

# Commonsense Oxycodone Prescribing & Safety

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## Key Practice Pointers for Oxycodone IR and CR

### Oxycodone Overall

- Oxycodone is approved for treating acute or chronic pain that is moderate to severe.
- Oxycodone is approximately 1.5 times more potent than morphine (20 mg oxycodone = 30 mg morphine).
- At equianalgesic doses, oxycodone IR or CR are equivalent in effectiveness to morphine IR or CR.
- When switching opioids, there is incomplete cross-tolerance, so the dose of the second agent is typically reduced by 33% to 50% to prevent toxicity.
- When opioids are used with adjuvant agents, there is enhanced analgesia; however, doses of combination products are limited by their nonopioid ingredients.
- When used in combination with other CNS depressants, oxycodone should be started at 30% to 50% of the usual daily dose.
- “Plain” oxycodone, rather than combination products, may be more beneficial for patients who have liver disease or risk factors for liver disease.
- In severe hepatic impairment, oxycodone should be initiated at 30% to 50% of the usual dose and titrated cautiously to avoid respiratory depression.
- Use oxycodone cautiously in renal dysfunction, and avoid using it with hemodialysis.
- No oxycodone dosing adjustments are required in patients older than age 65.
- Suggested upward adjustments of oxycodone are 25% to 50% of the current daily dose every 1-2 days.
- If a dose increase does not produce increased analgesia, maintain previously effective oxycodone dose and investigate other analgesic options. Raising the dose without notable analgesic benefit only furthers the risk of adverse effects.
- During chronic use, opioids have not been shown to specifically affect driving ability. However patients should be cautious about operating any vehicle until they feel that they will not be too sedated to drive. This is particularly important following initiation of therapy or a dose increase.

### Oxycodone IR

- Oxycodone IR is similar to morphine with an onset of about 15 minutes, peak blood levels after about 1 hour, and a 4 hour duration of action.
- Oxycodone IR formulations do not show any particular advantage or disadvantage compared with other short-acting opioids.

### Oxycodone CR

- At equivalent doses, there is no difference in analgesic effect between CR and IR oxycodone: eg, oxycodone CR 10 mg bid = oxycodone IR 5 mg QID.
- Oxycodone CR tablets must be swallowed whole; any tampering may be harmful.

**Abbreviations used in this document:** bid = twice daily; CR, ER, SR = long-acting formulations (Controlled-Release, Extended-Release, Sustained-Release); IR = short-acting formulation (immediate-release); prn = as needed; qid = four times daily; qd = once daily; tid = three times daily.

## Introduction

Oxycodone is FDA-approved for treating moderate to severe pain that is either acute or chronic in nature. It has been widely used in pain management practice for decades but has recently been receiving much negative attention due to abuse, overdose, and deaths associated with the controlled-release formulation. So, in the overall approach to pain management, what is the appropriate role of oxycodone?

A number of questions must be considered when choosing therapy. For example, how does oxycodone compare with other opioids? When should immediate-release oxycodone be used rather than the controlled-release product? Is oxycodone in combination with acetaminophen or an NSAID better than “plain” oxycodone? Are the risks of using oxycodone greater than the benefits? How can risks of misuse or abuse be minimized when prescribing oxycodone?

Those and other commonsense questions concerning oxycodone prescribing, safety, and risk management are addressed in this paper.

*Oxycodone is approved for moderate to severe pain that is either acute or chronic.*

A range of oxycodone products is available in the United States as single-agent immediate-release (IR) formulations – including tablets, capsules, and oral solution – and in combination with acetaminophen, aspirin, or ibuprofen (see **Table**). Oral oxycodone solutions must be used cautiously so the 2 different strengths – 1 mg/mL vs 20 mg/mL – are not confused. Many of the IR oxycodone products are more economically available as generics.

A controlled-release (CR) oxycodone product, sometimes referred to as long-acting or long-duration, is available (OxyContin®, Purdue Pharma LP), and generic versions of oxycodone CR have been marketed in recent years. Outside the US, oxycodone also is available as an injection (United Kingdom) and a rectal suppository (United Kingdom, Canada, and Australia). An intranasal formulation has been tested, although with variable results [Takala et al. 1997].

| Oxycodone Formulations                              |  |
|---|--|
| Oxycodone HCl                                       | 5 mg capsule; 5 mg, 15 mg, 30 mg tablet        |
| Oxycodone (mg) / Acetaminophen (mg)                 | 5/325, 7.5/325, 10/325; 5/500, 7.5/500; 10/650 |
| Oxycodone (mg) / Aspirin (mg)                       | 2.5/325, 5/325                                 |
| Oxycodone (mg) / Ibuprofen (mg)                     | 5/400  |
| Oxycodone (mg) / Acetaminophen (mg) / Caffeine (mg) | 4.5/325/0.38                                   |
| Oxycodone HCl Oral Solution                         | 1 mg/mL  |
| Oxycodone HCl Concentrate                           | 20 mg/mL                                       |
| Oxycodone CR (generic)                              | 20 mg, 40 mg                                   |
| OxyContin® (oxycodone CR brand)                     | 10 mg, 20 mg, 40 mg, 80mg, 160mg               |

Source: Red Book 2005, 2007

## Oxycodone Pharmacology

Oxycodone is a DEA Schedule II semisynthetic opioid analgesic derived from thebaine, an alkaloid in opium. Originally developed in 1916 and introduced into clinical practice in Germany in 1917 [Kalso 2005], it is a mu- and kappa-opioid receptor agonist structurally related to codeine, but it behaves pharmacodynamically like morphine. In addition to analgesia, oxycodone can produce anxiolysis, euphoria, feelings of relaxation, and cough suppression, as well as respiratory depression, constipation, miosis, sweating, and somnolence.

While its potency is approximately 1.5 times greater than morphine [Benziger et al. 1997], oxycodone has a similar onset, duration of action, and effectiveness in equianalgesic dosing (20mg of oxycodone = 30mg morphine; see **Table**). The minimum effective plasma concentration varies between patients, which occurs with all opioids. Also consistent with other pure opioids (as compared with mixed agonist/antagonist agents), oxycodone usually does not have a “ceiling effect” (a point where increasing the dose does not increase analgesia).

