Review of the Role of Opioids in Cancer Pain

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Opioids, cancer pain, opioid metabolism, morphine, codeine, hydrocodone, hydromorphone, fentanyl, methadone

Abstract
Cancer pain is unfortunately very prevalent, with opioids the mainstay of treatment. Knowledge of the types of pain caused by cancer and the effects of various opioids would be expected to improve pain therapy. This article addresses the use, side effects, formulations, and metabolism of the most commonly used opioids in cancer pain management, including morphine, codeine, hydrocodone, hydromorphone, fentanyl, and methadone. The role of opioid conversion and equipotent dosing when changing from one opioid to another is also described. (JNCCN 2010;8:1087–1094)

Epidemiology of Cancer Pain
The incidence of cancer is increasing worldwide. In 2000, approximately 11 million cases were diagnosed and approximately 7 million patients died of the disease. In 2030, approximately 27 million cases are expected worldwide, with an estimated 17 million cancer deaths annually. Overall, 75% of patients with cancer experience pain severe enough to require opioids. Many patients will present with pain as the first sign of cancer, and nearly two thirds are undertreated for this symptom.

Cancer pain has many causes, including the cancer itself (e.g., tumor invasion) and the effects of treatment (e.g., peripheral neuropathy after chemotherapy, postsurgical pain). Recently, a study of 217 oncology outpatients showed that 53% of the patients had pain only from their cancer or treatment, 25.3% had noncancer pain, and 21.7% had both cancer-related and noncancer-related pain. However, fewer than 25% received a prescription for a strong opioid, only 7% had a coanalgesic prescribed for pain, and approximately 20% received no analgesic prescription, suggesting that oncologists are not adequately addressing pain relief.

Opioid Genetics
Multiple opioid receptors have been described (mu, kappa, delta), each having a different activity and receptor affinity (which is genetically controlled). Traditionally, the interindividual variation in opioid effectiveness has been explained by differences in absorption or intensity of the painful stimulus. Cloning of the mu opioid receptor has greatly enhanced understanding of the complexity of this system and has provided possible mechanisms to explain these observations.

A single mu opioid receptor gene was identified, OPRM1, but it is now known to be polymorphic, generating a multitude of different mu opioid receptor subtypes, and approximately 20% to 30% of the population has heterozygous changes in the alleles associated with altered sensitivities to pain. Reyes-Gibby et al. evaluated 207 cancer inpatients on a stable dose of morphine for at least 3 days. Those carrying the OPRM1 GG genotype required 93% higher morphine doses than patients with the AA genotype.

Different opioids also have a different relative affinity for each receptor, and therefore the same
opioid may have very different effects on different people, and the same person might experience different effects from different opioids. This knowledge provides insights into the importance of individualizing therapy for every patient experiencing pain.

**Opioid Metabolism**

Although the pharmacokinetics of opioids (e.g., volume of distribution or half-life) have been known for a long time, the significance of opioid metabolism was only recently recognized. Many of the effects of opioids can be traced to the metabolites, and these effects help explain many of the puzzling clinical scenarios seen by practicing physicians. Effectiveness of various opioids depends on whether the patient is a slow or an extensive metabolizer. For example, CYP2D6 is a critical enzyme involved in the activation of various opioids described later. Approximately 8% to 10% of Caucasians and 1% to 3% of African Americans and people of Asian descent have an inactive form of this enzyme, and thus may have less than expected analgesia.

**Commonly Used Opioids**

**Morphine**

Morphine is the archetypal opioid used to control moderate to severe pain. It has a relatively poor bioavailability of approximately 15% to 65%, with considerable interindividual variability as a result of extensive presystemic elimination; approximately 90% of the parent drug is converted to metabolites. It takes at least 30 minutes for the immediate-release form and 90 minutes for any extended-release form to reach the brain and begin its analgesic effect, with 10 to 12 hours needed to reach steady-state plasma levels.

Morphine is metabolized by glucuronidation, producing morphine-6 glucuronide (M6G) and morphine-3 glucuronide (M3G) in a ratio of 6:1. M6G is believed to be responsible for some additional analgesic effects of morphine. M3G is believed to potentially lead to hyperalgesia, with increased pain, agitation, and myoclonus. Morphine is also metabolized in small amounts to the drugs codeine and hydrodromorphone. In one study, hydrodromorphine was present in 66% of morphine consumers without aberrant drug behavior; this usually occurred with doses higher than 100 mg daily.

