorphanol. When administered IV, concentrations of the glucuronide are initially lower than that of levorphanol before rapidly reaching concentrations 5-10 times greater than levorphanol.\[19\] Together these data suggest that levorphanol undergoes hepatic first pass metabolism. It has been shown that levorphanol can be a substrate for the
human UDP-glucuronosyltransferase (UGT) isoform 2B7Y (UGT2B7Y), however, for levorphanol the rate of glucuronidation by the expressed UGT2B7Y enzyme was less than 1% that for morphine and naloxone.[20] In the same study, levorphanol was one of the two poorest substrates for UGT2B7Y out of 20 opioids tested.[20] The rapid rate of in vivo glucuronidation and the poor in vitro glucuronidation by UGT2B7Y suggest that other isoforms of UGT may be involved in its glucuronidation.

The glucuronide metabolite is eliminated by renal excretion.[3] Following IV administration of levorphanol, the glucuronide reaches peak concentration at about 3 hours, then is eliminated in a similar rate to levorphanol (Figure 3, Panel A).[19] The authors of this review speculate that the rapid conversion of levorphanol to the glucuronide may not be compatible with the long half-life of levorphanol unless the glucuronide metabolite and levorphanol can be interconverted and are in equilibrium. The similar elimination of levorphanol and the glucuronide is consistent with interconversion. The large pool of the inactive and slowly excreted glucuronide may serve as a source for regenerating levorphanol thus leading to the observed long half-life of levorphanol. Although Dixon’s study of levorphanol in 1983[19] answered many questions about the PK of levorphanol, further studies are warranted.

Clinically and practically speaking, this translates to a drug that is well absorbed orally, is not dependent on p-glycoprotein in the gut for absorption, and does not undergo Phase I hepatic metabolism by CYP enzymes. All of these attributes culminate into a drug that has relatively few drug-drug or food-drug interactions. As with all CNS depressants, there still exists the potential additive effects from other sedative-hypnotics agents. Because levorphanol is metabolized by the liver and then eliminated by renal excretion, caution is warranted in using levorphanol in patients with severe hepatic [3,9] and/or renal insufficiencies.[7]
Dosage and Administration

The usual recommended starting oral dose of levorphanol is 2 mg and the preparation commercially available is levorphanol tartrate, 2 mg tablets (Sentynl Therapeutics, Inc).[3] The dose may be repeated in 6, 8 or 12 hours intervals as needed for pain relief; as with any opioid, especially in the opioid naïve patient, assessment for adverse effects such as hypoventilation or excessive sedation is recommended. Levorphanol has a long half-life, accumulates with multiple dosing and reaches steady-state in about 75-80 hours. It is therefore more appropriate for the treatment of chronic persistent pain as opposed to acute, as needed or breakthrough pain. Adequate time should be permitted between dose adjustments for the patient to reach the new steady state which generally is considered to be 5 half-lives. The dose may be increased to 3 mg (one and one half 2 mg tablets) or higher every 6 to 8 hours or less frequently, if necessary. Exceeding a total daily starting dose of 6 to 12 mg in 24 hours in non-opioid tolerant patients is not recommended.[3]

For patients with chronic pain, the dose of levorphanol must be individualized.[3] From a relative potency perspective, at steady state, a 2 mg oral dose of levorphanol is approximately equivalent to 10 mg oral oxycodone or 15 mg oral morphine.[21] Hence, levorphanol is approximately 7.5 times as potent as morphine.[3] From an opioid rotation standpoint, the total daily dose of levorphanol should be reduced by 25-50% of the total daily dose of oral morphine equivalents.[3] Again, adequate time (at least 72 hours, approximately equivalent to 5 half-lives) needs to be allowed to achieve steady-state before additional levorphanol dose adjustments are undertaken.[3, 22] When switching a patient who is taking high doses of opioid, McNulty, based on his review of the literature, recommended and used the following conversion factors: Oral morphine equivalent (OME) < 100 mg - morphine:levorphanol ratio of 12:1; OME 100-299 mg – 15:1; OME 300-599 mg – 20:1; and OME 600-700 mg – 25:1.[2]