*Oxycodone potency is approximately 1.5 times greater than morphine (eg, 20mg of oxycodone = 30mg morphine)*

### Absorption and Bioavailability

The oral bioavailability of oxycodone is 2-3 times greater than for morphine [Leow et al. 1992; Poyhia et al. 1992; Sawe et al. 1981] (see **Table**). Despite differences in bioavailability, the pharmacodynamic behavior of immediate-release oxycodone is similar to morphine with an onset of action within about 15 minutes and peak blood levels after about 1 hour [Poyhia et al. 1992].

In contrast, controlled-release oxycodone exhibits biphasic absorption, with an immediate-release component having an absorption half-life of 37 minutes, accounting for 38% of the total dose. The second phase is a slow release component with an average absorption half-life of 6.2 hours [Mandema et al.

| Pharmacokinetics Immediate-Release Oxycodone vs Morphine |           |              |
|--|-----------|--------------|
|  | Oxy IR    | Morph IR     |
| Bioavailability  | 60% - 87% | 30%          |
| Onset of Action  | 15 min    | 15 min       |
| Time to Peak Level                                       | 1.4 hr    | 1.5 – 2hr    |
| Duration of Action                                       | 4 hr      | 4 hr         |
| Half-Life  | 3.2 hr    | 1.4 - 4.5 hr |

| Pharmacokinetics Controlled-Release Oxycodone |            |
|---|------------|
| Peak Pain Relief                              | 1 hr       |
| Time to Peak Blood Level                      | 2-3 hr     |
| Half-Life                                     | 4.5 - 8 hr |
| Time to Steady State                          | 24 - 36 hr |

1996]. Peak pain relief occurs in approximately 1 hour, but peak blood levels are not reached for 2-3 hours [Mandema et al. 1996; Poyhia et al. 1992; Reder et al. 1996]. This complex release mechanism requires that the tablets be swallowed whole — crushing, splitting, or other tampering alters the release mechanism and may lead to drug overdose.

Absorption rate and extent have been found comparable between one 20 mg and two 10 mg oxycodone CR tablets [Benziger et al. 1997]. And, while absorption is generally not affected by food, a high-fat meal increases the extent of absorption and overall drug concentration (the AUC) while decreasing peak blood level [Benziger et al. 1996]. If doses are consistently taken at the same times during the day (preferably apart from meals), the clinical effects should not be altered significantly by food.

### Metabolism, Excretion

Oxycodone has two metabolic pathways including N-demethylation, accounting for 45% of a dose, and O-demethylation, which accounts for 10% of a dose. The principal active metabolite via the first pathway is *noroxycodone*, which has only weak affinity for the mu-opioid receptor [Lalovic et al. 2006]. A minor active metabolite is *oxymorphone*, which is 30 times more potent than oral morphine [APS 2003]; however, it has little clinical activity because it is produced in such small amounts.

The second metabolic pathway uses CYP450 2D6 enzymes. This may be genetically influenced, with some patients having multiple copies of the 2D6 gene, leading to rapid metabolism, or no gene at all, engendering slow or absent metabolism. Several other medications are metabolized via this pathway. However, research has shown very little clinical effect on oxycodone when this pathway is inhibited. Compared with its metabolites, the parent oxycodone compound contributes the major portion of pharmacodynamic (and analgesic) activity [Heiskanen et al. 1998; Kaiko et al. 1996; Lalovic et al. 2006].

Renal excretion of free oxycodone is estimated to be from 8% to 19%. Metabolites are excreted in the urine as conjugated oxycodone and oxymorphone, and as both free and conjugated noroxycodone [Poyhia et al. 1992]. Excretion and clearance of oxycodone are affected by renal or hepatic disease, influencing the need for dosing adjustments (discussed below).

*Compared with its metabolites, the parent oxycodone compound contributes the greatest portion of pharmacodynamic and analgesic activity.*

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## Oxycodone Dosing

Patients who have not been taking opioids should be started on the lowest recommended oxycodone dose, with escalation as needed for pain control. Recommended starting doses of oxycodone IR are *5 mg to 15 mg every 4 hours*. The typical adult dose ends up being *10 mg to 30 mg every 4 hours*, reflecting the degree of pain the patient is experiencing [Oxycodone PI 2005].

The starting dose of oxycodone CR in opioid-naïve patients is *10 mg every 12 hours*. The dose may be increased every 1-2 days, as it takes 24 to 36 hours to reach steady state after a change in dose [OxyContin PI 2007].

Suggested upward adjustments are 25%-50% of the current daily dose (eg, an increase of 10-20 mg in a patient taking 20 mg twice daily) [Kaplan et al. 1998]. For patients switching between IR and CR tablets, the total daily dose of oxycodone should remain about the same (eg, oxycodone IR 5 mg q 6 hr = 10 mg q 12 hr oxycodone CR) [Kaplan et al. 1998; Stambaugh et al. 2001].

**Author's Note:** In an opioid-naïve patient, I would recommend starting with an immediate-release product and titrate upward to adequate pain relief, followed by conversion to a long-acting product to improve compliance and avoid erratic blood levels.

## Equianalgesic Conversions

There is significant inter-patient variability in response to opioids. Kalso et al [2004] reviewed several opioid studies in the noncancer pain population and found a 30% mean decrease in pain (80% with at least one adverse effect). Watson and colleagues [2004] surveyed noncancer patients and found that one-third of patients reported a reduction from severe to moderate pain. Individual response depends on a number of factors: comorbid medical conditions may predispose patients to opioid toxicity, pain pathophysiology may be unresponsive to opioids, and pharmacogenetic variations in mu-receptor conformation may alter sensitivity to opioids. One strategy to improve responsiveness is to rotate opioids, involving an imprecise process of calculating a new regimen based on equianalgesic doses [Anderson et al. 2001].

Opioids have incomplete cross-tolerance, so the dose of the second agent is typically reduced by 33%-50% to prevent toxicity. However in cancer patients, if the disease process is expected to progress, the pain would be expected to escalate as well, and dose reduction may be detrimental to optimizing pain control.