Morphine is associated with histamine release (which can cause bronchospasm and hypotension) and direct respiratory depression mediated by the nucleus accumbens in the brain stem, resulting in a decreased response to the arterial carbon dioxide tension, and shifting the response curve to the right. Respiratory acidosis increases the delivery of morphine to the brain compartment, leading to increased respiratory compromise. Morphine may also decrease sympathetic nervous system tone, resulting in decreased tone in peripheral veins and causing venous pooling and orthostatic hypotension. Morphine has effects on the digestive tract, including spasm of biliary smooth muscle, sphincter of Oddi spasm, and decreased intestinal motility resulting in constipation. Similar effects occur in the genitourinary system, resulting in spasm of the bladder trigone, causing urinary retention. Morphine may induce nausea and vomiting through direct stimulation of the chemoreceptor trigger zone in the floor of the fourth ventricle. The parenteral forms of morphine contain sulfites and may cause anaphylactic or life-threatening, allergic-type reactions in individuals with sulfite allergies. Morphine is available in tablets, solutions, rectal suppositories, or injections. Oral formulations can be for immediate release (MSIR) or sustained release (MSContin, Avinza, Kadian, Oramorph).

**Codeine**

Codeine has a weak affinity to mu opioid receptors. Codeine has good oral bioavailability (60%), with the maximum concentration achieved in 1 to 2 hours (T_{max}) and an effective half-life of 4 hours. The analgesic activity from codeine is believed to occur from metabolism of codeine to morphine by CYP2D6, and therefore codeine is susceptible to drug–drug interactions, as well as the genetic influences discussed previously. This includes the inhibitors such as bupropion, celecoxib, cimetidine, and cocaine, and the inducers dexamethasone and rifampin. The CYP2D6 enzyme also has great heterogeneity, with both fast and slow metabolizers, and therefore codeine may not be an effective drug in all populations. Codeine has a side-effect profile that is similar to that for other opiate agonists. It is used for mild to moderate pain, and cough suppression. A low dose of codeine seems to be paradoxically more emetic than higher doses of codeine, presumably because of competing effects at the chemoreceptor trigger zone. Although codeine is often referred to as a
“weak” analgesic, a cancer pain study comparing 25 mg of hydrocodone (a “strong” analgesic) with 150 mg of codeine (a “weak” analgesic) showed that 58% of the patients taking codeine obtained relief compared with 57% of those taking hydrocodone.20

**Hydrocodone**

Hydrocodone is one of the most commonly used opioids and is indicated for moderate-to-moderately severe pain and symptomatic relief of nonproductive cough. Hydrocodone is only available for pain control as a combination product with nonopioid analgesics, such as ibuprofen (Vicoprofen) and acetaminophen (Lortab, Lor cet, Vicoden, Norco, Zydone). A liquid formulation is also available, but no intravenous form. Hydrocodone bioavailability after oral administration is high, and its half-life is 2.5 to 4 hours.

Hydrocodone is similar in structure to codeine and is a weak mu receptor agonist, but the CYP2D6 enzyme demethylates it into hydromorphone, which has much stronger mu binding.21 Like codeine, experts have proposed that hydrocodone is a prodrug. In other words, patients who are CYP2D6-deficient, or those taking CYP2D6 inhibitors, may not produce these analgesic metabolites and may experience less-than-expected analgesia. Unfortunately, studies that would help show that hydrocodone is a prodrug are scant, and no human studies have been performed using pain models or patients with pain.

**Oxycodone**

Oxycodone is available in its pure form or in combination with acetaminophen or aspirin. Oxycodone has activity at multiple opiate receptors, including the kappa receptor, and has a high bioavailability in oral dosage, with a half-life of 2.5 to 3 hours. It undergoes extensive hepatic metabolism by glucuronidation to noroxycodone (which has < 1% of the analgesia potency of oxycodone) and by CYP2D6 to oxymorphone.22 Because oxycodone is dependent on the 2D6 pathway for clearance, drug–drug interactions may occur with 2D6 inhibitors. Oxycodone is available in immediate-acting pill formulations, with acetaminophen (Percocet, Tylox) or without (OxyIR), and in extended-release forms (OxyContin). It is also available in a liquid (Oxifast) in 5 or 20 mg/mL.

**Oxymorphone**

Although oxycodone has activity at multiple receptors, its metabolite oxymorphone is a pure mu agonist. Oxymorphone is approximately 10 times more potent than morphine. It has limited protein binding and is not affected by CY2D6 or CY3A4, which decreases the risk of drug–drug interactions.23 Oxymorphone has a reduced histamine effect and may be of use in patients who complain of headache or itching with other opioids.24 It recently became available in immediate-release (Opana) and sustained-release formulations (Opana ER).