Cross-tolerance is a phenomenon where tolerance develops to one drug that results in tolerance to other drugs. Incomplete cross-tolerance can exist between opioids, which is tolerance that does not extend completely to other opioids. An interesting
observation was noted in a study of cross-tolerance to levorphanol and morphine in rats. Cross-tolerance was found to be unidirectional. Rats tolerant to levorphanol were also tolerant to morphine, but rats tolerant to morphine were not tolerant to levorphanol.[23] It is not known whether this phenomenon with morphine and levorphanol also exists in humans.

Adverse Reactions
The side effects and adverse reactions that are observed with levorphanol are similar to those of most mu opioid analgesics.[3] These include nausea, vomiting, altered mood and mentation, pruritis, flushing, difficulties in urination, constipation and biliary spasm.[3] No unusual toxicities or effects of levorphanol on QT interval have been reported in clinical trials.[3]

Abuse and Misuse Potential of Levorphanol
Levorphanol is classified as a schedule II control substance.[3] It can be abused in a manner similar to other opioid agonists, legal or illicit. Before prescribing levorphanol, the potential of the patient for addiction, abuse or misuse should be evaluated. After prescribing, the patients need to be monitored for addictive, abuse or misuse behaviors.[3]

Clinical Trials of Levorphanol
The prescribing information for levorphanol states that approximately 1400 patients were treated in controlled clinical trials early in its development.[3] In one study, Glazebrook reported on 200 chronic pain patients (primarily malignancies or chronic bone or joint disease patients) treated with levorphanol.[9] Levorphanol doses up to 4 mg produced successful analgesia in 159 (79.5%) of the cases. The average duration of the analgesia was 8 hrs for a 1.3 mg dose (42 patients), 10 hrs for a 2 mg dose, 11 hrs for a 2.6 mg dose, and 14 hrs for a 4 mg dose. Respiratory depression (respiratory rate falling by more than 2 excursions a minute) was observed in 5% of cases of patients
given an initial dose of 2.6 mg or less. This increased to 33% in patients given a dose of 4 mg.[9]

Three clinical studies reported on the efficacy of levorphanol in the relief of postoperative pain.[24-26] Morrison et al. studied 13 analgesic drugs in abdominal surgery patients.[24] Four of the drugs (morphine, pentazocine, phenoperidine and fentanyl) were studied at two doses each. Four combinations (pethidine/levallorphan, morphine/cycloclizine, fentanyl/droperido, and phenoperidine/droperidol) were also included in the study. Groups for each drug/dose/comination consisted of 20 to 80 patients. Levorphanol, 2 mg, was the only treatment to achieve an incidence of “success” of >75%. This led the authors to state that: “Levorphanol, at a dose of 2 mg, clearly emerged as the most effective agent according to the criteria adopted in this trial.”[24] On the other hand, Banister studied 6 potent analgesic drugs (5 were the same as those included in the Morrison et al study) for post-operative pain relief and levorphanol (2 mg) was noted as the weakest analgesic in the trial.[25]. Although reported as the weakest analgesic in the trial, 79.1% of the 86 levorphanol patients reported no or only slight residual pain as all six of the drugs were found to be effective.[25] No mention of relative potency or equianalgesic estimates between agents was mentioned in this study.[25]

More recently, levorphanol has been investigated in two clinical trials.[2, 10] The first was a prospective study of 81 patients with neuropathic pain who were randomized to receive treatment with either a high-strength (0.75 mg/capsule) or a low-strength dose (0.15 mg/capsule) of levorphanol for an 8 week period. Patients in both groups titrated their intake of capsules to a maximum of 21 capsules/day. On average the high-strength group took 8.9 mg/day and the low-strength group took 2.7 mg/day. Causes of pain in this study were multiple sclerosis (8 patients), spinal cord injury (5 patients), central pain after stroke or brain lesion (10 patients), postherpetic neuralgia (PHN) (26 patients), and peripheral neuropathy or nerve injury (32 patients). In the high-strength group, pain was reduced by 36% compared to a 21% reduction in the low-strength group. In addition, 66% of patients in the high-strength group achieved moderate or better pain relief. The
level of reduction of neuropathic pain in the high-strength group was comparable to that achieved by gabapentin in a placebo-controlled study of PHN patients.[10] The authors concluded that the higher doses of levorphanol were more effective in treating neuropathic pain. As with most refractory painful conditions, pain relief was not achieved in many patients or was accompanied by intolerable side effects.[10]. Based on these results, we feel the potential benefit of Levorphanol in neuropathic pain needs to be further investigated.