Published oral morphine-to-oxycodone equianalgesic dose ratios range from 1-to-1 to 2.3-to-1, reflecting the differences in bioavailability and incomplete cross-tolerance. Practitioners should always take the patient’s clinical status into account when determining whether a more conservative or more aggressive conversion is needed. Conversion factors published by the America Pain Society [2003] are a dependable resource (see excerpt in **Table**). With long-duration opioids, some practitioners employ a more conservative conversion and use an immediate-release opioid for initial titration to optimal analgesia.

| Equianalgesic Conversions                 |        |        |
|---|--------|--------|
|   | IM/IV  | PO     |
| Morphine                                  | 10 mg  | 30 mg  |
| Oxycodone                                 | –      | 20 mg  |
| Hydrocodone                               | –      | 20 mg  |
| Hydromorphone                             | 1.5 mg | 7.5 mg |
| <i>Partial list adapted from APS 2003</i> |        |        |

### EXAMPLE OF DOSING CONVERSION

A patient has been taking controlled release (CR) morphine, 90 mg bid, for pain related to degenerative joint disease in his spine. He reports that he can no longer tolerate the nausea, despite using an antiemetic, so he will be switched to oxycodone. What would be the appropriate starting dose?

- > Total daily dose of morphine = 180 mg.
- > Conversion: 30 mg oral morphine = 20 mg oral oxycodone.
- > # mg/day oxycodone / 180 mg/day morphine = 20 mg oxycodone / 30 mg morphine
- > # mg/day oxycodone = 2/3 x 180 mg/day = 120 mg/day oxycodone
- > Reduce by 1/3 due to incomplete cross-tolerance between opioids = 80 mg/day oxycodone

Since oxycodone is available in both long-acting and short-acting formulations, either of the following might be appropriate...

- oxycodone CR 40 mg PO bid, or...
- oxycodone CR 20 mg PO tid plus a short-acting oxycodone (or oxycodone/acetaminophen) product 5-10 mg q6h as needed

**Note:** If the calculation results in a dose between 2 available dosage forms (eg, 30 mg, and either 20 mg or 40 mg tabs are available), choose the lower strength product and allow titration upward if the patient requires it. Many times, dosing titration is done with a short-acting agent for more precise adjustments.

## Special Considerations

### Renal Disease

Excretion of oxycodone is impaired with renal compromise [Poyhia et al. 1992]. In the presence of renal failure, the half-life is significantly prolonged for both the parent compound and metabolites (by more than 20 hours in one patient [Kirvela et al. 1996]). Some authors have recommended that oxycodone be used with caution in patients with renal dysfunction and avoided in those undergoing hemodialysis, as there is no data to support its safety in this situation [Dean, 2004]. A recent case report describes significant respiratory depression in a hemodialysis patient who received several doses of oxycodone-acetaminophen over several days [Foral et al. 2007] (see **Table**).

| Oxycodone Rx Special Considerations                   |  |
|---|--|
| Kidney Disease  | Start at 50% of the usual dose. Titrate cautiously. Avoid products containing ibuprofen. Avoid during hemodialysis.        |
| Liver Disease   | Start at 30%-50% of the usual dose. Titrate cautiously to avoid respiratory depression. Avoid products with acetaminophen. |
| Elderly Patients                                      | Dosing adjustments not necessary unless the patient is debilitated.  |
| Patients Taking CNS Depressants (eg, benzodiazepines) | Start with 30%-50% of the usual dose.  |

### Hepatic Disease

Clearance of oxycodone is impaired in the presence of liver disease, requiring a dose reduction. Patients with mild or moderate hepatic dysfunction exhibit accumulation of oxycodone: a 50% increase in peak blood levels and a 95% increase in overall blood concentrations (AUC). For the oxymorphone metabolite, liver disease results in a 30% lower peak blood level and 40% lower AUC (which is expected because metabolites are not being produced as efficiently) [OxyContin PI 2007].

Patients with cirrhosis exhibit a significant reduction in clearance of oxycodone, with a half-life of about 14 hours [Tallgren et al. 1997], which correlates with an increase in respiratory depression. Patients with severe hepatic impairment should be initiated at 30% to 50% of the usual dose and should be titrated cautiously to avoid respiratory depression [Lugo and Kern 2004] (see **Table**).

### Elderly Patients

No dosing adjustments are required in patients older than 65 years of age. The plasma concentration in these patients is about 15% greater than in younger patients, but no adverse clinical consequences have been noted [Coluzzi and Mattia, 2005]. However, debilitated elderly patients may require a dosage reduction (see **Table**).

### Drug Interactions

The most significant drug-drug interactions with oxycodone are the same as with most other opioids. The greatest of these is concurrent administration of other CNS depressants, such as alcohol, benzodiazepines, barbiturates, or other opioids, which increases the risk of respiratory depression. It is suggested that oxycodone should be started at 30% to 50% of the usual daily dose when used in combination with other CNS depressants [OxyContin PI, 2007] (see **Table**).

The potential for hepatic enzymes to variably influence metabolism of oxycodone was discussed above and is unlikely to significantly affect oxycodone, even when using a strong 2D6 inhibitor like quinidine [Heiskanen et al. 1998]. There have been case reports of fluoxetine inhibiting the 2D6 enzymes [Otton et al. 1993], and patients taking cyclosporine also have been reported to be at risk for a drug interaction with oxycodone [Rosebraugh

**Editor's Note:** For a more complete discussion of opioid safety in patients with renal or hepatic dysfunction, see Johnson 2007 [listed in references with URL link].

***Start at 30% - 50% of the usual daily dose when used in combination with other CNS depressants***

et al. 2001], but neither of these has been reported widely in clinical practice. Serotonin syndrome during concurrent use of serotonergic agents and oxycodone has been reported [Karunatilake and Buckley 2006; Rosebraugh et al. 2001], possibly because opioids increase serotonin concentrations in the CNS, but this is not frequently observed in clinical practice.