**Hydromorphone**

Hydromorphone (Dilaudid) is a semisynthetic opioid agonist, which is a hydrogenated ketone of morphine.25 Like morphine, it acts primarily on mu opioid receptors and, to a lesser degree, on delta receptors. In single-dose studies, hydromorphone is 7 to 10 times more potent than morphine,26 although the oral and parenteral steady-state equivalence is 1:5, whereas the equivalence of chronic infusions may be as little as 1:3.5.27 It is highly water-soluble, which allows for very concentrated formulations. In patients with renal failure, it may be preferred over morphine. Hydromorphone is extensively metabolized in the liver, with approximately 62% of the oral dose being eliminated by the liver on the first pass.

For orally administered immediate-release preparations, the onset of action is approximately 30 minutes, with a duration of action of approximately 4 hours. It was briefly available as an extended-release formulation in 2005 as Palladone, and a new extended-release formulation (Exalgo) is expected to be approved by the FDA in 2010. Hydromorphone can also be administered parenterally through intravenous, intramuscular, rectal, and subcutaneous routes. Hydromorphone is metabolized primarily to hydromorphone-3-glucuronide (H3G), which, like the corresponding M3G, not only is devoid of analgesic activity but also evokes a range of dose-dependent excited behaviors, including allodynia, myoclonus, and seizures in animal models.28

**Methadone**

Methadone is a synthetic mu opioid receptor agonist medication; in addition to its opioid receptor activity, it is also an antagonist of the N-methyl-D-aspartate (NMDA) receptor. Methadone is a racemic mixture of 2 enantiomers; the R form is more potent, with a 10-fold higher affinity for opioid receptors (accounting for virtually all of its analgesic effect), whereas S-methadone is the NMDA antagonist.29 The inherent NMDA antagonistic effects make it potentially

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useful in severe neuropathic and “opioid-resistant” pain states. The S isomer also inhibits reuptake of serotonin and norepinephrine, which should be recognized when using methadone in combination with selective serotonin reuptake inhibitors and tricyclic antidepressants.

Methadone is a unique synthetic opioid, unrelated to standard opioids (leading to its usefulness in patients with “true” morphine allergies). It is a basic and lipophilic drug with an excellent (though highly variable) oral bioavailability (40%–100%). The pill form can be crushed or dissolved for nasogastric delivery, and it is also available as a liquid and in an intravenous formulation, which contains chlorobutanol. Methadone is metabolized in the liver and intestines and excreted almost exclusively in feces, which is advantageous for patients with renal insufficiency or failure. Because of its high lipid solubility, it is redistributed to the fat tissues and has a very long elimination phase, with a half-life of 12 to 150 hours. It may cause less constipation than morphine, and is very inexpensive.

Although it was traditionally used to treat heroin addicts, methadone’s flexibility in dosing, use in neuropathic pain, and cheap price have led to a recent increase in its use in treating cancer-related pain. Unfortunately, a lack of awareness of its metabolism and potential drug interactions, and its long half-life, have led to a dramatic increase in deaths associated with this medication.

The metabolism of methadone is always variable. Methadone is metabolized by CYP3A4 primarily and CYP2D6 secondarily; CYP2D6 preferentially metabolizes the R-methadone, whereas CYP3A4 and CYP1A2 metabolize both enantiomers. An intestinal CYP3A4 transport enzyme may also be involved in absorption. CYP3A4 expression can vary up to 30-fold, and there can be genetic polymorphism of CYP2D6, ranging from poor to rapid metabolism. The initiation of methadone therapy can induce the CYP3A4 enzyme for 5 to 7 days, leading to low blood levels initially, but unexpectedly high levels may follow approximately a week later if the medication has been rapidly titrated upward. A wide variety of substances can also induce or inhibit these enzymes. The potential differences in enzymatic metabolic conversion of methadone may explain the inconsistency of observed half-life.

Methadone has no active metabolites, and therefore may result in less hyperalgesia, myoclonus, and neurotoxicity than morphine. It may be unique in its lack of profound euphoria, but its analgesic action (3–6 hours at initiation and extended to 8–12 hours with repeated dosing) is significantly shorter than its elimination half-life (~22 hours), and patient self-directed redosing and a long half-life may lead to respiratory depression and death.