Another study reported a 5-year retrospective analysis of records from a single palliative medicine practice where 20 out of 244 patients with chronic nonmalignant pain and 11 of 1508 terminally ill patients whose severe chronic pain was not relieved by treatment with other opioids were treated with levorphanol.[2] Excellent pain relief was reported in 16 (52%) patients, and fair relief in another 7 (22%) for a total response rate of 74%. The author (McNulty) suggested that: “levorphanol has a role in the treatment of pain syndromes that are refractory to other opioids” and that “Levorphanol should be considered as a candidate for opioid rotation when other opioids are ineffective…”.[2]

**Safety with Levorphanol**

Levorphanol’s prescribing information contains warnings similar to other opioids in the class, such as the potential for respiratory depression, and caution in patients with preexisting pulmonary disease, head injuries or increased intracranial pressure.[3] It should be used with caution and the initial dose reduced by 50% or more when given to individuals with any condition affecting respiratory reserve or with other drugs affecting the respiratory center.[3] Because it requires hepatic metabolism to the glucuronated form for elimination, caution should be used when administering levorphanol to patients with severe hepatic dysfunction.[3]

As mentioned, concurrent use of any central nervous system depressants with levorphanol may result in additive effects, respiratory depression, hypotension, profound sedation, or coma. The dose of one or both should be reduced if such combination therapy is considered. The use of levorphanol with monoamine oxidase inhibitors is not
recommended.[3] Caution should be used in elderly patients, where the initial dose should be reduced by 50% or more.[3]

**The Potential Clinical Utility of Levorphanol**

*Levorphanol in the treatment of chronic pain*

Opioid analgesics are widely used for the treatment of moderate to severe pain, especially when other modalities have proven ineffective. Levorphanol has been shown to be effective in the treatment of patients with chronic pain as noted above.[2, 9] The success rate was high and in one study, pain control with other major opioids, anticonvulsants, or tricyclic agents was ineffective or caused adverse effects.[2] The known diverse pharmacological mechanisms including mu receptor agonism, NMDA receptor blockade, and serotonin and norepinephrine reuptake inhibition make levorphanol a unique single-agent multimodal analgesic. Its lack of QT prolongation or cytochrome P450 drug interactions suggests some degree of safety over other currently available long-acting opioids, especially methadone.[6] Clinicians should consider levorphanol as an option when choosing or rotating to an opioid for the treatment of chronic pain.

Factors to consider with the use of levorphanol for the opioid rotation are summarized in Table II. Smith and Peppin reviewed the process of opioid rotation and made suggestions for a more systematic approach.[14] Patient characteristics are the first thing they suggest be evaluated; these characteristics included age, gender, race, comorbidities and likelihood of abuse. Since levorphanol is a strong κ opioid receptor agonist, and women are more sensitive to the effects of κ agonists than men,[15, 27] levorphanol may be a more effective analgesic in women. No studies confirming an effect of levorphanol based on gender have been done. Comorbidities are a second patient factor that should be considered in selecting an analgesic drug in the rotation. Although levorphanol has not been formally studied in heart failure patients, there have been no reports of effects on the QT interval as there have been for methadone, hydrocodone[28] or buprenorphine.[29] As discussed earlier, levorphanol is glucuronidated in the liver and eliminated by renal excretion. It has not been studied in
patients with hepatic or renal impairment, but caution may be warranted in these patients. The label states levorphanol should be administered with caution to patients with extensive liver disease who may be vulnerable to excessive sedation due to increased pharmacodynamic sensitivity or impaired metabolism of the drug.[3] Prommer recommended increasing the dosing interval in these patients.[1]