### Adverse Effects & Safety

The greatest risks when prescribing any opioids are overdose and, potentially, death. Prescribers take great care to avoid this; however, a recent report showed that the number of unintentional opioid-associated deaths in the US is growing. Mortality due to drug poisoning overall increased by roughly 68% between 1999 and 2004 [CDC 2007], and this trend has been linked to increasing numbers of deaths associated with prescription opioid analgesics [Paulozzi et al. 2006]. Despite this, there is a need to treat pain effectively with adequate doses of potent analgesics, including oxycodone.

Even when opioids are used appropriately for pain management by educated healthcare providers, there are inevitable adverse effects in a proportion of patients. Respiratory depression is obviously a concern, but is less likely to occur than some of the other common adverse effects; furthermore, its likelihood diminishes with continued use due to tolerance, as long as doses are not increased excessively or other CNS depressants added.

Oxycodone may cause constipation, nausea, and sedation, like all opioids; although some authors report that it is less likely to cause hallucinations, nausea, or itching than morphine [Kalso and Vainio 1990; Mucci-LoRusso et al. 1998]. Opioids also are associated with histamine-related side effects like itching, flushing, and rash; however, oxycodone's semisynthetic chemistry incurs less histamine release (compared with natural opioids like morphine and codeine) and is usually better tolerated. The **Table** lists common adverse effects with oxycodone.

Oxycodone's adverse effects are associated with blood levels of the drug; therefore, *a dose reduction may alleviate or reduce the severity of CNS effects such as sedation, dizziness, and respiratory depression*. If a reduction is not feasible due to a patient's escalating pain (eg, a patient with cancer), an opioid rotation may be a reasonable option.

For some of the common adverse effects, such as sedation and nausea, patients develop tolerance with continued use. For adverse effects that do not subside with continued use, concurrent pharmacotherapy may be given to reduce severity or prevent symptoms, such as a bowel regimen for constipation [see Goodheart and Leavitt 2006]. Other effects, such as sweating, are not predictable, preventable, or treatable. If these symptoms become intolerable, an opioid rotation may be necessary.

One of the concerns with opioids shared by patients, healthcare providers, and employers is the extent of cognitive impairment caused by these agents. Patients may ask if they should refrain from driving while taking oxycodone. Several investigators have evaluated the effect of opioids on cognitive and psychomotor function with inconclusive results. Hanks et al [1995] found that single doses of immediate-release morphine caused some difficulty with memory retrieval, but was not as significant as that seen with lorazepam. Drowsiness and cognitive dysfunction may be predicted early in therapy or with dose increases, but with chronic use of opioids, tolerance to these effects develops and they theoretically would not cause impairment. Caution should always

| Common Oxycodone Adverse Effects<br>(% of Patients Affected) |     |
|--|-----|
| Constipation   | 26% |
| Nausea   | 27% |
| Somnolence   | 24% |
| Dizziness  | 16% |
| Vomiting   | 14% |
| Pruritus   | 12% |
| Headache   | 8%  |
| Dry mouth  | 7%  |
| Asthenia   | 7%  |
| Sweating   | 6%  |
| <i>Source: OxyContin PI 2007</i>                             |     |

**Author's Comment:** To date, opioids have not been shown to specifically affect driving ability with chronic use. However, patients should be very cautious about operating any motor vehicle until they feel that they will not be too sedated to drive. This is particularly important following initiation of therapy or a dose increase, when blood levels are not at steady state.

be exercised when using opioids and patients should not attempt to drive or operate heavy machinery until they know how they respond to the medication.

Another risk of long-term opioid therapy is the suppression of gonadotropin hormones, including testosterone, leuteinizing hormone, estradiol, and progesterone. This may lead to sexual dysfunction, osteopenia, and osteoporosis [Abs et al 2000; Daniell 2002]. This has been reported with several opioids, although no studies have specifically examined oxycodone. The adverse sequelae are related to degree and duration of gonadotropin suppression. Treatment usually includes hormone replacement therapy and osteoporosis medications where appropriate.

Opioid-induced hyperalgesia is another phenomenon that is a concern with opioid use [Chang et al. 2007]. This presents clinically as an increase in pain with opioid administration or dose increase. Sometimes it is difficult to determine whether a patient is exhibiting opioid tolerance or hyperalgesia. If tolerance is occurring, an opioid dose increase should produce an increase in analgesia. If this does not occur, or if pain increases, hyperalgesia may be a factor.

Physiologic tolerance and dependence (*not* addiction) are expected consequences with long-term use of oxycodone, or any opioid. These should be managed on an individualized basis and handled with either slow titration for dose increases or gradual dose reductions during tapering to prevent withdrawal symptoms.

Psychological dependence, or addiction, cannot always be predicted. Very few patients taking opioids continuously for pain will exhibit addictive behavior; however, patients with a history of substance addiction or active addiction to other drugs or alcohol are at risk for addiction with oxycodone as well. (See Joint Statement... [1996] for definitions of tolerance, dependence, addiction, and pseudoaddiction.)

It must be recognized that there is an overlap of patients who have opioid addiction and those who have legitimate pain. Such patients may require aggressive pain relief measures, but opioid therapy must be handled judiciously, ideally involving experts in pain management and in addiction medicine.

***If tolerance is occurring, an opioid dose increase should produce an increase in analgesia. If this does not occur, or if pain increases, hyperalgesia may be a factor.***

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## Oxycodone Prescribing Decisions: FAQs

In deciding on an appropriate opioid analgesic for patients with acute or chronic pain, a number of questions arise. To the extent possible, decisions should be based on available evidence, as noted in the following FAQs (Frequently Asked Questions... and answers).

### Is oxycodone as effective as other opioids?

Pain management usually must be individualized to patient needs, especially when using opioids. Different factors determine a patient's response to a particular agent, including genetics, opioid receptor sensitivity in the central nervous system, and tolerability of a particular agent. Semisynthetic opioids, like oxycodone, tend to be tolerated better than the natural opioids, like morphine and codeine. The semisynthetics cause less histamine release than the natural opioids, and, therefore, produce less vasodilation, flushing, itching, and/or rash. Many times patients who report an opioid allergy actually are experiencing symptoms occurring due to histamine release.