Methadone also has the potential to cause cardiac arrhythmias, specifically prolonged QTc intervals or Torsade de Pointes, under certain circumstances. Congenital QT prolongation, high methadone levels (usually >100 mg/d), and conditions that increase QT prolongation (such as hypokalemia and hypomagnesemia) or intravenous methadone (because it contains chlorobutanol, which prolongs QTc intervals) may increase the risk for arrhythmias. Combining methadone with a CYP3A4 inhibitor such as ciprofloxin, or even grapefruit, can potentially increase arrhythmia risk. Experts recommend a switch to methadone from another opioid be accompanied by a large (50%–90%) decrease in the calculated equipotent dose. It cannot be too strongly emphasized that methadone dosing can be potentially lethal and must be performed with knowledge and caution. Methadone should be prescribed only by physicians who have significant knowledge of its complex pharmacology and experience prescribing it.

Fentanyl
Fentanyl is a strong opioid agonist, available in parenteral, transdermal, and transbuccal preparations. It is approximately 80 times more potent than morphine, is highly lipophilic, and binds strongly to plasma proteins. Fentanyl undergoes extensive metabolism in the liver. It is most commonly administered for treating cancer pain as a transdermal patch (Duragesic), intravenously, or in the epidural or intrathecal space. It is also available as a transmucosal oral “lollipop” (Actiq) or buccal tablets (Fentora). Fentanyl is metabolized by CYP3A4, but to inactive and nontoxic metabolites; however, CYP3A4 inhibitors may lead to increased fentanyl blood levels. After application, the transdermal formulation has a lag time, with no detectable fentanyl in the systemic circulation for 1 to 2 hours and a delay of 8 to 16 hours to onset of analgesia after application. Transdermal fentanyl typically reaches steady state in approximately 72 hours. When a patch is removed, a
subcutaneous reservoir remains, and drug clearance may take up to 24 hours.

Some debate exists regarding the relative potency ratio to be used when converting oral morphine to fentanyl. The usual recommendation for calculating the equipotent dose of different opioids involves calculating the 24-hour dose as “morphine equivalents” (see Opioid Conversions, opposite column). However, Hanks and Fallon\(^4^\) instead suggest relating the starting doses to 4-hour doses of morphine rather than 24-hour doses. For example, patients receiving 5 to 20 mg of oral morphine every 4 hours (or the equivalent in controlled-release morphine) would start with 25-μg/h fentanyl patches every 72 hours; patients on 25 to 35 mg of oral morphine every 4 hours would start with 50 μg/h of fentanyl; those on 40 to 50 mg oral morphine every 4 hours would start with 75 μg/h of fentanyl; and those on 55 to 65 mg of oral morphine every 4 hours would start with 100 μg/h of fentanyl. These investigators believe that the controversies over appropriate morphine-to-fentanyl potency ratio calculations overlook the fact that fentanyl given transdermally behaves differently and cannot be equated with morphine given orally when calculating relative potency.

**Tramadol**

A unique analgesic and an atypical opioid, tramadol is a synthetic analogue of codeine.\(^4^5\) The M1 derivative (O-demethyl tramadol) produced by CYP2D6 has a higher affinity for the mu receptor than the parent compound (as much as 6 times). Tramadol is a racemic mixture of 2 enantiomers: one form is a selective mu agonist and inhibits serotonin reuptake, whereas the other mainly inhibits norepinephrine reuptake.\(^4^6\) The maximum dose is 400 mg daily, and toxic doses cause central nervous system excitation and seizures. Tramadol is absorbed rapidly and extensively after oral doses, and is equal in analgesic potency to codeine. It is available in short-acting (Ultram) and sustained-release (UltramER) once-a-day formulations.

Presumably because the extended-release form allows the serotonin–norepinephrine reuptake inhibitor activity to be active, it has been associated with significant neuropathic pain relief, such as for chemotherapy-related painful peripheral neuropathies.\(^4^7\)

Because tramadol requires CYP2D6 metabolism for maximal analgesic effect, coadministration of CYP2D6 inhibitors, such as fluoxetine, paroxetine, and sertraline, results in decreased effectiveness.\(^4^8\) In addition, because tramadol has serotonin activity, serotonin reuptake inhibitors are relatively contraindicated because of the potential for a serotonin syndrome; in the same way, as a norepinephrine reuptake inhibitor, tramadol should not be used with monoamine oxidase inhibitors or tricyclic antidepressants. Tramadol analgesia can be attenuated through concomitant administration of ondansetron (5HT3 receptor–selective antagonist), probably because ondansetron blocks spinal serotonin receptors.\(^4^9\)

Although considered a “weak” opioid, tramadol can have significant analgesic qualities (perhaps because of its dual action), especially in its extended-release formulation. In a study comparing 25 mg of hydrocodone (a “strong” analgesic) to 200 mg of tramadol (a “weak” analgesic) in 118 patients with moderate to severe cancer pain, 62% of patients taking tramadol obtained relief compared with 57% of those taking hydrocodone.\(^5^0\)