**Levorphanol in the treatment of neuropathic pain**
Most analgesics, particularly when used as single agents, often fail in the treatment of neuropathic pain as the condition is usually quite refractory to treatment.[8] Prolonged and repeated activation of NMDA receptors by glutamate is characteristic of neuropathic pain.[8] Two opioids, levorphanol and methadone, have NMDA receptor blockade activity and therefore are relevant to the pathophysiology of neuropathic pain.[8]

Levorphanol was studied in 81 patients with neuropathic pain in a trial described earlier in this review.[10] The 36% reduction in pain achieved with the higher strength dosing regimen was comparable to that achieved with other agents used to treat neuropathic pain in placebo controlled trials.[10] The treatment of neuropathic pain, and in particular the role of unique opioid agents, was recently reviewed; it was concluded that the data on levorphanol suggests “it could be used in treating neuropathic pain when other therapies are ineffective”. These authors agree that further assessment of its utility in the treatment of neuropathic pain is warranted.[8]

**Levorphanol as an alternative to methadone**
The advantages of levorphanol over methadone were recently reviewed.[6] Both methadone and levorphanol have activities beyond pure mu opioid receptor agonism (Table I). However, levorphanol is a more potent mu receptor agonist and has potent delta and kappa receptor binding, more potent NMDA receptor antagonism, but less activity inhibiting norepinephrine and serotonin uptake. The cross-over in activities would suggest the two drugs would be efficacious in many of the same patients. However, levorphanol is probably safer to use than methadone. Levorphanol has no reported effects on QT interval in contrast to effects of methadone.[30-33] Drug-drug interactions (DDIs) are a major concern with methadone, because it is largely
metabolized by CYP enzymes. DDIs can lead to unsafe levels serum levels of methadone. Methadone has highly variable PK and metabolic characteristics that lead to a risk of drug accumulation. The risks with methadone are apparent when one considers that in 2009 methadone represented less than 2% of all opioid prescriptions but >30% of opioid related deaths. Levorphanol has a much more predictable PK profile with a shorter half-life. The major disadvantages of levorphanol are its lack of practitioner familiarity, lack of data, and limited commercial availability. Considering the risks associated with methadone, levorphanol may be a better option.

**Levorphanol for opioid induced hyperalgesia**

Opioid-induced hyperalgesia (OIH), a complication of opioid therapy, is the increased sensitivity to pain caused by exposure to opioids. OIH pain is more severe than the original pain, the quality and location of the pain is poorly defined, and there is a reduction in tolerability for the pain. The activation of NMDA receptors by glutamate has a central role in OIH. NMDA receptor antagonists, such as ketamine, have been used to prevent or reduce the development of OIH.

As mentioned, levorphanol is a strong NMDA receptor antagonist ($K_i = 640$ nM), slightly stronger than ketamine ($K_i = 800$ nM) and several times stronger than methadone ($K_i = 2600$ nM). On the other hand, levorphanol also has strong kappa receptor binding which has been implicated in contributing to OIH. Levorphanol’s role in treatment or prevention of hyperalgesia is worthy of further investigation.

**Testing for Levorphanol**

An emerging consensus among many professional organizations, as well as state guidelines, recommend routine and random urine drug monitoring as a part of treating patients on chronic opioid therapy. Although levorphanol screening by immunoassay (IA) is currently unavailable for clinician use, definitive confirmation of levorphanol by chromatography is readily available by many commercial laboratories. If the use of levorphanol as an analgesic for chronic pain grows, clinical laboratory testing protocols may need to include this specific opioid on standard IA screens. As mentioned above,
dextromethorphan is the methylated dextro-isomer of levorphanol and therefore DM may cause a false positive levorphanol test if future IA testing included levorphanol.