Semisynthetic opioids like oxycodone also tend to be less constipating, although this is highly dependent on the patient. Therefore, patients who do not tolerate natural opioids may do very well with oxycodone.

***Patients who do not tolerate natural opioids, like morphine or codeine, may do well with oxycodone.***



In terms of analgesic effectiveness, several investigators have found that oxycodone CR is equivalent to morphine CR [Rischitelli and Karbowicz 2002]. This has been noted in several studies in the cancer population [Bruera et al. 1998; Heiskanen et al. 2000; Mucci-LoRusso et al. 1998]. However, one study showed that patients consumed significantly more rescue doses and average pain intensities were significantly greater with oxycodone CR [Heiskanen and Kalso 1997]. At the same time, more patients had vomiting with morphine and more patients experienced constipation with oxycodone.

Heiskanen et al [2000] and Mucci-LoRusso et al [1998] found less fluctuation in blood levels when using oxycodone CR, compared with morphine CR. However, Nicholson et al [2006] concluded that oxycodone CR may need to be administered 3 or 4 times daily, which could be a disadvantage.

In noncancer pain, morphine CR was found to be equivalent to oxycodone CR in terms of pain reduction, sleep quality, and most other quality of life scores. However, only the morphine product achieved a clinically meaningful reduction in pain (difference of 2 or more points on a 0 to 10 Likert scale) at 8 and at 24 weeks [Nicholson et al 2006].

Morphine CR is generally chosen as the first-line long-duration opioid because of its familiarity and safety, compared with methadone, and due to its lower cost and lower risk of diversion and abuse, compared with oxycodone CR. If patients do not tolerate morphine and prescribers are not comfortable prescribing methadone, oxycodone CR is a reasonable third-choice option [VA Criteria 2003].

As for immediate-release oxycodone products, they are comparable to their hydrocodone counterparts for acute pain management [Marco et al. 2005]. Oxycodone IR formulations do not show any particular advantage or disadvantage compared with other short-acting opioids. Therefore choosing an agent is based on nonpharmacologic factors, such as cost, insurance coverage, and nonopioid components, if applicable. Use of a particular short-acting agent also is generally influenced by prescriber preference and patient response.

**Author's Note** – because of its safety issues, expense, and need for multiple daily doses in some patients, oxycodone CR is considered a 3<sup>rd</sup> line agent for chronic pain.

### When should an immediate-release (IR) oxycodone be used?

Oxycodone IR is very effective for use in acute pain and for titration in chronic therapy. It is commonly given for acute pain in the post-operative setting [Fricke et al. 2002; Gammaitoni et al. 2003]. Short-acting oxycodone products also are used in the emergency department and the outpatient clinic after an acute injury such as back pain [Palangio et al. 2002] or bone fracture [Marco et al. 2005].

*Oxycodone IR is very effective for use in acute pain and for titration in chronic therapy.*

In cancer pain, it is common to use short-acting agents for “breakthrough” pain, in addition to a long-duration agent for “baseline” analgesia. Short-acting agents also help patients titrate gradually to the next higher strength of a long-duration agent. Particularly in the setting of hospice care, there is a need to provide analgesia with a fast onset of pain relief, and oxycodone provides pain relief onset within 15 minutes.

For chronic noncancer pain the use of short-acting opioids is a bit more controversial. Some practitioners believe only long-duration opioids should be used for chronic pain so that the patient is not focused on the clock in anticipation of the next dose. Others believe that short-acting opioids can and should be used, either as a scheduled regimen (eg, 1 dose 4 times daily) or on an “as needed” (prn) basis (eg, 1 dose every 4-6 hours prn) for acute flares in chronic pain. Since there is no difference in analgesic effect between short-acting and long-acting oxycodone [Kaplan et al. 1998], providers must weigh the risks and benefits for each patient and situation and decide what is in the patient's best interest.

There are certainly situations when a short-acting opioid is advantageous. An example of this would be an elderly patient with osteoarthritis who has reached the point of needing an opioid to maintain daily activities. The short half-life of IR agents may prevent cognitive difficulties potentially experienced when serum levels remain elevated with long-duration agents.

*Short-acting opioids may cause fewer cognitive difficulties in elderly patients than long-acting agents.*

### Is a combination product or “plain” oxycodone preferred?

There is an enhanced analgesic effect when opioids are used in conjunction with an NSAID or acetaminophen. Therefore, using combination products may confer better pain relief along with patient convenience and increased compliance; that is, patients may take one combination tablet instead of 2 separate medications.

For the patient with osteoarthritis mentioned above, the combination product may be a good choice. Acetaminophen is regarded as first line therapy for osteoarthritis, so it is convenient to use a combination product that allows the nonopioid to be given with each dose of oxycodone. The doses still must be taken frequently throughout the day (usually every 6 hours on either a scheduled or prn basis); however, in elderly patients, this may be an advantage, as mentioned above.

The combination products must be used with caution, and their dosing is limited by the nonopioid ingredients. Opioids and NSAIDs are used in combination frequently, as NSAIDs are also considered first-line therapy for both rheumatoid arthritis and osteoarthritis, as well as any type of inflammatory pain. While this is a very effective combination, one must also take into consideration the risks associated with either short-term or long-term NSAID therapy, specifically the risks of GI bleeding, platelet dysfunction, acute renal failure, and possibly respiratory or cardiovascular events [FDA NSAIDs 2007]. Risks of GI bleeding and platelet dysfunction have historically limited the use of aspirin-containing products.

*Combination products must be used with caution, and doses of these products are limited by their nonopioid ingredients.*

With the introduction of the acetaminophen/oxycodone combinations and the recommendations of acetaminophen as a first-line therapy for osteoarthritis, aspirin for analgesic use has fallen out of favor. However, the recommended maximum daily dose of acetaminophen is 4000 mg or less to avoid liver toxicity. For example, a patient may take up to 12 tablets daily of a product that contains 325 mg of acetaminophen, but only 8 tablets of a product that contains 500 mg. The combination oxycodone/ibuprofen product is restricted to use in the acute pain setting and has a maximum recommended dose of 4 tablets daily for a 7 day course of therapy [Combunox<sup>®</sup> PI 2004].