**Opioid Conversions**

Although multiple opioid conversion charts have been developed, none are reliable or take into consideration the vast individual differences in effect and metabolism among patients and within medications. Brand name and generic medications may have significant differences in bioavailability, and metabolism of medications may be influenced by genetic polymorphism and drug interactions. Therefore, it is important to recognize that “equipotent” doses of medications may have very different degrees of analgesia and side effects (Table 1).\(^5^1\)

With chronic administration, the ratio of oral to intravenous morphine is 3:1. Initially, parenteral hydromorphone was believed to be approximately 7 times more potent than morphine, but recent studies support a 5:1 relative potency.\(^5^2\) When converting morphine to fentanyl, Levy\(^5^3\) suggested that the dose of transdermal fentanyl is roughly equivalent to the sustained-release morphine dose given twice daily. For instance, 150 mg of sustained-release morphine given twice daily would be equivalent to a 150-μg fentanyl patch. Similarly, 25 μg of transdermal fentanyl is roughly equivalent to 45 mg of oral oxycodeone or 12 mg of oral hydromorphone per day. Although methadone has been described as equipotent to morphine, it is now clearer that dosing metha-
done on a milligram-for-milligram basis will lead to a life-threatening overdose. For doses of oral morphine lower than 100 mg, a morphine-to-methadone ratio of 4:1 may be appropriate, whereas for higher doses of morphine, a ratio of 20 mg of morphine for each milligram of methadone may be appropriate (Table 2). Methadone seems to be significantly more potent through the intravenous route, perhaps because it bypasses the intestinal CYP3A4 metabolism.

In general, to switch between medications, clinicians must calculate a rough equivalent 24-hour dose, divide by the dosing schedule, and then “underdose,” with subsequent titration to effect. For instance, morphine, 60 mg, every 8 hours would be 240 mg in 24 hours. To change this dose to oxycodone, which has a conversion factor of 1:0.66, multiply 240 times 0.66 (160 mg/d), and then start with a lower dose, such as 120 mg/d (40 mg every 8 hours). The exception may be with transdermal fentanyl (see Fentanyl, page 1090) and methadone, which can be difficult to convert because of the pharmacokinetic variability (see Methadone, page 1089). Again, methadone should be prescribed only by physicians who have significant knowledge of its complex pharmacology and experience prescribing it.

### Conclusions

Unrelieved pain makes cancer one of the most feared diseases, and opioids are the mainstay of pain treatment. Knowledge regarding the use of opioids can improve the care provided to patients with cancer. Recognizing that genetics and other drugs may alter opioid metabolism, the best way to treat pain is to believe the patient’s subjective report regarding the relief obtained from a specific opioid dose and the side effects experienced. Poor pain control suggests the need for dose titration, and poor pain control with intolerable symptoms suggests the need for opioid rotation.

### References


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**Table 1 Opioid Conversions**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial PO Dose</th>
<th>PO:IV</th>
<th>PO MS:PO Drug</th>
<th>PO Drug:PO MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>2.5–15 mg</td>
<td>3:1</td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1, 2, or 4 mg</td>
<td>4:1</td>
<td>1:0.25</td>
<td>1:4</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>5 or 10 mg</td>
<td>N/A</td>
<td>1:0.66</td>
<td>1:1.5</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>2.5, 5, or 10 mg</td>
<td>10:1</td>
<td>1:0.33</td>
<td>1:3</td>
</tr>
<tr>
<td>Methadone</td>
<td>2.5 or 5 mg</td>
<td>2:1</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>TD fentanyl</td>
<td>25 mcg/h</td>
<td>TD = IV/h</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; MS, morphine; N/A, not applicable; PO, oral; TD, transdermal.

*See Table 2.
†See fentanyl section.

**Table 2 Oral Morphine to Methadone Conversion**

<table>
<thead>
<tr>
<th>PO MS Dose</th>
<th>MS:Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–90 mg</td>
<td>4:1</td>
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<tr>
<td>90–300 mg</td>
<td>8:1</td>
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<tr>
<td>300–800 mg</td>
<td>12:1</td>
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<tr>
<td>800–1000 mg</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt; 1000 mg</td>
<td>20:1</td>
</tr>
</tbody>
</table>

Abbreviations: MS, morphine; PO, orally.
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47. Xiao W, Naso L, Bennett GJ. Experimental studies of potential analgesics for the treatment of chemotherapy-evoked painful