Conclusions
Levorphanol, the “forgotten opioid”, may prove beneficial for pain management because of its unique set of affinities at the opioid receptors, the NMDA receptor, and with its inherent inhibition of norepinephrine and serotonin reuptake. This is coupled to a simple metabolism with less potential for adverse drug-drug and drug-food interactions seen with many opioids, and a limited risk of known concerns with comorbidities, such as cardiac QT prolongation. Since it is an opioid with a longer half-life, the potential for drug accumulation exists, but this is consistent and manageable. It should have a place in the opioid rotation, especially for pain that proves refractory to treatment with other opioids. It is well suited for cancer and neuropathic pain, pain associated with radicular symptomatology, and any pain where chronic opioid therapy is indicated and a suitable replacement for methadone is desired. These authors suggest further laboratory investigations and clinical studies to better define levorphanol’s properties and clinical utility.

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co-developer of Practical Pain Management’s Online Opioid Conversion Calculator; and owner of Remitigate, LLC. Dr. Fudin disclosed that his participation and opinions are his own and not reflective of any pharmaceutical companies listed nor was it prepared as part of his official government duties. SR Nalamachu has been a consultant/speaker for or received a research grant from Astra Zeneca, Allergan, Collegium, Daiichi, Depomed, Eagle, Endo, Insipiron, Insys, Ipsen, Iroko, Janssen, Kashiv, KemPharm, Lilly, Mallinckrodt, Purdue, Recro, Salix, Scilex, Sentynl, Teva, Zogenix. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Table I. Receptor and other activities of Levorphanol

<table>
<thead>
<tr>
<th>Activity</th>
<th>Levorphanol</th>
<th>(±)-Methadone</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>mu-opioid receptor binding</td>
<td>0.21 nM</td>
<td>1.7 nM</td>
<td>[17,5]</td>
</tr>
<tr>
<td>delta-opioid receptor binding</td>
<td>4.2 nM</td>
<td>435 nM</td>
<td>[17,5]</td>
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<td>kappa-opioid receptor binding</td>
<td>2.3 nM</td>
<td>405 nM</td>
<td>[17,5]</td>
</tr>
<tr>
<td>kappa1</td>
<td>8.1 nM</td>
<td>-</td>
<td>[15]</td>
</tr>
<tr>
<td>kappa2</td>
<td>Poor affinity</td>
<td>-</td>
<td>[16]</td>
</tr>
<tr>
<td>kappa3</td>
<td>5.6 nM</td>
<td>-</td>
<td>[15]</td>
</tr>
<tr>
<td>NMDA receptor (displacing [³H]-MK-801)</td>
<td>630 nM</td>
<td>2600 nM</td>
<td>[4]</td>
</tr>
<tr>
<td>Serotonin uptake</td>
<td>86.3 nM</td>
<td>14.1 nM*</td>
<td>[5]</td>
</tr>
<tr>
<td>5-HT</td>
<td>1210 nM</td>
<td>702 nM*</td>
<td>[5]</td>
</tr>
</tbody>
</table>

*Value is for (R)-(−)-methadone as (S)-(+) -methadone was much less active in both assays, (±)-Methadone was not measured by Codd et al.[5] in these two assays
Table II. Factors to consider with levorphanol use in the opioid rotation