*When using an oxycodone-acetaminophen combination product, monitor the total daily dose of acetaminophen. Daily doses greater than 4000 mg can be hepatotoxic.*

Use of “plain,” single-agent, oxycodone may be beneficial for patients who have liver disease or have risk factors for liver disease (such as avoiding acetaminophen in patients who drink alcohol). It also may be beneficial in patients who have significant comorbidities, such as diabetes, renal insufficiency, coronary artery disease, or congestive heart failure (to avoid ibuprofen). Single-agent oxycodone may also be more beneficial than the combination products if a patient requires frequent changes in therapy. Giving the oxycodone and the nonopioid agent separately allows more freedom to individualize therapy, such as exchanging acetaminophen for an NSAID (or conversely) without altering the opioid component.

## When should the CR (long-duration) oxycodone be used?

Oxycodone CR is intended for use in patients with moderate to severe pain who require around-the-clock pain control on a long-term basis. It is not intended for intermittent administration, nor is it indicated for the acute postoperative setting unless the patient has been taking it preoperatively. In equivalent daily dosing, oxycodone CR is considered to be bioequivalent to the immediate-release formulation [Mandema et al. 1996; Reder et al. 1996; Stambaugh et al. 2001].

During long-term use, as with all long-acting analgesics, oxycodone CR offers increased compliance, as the patient is required to take fewer doses throughout the day. The CR formulation also removes the need for “clock watching” and the anxiety about taking doses at the right time to prevent an increase in pain.

Oxycodone CR has been demonstrated as effective in chronic painful conditions, such as painful diabetic neuropathy [Watson et al. 2003], chronic back pain [Hale et al. 1999], osteoarthritis [Caldwell et al. 1999; Roth et al. 2000], and cancer pain [Kaplan et al. 1998]. Recommended dosing for oxycodone CR is 1 dose every 12 hours; however, in research studies [Nicholson et al. 2006], as well as in clinical practice, it is not uncommon for patients to require administration 3 to 4 times per day, which decreases the compliance advantage of a long-duration formulation.

An important caution about the use of oxycodone CR products is that the tablets must be swallowed whole. If they are crushed, split, or otherwise altered, the medication-release mechanism is destroyed and may cause a large bolus dose to be delivered, possibly causing overdose and death. Hence, patients who might misuse the drug or have difficulty swallowing tablets are not good candidates for this product.

Altering the dosage form has caused oxycodone CR to become a widespread drug of abuse. Because of cost and concerns about diversion and abuse, several government agencies (eg, public-aid programs) have removed oxycodone CR from their “preferred” lists of medications [eg, Preferred Drug List... 2007]. In this regard, the US Veterans Administration has published a guidance paper outlining criteria for the safe use of oxycodone CR [VA Criteria 2003]. This document contains evidence-based information about the drug, as well as cost comparison and equianalgesic dosing tables.

## Is oxycodone CR a better choice than oxycodone IR?

Several authors have compared the analgesic effectiveness of long-acting with short-acting oxycodone agents and found that they are equally effective [Caldwell et al. 1999; Hale et al. 1999; Kaplan et al. 1998; Parris et al. 1998]. Rischitelli and Karbowicz [2002] did an extensive literature review and also concluded that the immediate-release and controlled-release products were analgesically equivalent.

Furthermore, the two formulations also were comparable in adverse effects, although some studies have reported fewer adverse effects with the controlled-release formulation [Kaplan et al. 1998; Caldwell et al. 1999]. There is a potential advantage with the controlled-release agent if it can be dosed only twice daily; however, if it must be taken 3 to 4 times daily, the immediate-release product is a more cost-effective choice, with or without a nonopioid component in combination.

## Can oxycodone products be used safely in children?

Oxycodone has not been studied in patients under age 18, and the FDA has not approved it for pediatric use. Although some sources offer dosing suggestions in pediatric patients [Bonica 2001], the use of oxycodone is not currently considered a standard therapy for analgesia in chil-

***Oxycodone IR and CR are bioequivalent in effectiveness: 5 mg IR qid = 10 mg CR bid.***

***Oxycodone CR tablets must be swallowed whole. Any alteration of the tablet may be hazardous.***

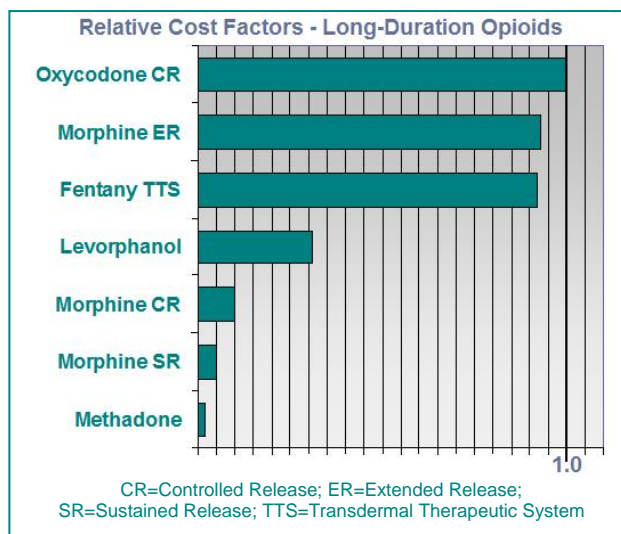
***Long-acting and short-acting oxycodone are equivalent in terms of analgesic effectiveness.***

dren. Furthermore, young children present a challenge in that they may be unwilling or unable to swallow oral tablets.

### How does oxycodone CR compare in cost with other long-duration opioids?

Cost is frequently a factor when choosing analgesic therapy, and monthly costs of long-duration opioids can vary considerably, depending on how calculations are done. Using actual doses of different opioids required for achieving comparably adequate analgesia would be best in determining cost differentials.

The **Table** depicts relative costs of long-duration opioids compared with oxycodone CR (baseline factor of 1.0) calculated by the US Veterans Administration [VA 2003], using manufacturer-recommended initial dosing and equianalgesic dose conversion ratios recommended by the American Pain Society [APS 2003]. Drug prices were based on lowest available costs of products in the VA formulary as of June 2003; however, current product availability (including generics) and pricing for individual purchasing organizations may vary.



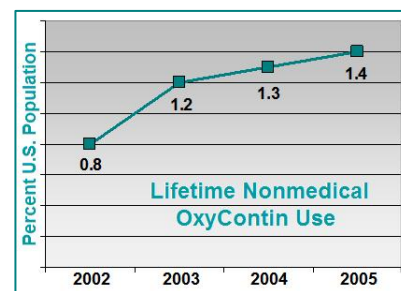
According to the VA analysis, oxycodone CR was a relatively premium-priced choice for long-duration opioid analgesia, more expensive than morphine CR by a factor of about 10. The least expensive agent was methadone. The VA and others [Rischitelli and Karbowicz 2002] concluded that, due to similar efficacy, comparable adverse effects, and substantial cost savings, morphine CR or SR might be a preferred choice, and methadone secondarily. Oxycodone CR would be reserved for patients having intolerable adverse effects from morphine or methadone that prevent adequate titration for desired analgesia.

## Oxycodone Risk Management: FAQs

### How extensive is the problem of oxycodone abuse?

Abuse and misuse of prescription opioid analgesics is not new. It is hardly surprising that, with the dawn of the “Decade of Pain Control and Research” in 2001, there would be greater use of opioid analgesics and, consequently, greater abuse of this therapy as well. Abuse of oxycodone was noted as early as the 1960’s when it was placed on the DEA’s Schedule II drug list, and reports of abuse increased substantially when the long-acting formulation (OxyContin) was introduced in 1996.

More recently, the FDA strengthened warnings of potential OxyContin diversion and abuse [FDA 2006], and trends in US national survey data portray the scope of the problem. Lifetime nonmedical use of OxyContin has been steadily increasing (see **Graph**), reaching more than 3 million persons in the US age 12 and older in 2005, according to the government’s National Survey on Drug Use and Health (NSDUH) [SAMHSA 2006].



The Drug Abuse Warning Network [SAMHSA 2007] reported that in 2005 (the most recent data available), drug abuse-related emergency department visits involving opioid analgesics rose 21% from 2004 to 2005. This is significant because the number of visits related to abuse of illicit drugs or alcohol was stable during this time. In 2005 alone, there were nearly 43,000

emergency department visits related to the nonmedical use of oxycodone products, exceeded only by incidents involving the misuse of hydrocodone products.

### Why has OxyContin® been so widely abused?

Oxycodone CR products offer a relatively large dose of drug per tablet, providing greater euphoria or other desired reinforcing effects. Whereas, a typical immediate-release oxycodone product may have only 5 mg to 10 mg of oxycodone per tablet, a long-acting formulation contains up to 160 mg in each tablet, and altering the dosage form leads to rapid release of the total dose. Those who abuse the drug usually do so by crushing the tablet and snorting or chewing it, or dissolving it in water for intravenous injection [SAMHSA 2006]. Unfortunately, some of those people have low opioid tolerance and/or may mix the drug with alcohol or other drugs, like benzodiazepines, resulting in overdose and/or death.

One reason the OxyContin brand product, in particular, has been so widely diverted for abuse is that selling it “on the street” is profitable. According to government estimates, the drug can garner upwards of \$1-per-milligram via illicit trafficking [SAMHSA 2006].

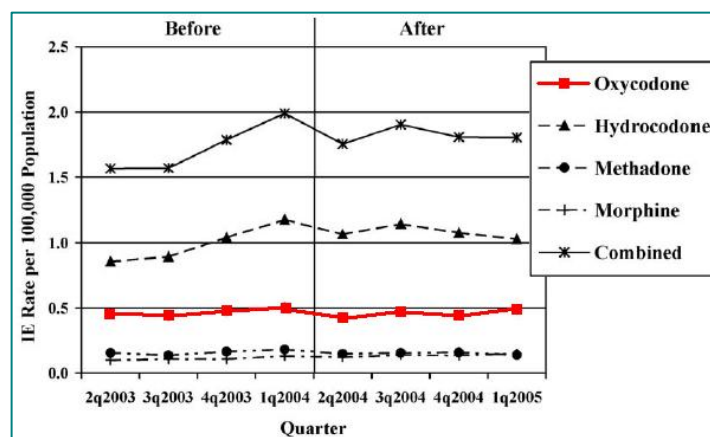
It also came to light that the manufacturer of OxyContin had falsely and aggressively promoted the product as producing less euphoria and being less addictive than other opioids, and as capable of abrupt discontinuation without patients suffering withdrawal symptoms. In May 2007, the manufacturer agreed to pay more than \$600 million in fines to resolve criminal charges and civil liabilities in connection with those deceptive practices [FDA News 2007].

Meanwhile, since OxyContin had been erroneously portrayed and perceived as a safer opioid alternative, it may have been over-prescribed as a first-line choice by well-meaning healthcare providers, rather than a third-line option as recommended by guidelines [eg, VA 2003]. And, it might have been inadvertently prescribed for patients most at risk for abusing an opioid medication. With greatly increasing amounts of OxyContin in circulation, often in the “wrong” hands, there was likely to be more abuse and associated overdoses or deaths. Expectedly, more prudent prescribing practices, and appropriate efforts to better manage the risks (discussed below), will significantly curtail the trend of oxycodone abuses and overdoses.

*Oxycodone CR products offer a relatively large dose of opioid, providing greater euphoria or other desired reinforcing effects.*

### Does generic oxycodone CR have the same risks of abuse and diversion?

When a generic oxycodone CR was approved by the FDA in 2004, there was concern that a less expensive version of OxyContin would spark a significant increase in prescribing and subsequent abuse and misuse of this drug. Bailey et al [2006] found no increase in rates of oxycodone CR abuse (IE rate, see **Graph**) in the year following release of the generic product, compared with the quarter prior to its release. There was no way to distinguish if the branded or generic oxycodone was involved in specific cases recorded; however, overall, there was *no increase* in rates of oxycodone abuse. Interestingly, the same trend was found for the other opioids investigated: hydrocodone, methadone, and morphine.