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<thead>
<tr>
<th>Factor to Consider</th>
<th>Levorphanol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>• Dose should be reduced 50% or more in the infirm elderly patient[3]</td>
</tr>
</tbody>
</table>
| **Sex**            | • Levorphanol is a strong kappa agonist and women are more sensitive to kappa agonists[27]  
|                    | • Consider a lower dose in women |
| **Ethnicity**      | • No effect[14] |
| **Comorbidities**  |             |
| Heart Failure      | • Not studied  
|                    | • No reported QT effects for levorphanol |
| Hepatic Impairment| • Not studied  
|                    | • Glucuronidation of levorphanol occurs in the liver and may be impaired in liver disease. |
| Renal Impairment  | • Not studied  
|                    | • The glucuronide of levorphanol is eliminated by renal excretion |
| **Abuse Potential**| • High  
|                    | • Levorphanol is a schedule II controlled substance  
|                    | • Levorphanol may not be appropriate in patients considered a risk for abuse |
| **Receptor Binding Profile** | • A potent agonist on mu, delta, and kappa opioid receptors  
|                    | • NMDA – strong inhibition  
|                    | • Inhibits serotonin and norepinephrine uptake  
|                    | • Levorphanol may have analgesic properties beyond that of most other opioids |
| **Drug-Drug Interactions** | • Not metabolized by cytochrome P450s  
|                    | • As with other pure agonist opioid analgesics, agonist/antagonist analgesics (e.g. pentazocine, nalbuphine, butorphaol, dezocine and buprenorphine) should not be administered with levorphanol[3]  
|                    | • Concurrent use with central nervous system depressants increases risk of respiratory depression and profound sedation, dose adjustments are advised[3] |
| **Route of Administration** | • Oral |
| **Adverse Events** | • Typical opioid effects, no unusual toxicities reported[3] |
| **Equianalgesic Dose** | • 4 to 8 times as potent as morphine  
|                    | • Start on 1/15 to 1/12 the daily dose of oral morphine  
|                    | o Dose should be individualized taking in factors such as comorbidities, age, sex, etc.[3]  
|                    | • Dose adjustments – allow at least 72 hours between |
Figure 1. Structures of Levorphanol, Dextromethorphan, and Morphine

<table>
<thead>
<tr>
<th>PHENANTHRENES</th>
<th>BENZOMORPHANS</th>
<th>PHENYLPIPERIDINES</th>
<th>DIPHENYLMETHANES</th>
<th>PHENYLPROPYL AMINES</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Morphine" /></td>
<td><img src="image2" alt="Pentazocine" /></td>
<td><img src="image3" alt="Meperidine" /></td>
<td><img src="image4" alt="Methadone" /></td>
<td><img src="image5" alt="Tramadol" /></td>
</tr>
<tr>
<td>Buprenorphine*</td>
<td>Diphenoxylate</td>
<td>Alfentanil</td>
<td>Methadone</td>
<td>Tapentadol</td>
</tr>
<tr>
<td>Butorphanol*</td>
<td>Loperamide</td>
<td>Fentanyl</td>
<td>Propoxyphene</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Codeine</td>
<td>Pentazocine</td>
<td>Meperidine</td>
<td>Remifentanil</td>
<td></td>
</tr>
<tr>
<td>Heroin (diacetyl-morphine)</td>
<td></td>
<td>Sufentanil</td>
<td></td>
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<tr>
<td>Hydrocodone*</td>
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<tr>
<td>Hydromorphone*</td>
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</tr>
<tr>
<td>Levorphanol*</td>
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<tr>
<td>Morphine</td>
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<tr>
<td>Naltrexone*</td>
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<tr>
<td>Nalbuphine</td>
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<tr>
<td>Oxycodone*</td>
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<td></td>
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<tr>
<td>Oxymorphone*</td>
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</table>

**CROSS-SENSITIVITY RISK**

<table>
<thead>
<tr>
<th>PROBABLE</th>
<th>POSSIBLE</th>
<th>LOW RISK</th>
<th>LOW RISK</th>
<th>LOW RISK</th>
</tr>
</thead>
</table>

*Agents lacking the 6-OH group of morphine, possibly decreases cross-sensitivity within the phenanthrene group.
Figure 3. Human PK studies on Levorphanol from Dixon et al.[19] Panel A – Plasma concentrations of levorphanol (x) and its glucuronide (o) following the IV administration of a 2 mg dose of levorphanol. Panel B – Plasma concentrations of levorphanol (x) and its glucuronide (o) following the oral administration of a single 18 mg dose of levorphanol. The data demonstrate the rapid appearance of the glucuronide to concentrations 5-10 times that of levorphanol, the parallel decay of each of their levels and the long terminal half-life of levorphanol. Adapted from Dixon et al. 1983.[19] Best efforts have been taken to identify and contact copyright holders to request permission.