**Author’s Note:** Anecdotally, it has been observed that generic versions of popularly abused opioids usually are less appealing; persons buying drugs for illicit purposes prefer brand names

because they are more recognizable and the generics have a lower value “on the street,” which also makes them less alluring for drug dealers.

### How can healthcare providers minimize oxycodone misuse/abuse?

There is no evidence that oxycodone, compared with other opioid analgesics, is any more or any less prone to causing addiction – *IF* it is properly prescribed – and most people who take oxycodone for pain relief do not become addicted to it. However, like all opioids, it can produce physiologic dependence, whether used for pain or illicit purposes.

In general, a key to any risk management strategy is determining the individual risks of using an opioid as compared with the benefits. The first step is to evaluate the patient, which includes a thorough history-taking and physical examination as well as reviewing the patient’s previously recorded medical history and any prior medical assessments. Treatment plans should be developed with the patient’s (and any caregiver’s) input and commitment, so that all involved persons understand the recommended therapies and expectations.

If an opioid trial is initiated, periodic reassessment must be done, documenting efficacy and any adverse effects. After each assessment, a decision must be made to either continue the same course of therapy or alter that course. Again expectations must be explained to all parties involved, reassessed, and adjusted if necessary.

It is essential to document all of the above as part of the ongoing treatment plan. The American Academy of Pain Medicine and the American Pain Society published a brief list summarizing principles of good medical practice that can be applied to all aspects of medical care, including opioids in pain management (see **Table**).

More specific guidance for assessing, anticipating, and managing individual patient risks for oxycodone misuse or abuse is an important and complex subject, beyond the scope of this paper. A number of excellent resources for healthcare providers in this regard are available for free access at the *Pain Treatment Topics* website, in the “Opioid Rx” tab section.

To view the resources, go to...

[http://www.pain-topics.org/opioid\\_rx/risk.php](http://www.pain-topics.org/opioid_rx/risk.php)

The other essential element in managing risk hinges on patients (and their caregivers) accepting responsibility for following the agreed upon treatment plan and complying with using oxycodone safely. To facilitate that, and to help prevent misuse and avoidable adverse events potentially associated with oxycodone, patients and their caregivers need proper instructions. A 2-page patient instructions handout – *Safely Taking Oxycodone* – is available in English and Spanish from *Pain Treatment Topics* and may be freely duplicated for distribution.

The handouts can be downloaded at...

<http://www.pain-topics.org/pdf/OxycodoneHandout.pdf>

*Most people who take oxycodone do not become addicted to the medication.*

**Principles of Good Medical Practice**

- Evaluate the patient.
- Develop and follow a comprehensive treatment plan.
- Consult specialists as needed.
- Review efficacy of treatment periodically.
- Document therapeutic response.

Source: Joint Statement... 1996.

**Patient Instructions**

**Safely Taking Oxycodone**

Please read this handout carefully and share it with family members or caregivers. This does not take the place of your healthcare provider's guidance or the medicine package insert.

Your healthcare provider has prescribed oxycodone to help control pain. This is a strong pain reliever that has been used successfully for many years in a variety of people worldwide. It is a partially man-made, or synthetic, opioid (opiate) that works with other medicines to reduce the pain. It is not addictive. However, its misuse can be harmful and even fatal (cause a death). Therefore, it is very important that you read, understand, and follow the safety instructions below.

Always take oxycodone exactly as directed.

Taking extra oxycodone or combining it with other drugs, alcohol, or over-the-counter products, unless approved by your healthcare provider, can be harmful or fatal.

Make sure you tell your provider about all medicines, products and drugs prescribed or sold that you are taking, and your complete medical history. Oxycodone, especially if combined with other medicines like anesthesia or sedatives, could be harmful if used together with other products or with other medicines. Taking large amounts of these products can be harmful.

You must take only the prescribed amount of oxycodone and at the specified times.

If you were prescribed the long-acting oxycodone product, DO NOT crush, split, or alter the tablet in any way. It will alter the effects of the oxycodone and may cause a sleep overdose and possibly death.

With the long-acting oxycodone product, you may need to take extra in your chest. There is an extra for extra, the extra coating is not crushed and passes through your gut. You may still crush the immediate-release tablets.

If you were prescribed the oxycodone oral tablets, use a marked spoon (like the pharmacy or a dropper) to measure 5 mL (a rounded spoon) to measure.

You must save any oxycodone medication with a certain level.

If you forget to take your oxycodone dose on time, you can take it very soon thereafter. Otherwise, wait until it is time for the next dose and take only that. Do not take extra oxycodone to make up for a missed dose.

To help avoid missing doses or taking extra doses, use a dosing chart or medicine log to keep track of when you take each dose of oxycodone. This is especially helpful if you were prescribed a short-acting product to use for "breakthrough" pain or "as needed."

If you are forgetful, have someone else give you each dose of oxycodone and keep a record of it.

Tell all of your healthcare providers that you are taking oxycodone. Let them know if you, they might prescribe medications that will alter the effects of oxycodone. If there are questions, they should contact the oxycodone prescriber.

Taking extra oxycodone, or with other drugs or alcohol, can be harmful or even fatal.

Keep careful track of when you take your oxycodone.

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## Summary

Oxycodone is a versatile oral opioid that is effective in treating many types of cancer and noncancer pain. Dosage forms are flexible and easily interchangeable. It is not subject to significant alterations in pharmacokinetics, but dosing must be adjusted for hepatic and renal dysfunction, and it should be avoided in patients receiving hemodialysis. There are very few pharmacokinetic oxycodone-drug interactions, although caution regarding additive effects should be used when administering any other CNS depressants. Side effects reported with oxycodone are predictable and similar to other opioids, although oxycodone may be better tolerated than morphine in some patients. Its ultimate role depends on patient response, prescriber comfort in using the agent, and relative cost considerations. Concerns about diversion, misuse, and abuse of oxycodone are justified, but with appropriate risk management and patient education, it remains a useful analgesic option in the practice of pain management.

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