Criteria for Use of Controlled-release Oxycodone

These criteria were developed using the best evidence currently available.

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Summary

- Oxycodone controlled release (CR) is an effective analgesic that offers a 12-hourly dosing schedule for patients who require continuous treatment of moderate to severe pain over an extended period of time.
- In terms of analgesic efficacy, oxycodone CR offers no advantages over the immediate-release (IR) preparation,[1-5] and has been found to be inferior to a combination of IR oxycodone plus acetaminophen for oral surgery pain.[6] It is not clear whether the CR formulation offers any advantages over the IR formulation in terms of safety. The main clinical advantage of the CR over the IR preparation is less frequent dosing.
- There are no clear clinical advantages of oxycodone CR over other long-duration opioids in terms of analgesic efficacy or safety.[4]
- Similar to long-acting morphine products, oxycodone CR tablets cannot be crushed for patients who have difficulty swallowing or require administration of medications through nasograstric or gastrostomy tubes. Crushing the CR tablet results in immediate release of the full dose of oxycodone, which may lead to a potentially fatal overdose.[a]
- At approximate equianalgesic doses, oxycodone CR has the highest monthly cost of the orally administered long-duration opioids, and its monthly cost may be higher than or second to that of transdermal fentanyl.
- For these reasons, oxycodone CR should be reserved for patients who require continuous, around-the-clock opioid analgesia for an extended period of time AND who cannot tolerate the other, less expensive orally administered formulary agents (morphine CR / SR and methadone). Transdermal fentanyl should be reserved for patients who are unable to take or unable to tolerate oral morphine CR / SR and methadone.
- ***However, methadone (as well as other opioids) should ideally be initiated by or in consultation with a practitioner who has the relevant experience of treating patients with long-acting opioids.*** If a practitioner or consultant with experience in using methadone for chronic pain is not available, then another long-duration opioid may be used until such consultation can be obtained.

FDA-approved Indications

Oxycodone CR is FDA-approved for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

VA Criteria for Use

Oxycodone CR should be reserved for patients who	**Oxycodone CR is NOT recommended in patients who**
– have moderate to severe chronic pain; – require continuous, around-the-clock analgesia for an extended period of time; – are able to take oral solid medications (intact pills); and – have a documented current or past history of intolerable morphine (CR, ER, or SR) and methadone related adverse effects that persisted despite aggressive measures to alleviate them and that prevented upward titration of dosage to achieve a satisfactory level of analgesia. – have a documented current or past history of intolerable morphine (CR, SR, or ER) related adverse effects but an organized pain clinic or local pain management expert with experience in dosing methadone is not readily available for referral or consultation.	– have mild pain; – are not expected to have pain for an extended period of time; – are unable to swallow (e.g., patients who have dysphagia, decreased consciousness, or gastrointestinal obstruction) or require tablets to be crushed before administration; – are not previously taking the drug and require rapid onset of analgesia for pain in the immediate post-operative period (first 12 to 24 h after surgery); – only require rapid onset of analgesia, such as in the treatment of acute pain, incident pain (episodic increases in chronic pain intensity that may or may not be related to movement or activity), or breakthrough pain (chronic pain that is inadequately treated); – only require an as-needed (p.r.n.) analgesic; or – have a contraindication to the use of oxycodone (e.g., documented or suspected hypersensitivity to the drug) or other opioids (e.g., significant respiratory depression, acute or severe bronchial asthma or hypercarbia, or known or suspected paralytic ileus).

CR = Controlled release; ER = Extended release; SR = Sustained release. Also refer to the addendum, *Treatment Algorithm, Criteria for Use of Controlled-Release Oxycodone*. Available at: http://www.vapbm.org or http://vaww.pbm.med.va.gov.

a Only methadone oral solution offers a long duration of effect (by virtue of its long half-life) without depending on an intact pill structure.

Note:

- Morphine CR / SR and methadone can be used before oxycodone CR in most patients. There may be cases where exceptions to this general recommendation are appropriate.
- *Methadone should ideally be initiated by or in consultation with a practitioner who has knowledge of titrating this agent.* In situations where there is no practitioner or consultant with experience in using methadone for chronic pain, another long-duration opioid may be used until such consultation can be obtained. Also refer to *Methadone Dosing Recommendations for Treatment of Chronic Pain* available at: http://vapbm.org.
- Long-term opioid use should be undertaken in the context of a comprehensive pain management plan.

For patients who cannot take oral morphine and methadone, and who have moderate to severe chronic pain, transdermal fentanyl is an option.[b]

The use of methadone for pain should ideally be done in the context of an organized pain clinic or with assistance of local pain management experts, including health care providers or pharmacists, who have experience with methadone use. If such resources were not readily available, oxycodone CR or transdermal fentanyl would generally be the alternative long-acting opioid to morphine.

Co-therapy using a long-duration opioid and a nonopioid analgesic (acetaminophen or nonsteroidal anti-inflammatory drug [NSAID]) or fixed-combination analgesic is recommended for opioid-sparing effects or additive analgesia. In the treatment of chronic neuropathic pain of noncancer origin, tricyclic antidepressant or antiepileptic agents are advocated before opioid therapy.[7] The use of a single opioid agent is usually appropriate for around-the-clock therapy.

Before starting a patient with chronic noncancer pain on any opioid for long-term therapy, consultation with a pain specialist is recommended. It is wise for practitioners to obtain informed consent and a written agreement ("contract") from the patient explaining the risks, benefits, and obligatory terms of treatment with opioids. All federal and state guidelines on prescribing and dispensing opioids should be strictly followed. General principles of pain management, particularly pertaining to chronic pain, should guide therapy with long-duration opioids.[c]

The use of opioids for the treatment of patients with chronic noncancer pain and a history of opioid abuse, addiction, or diversion is controversial. The use of opioids in such patients requires very cautious, structured prescribing. Referrals to a pain management specialist and a drug addiction specialist are desirable.[c]

Dosage and Administration

A reasonable initial dose of oxycodone CR in patients who are not opioid-tolerant is 10 mg q 12 h.

Patients who are already taking other opioids but who cannot tolerate those agents should have their previous opioid dose converted to the equivalent of oral oxycodone using standard equianalgesic dosage estimates such as those suggested by the American Pain Society (Table 1). Many other equianalgesic dosing tables are available, and practitioners are encouraged to use one that they are familiar with and have successfully used to convert between different opioid analgesics.

[b] Individual requests that do not meet the criteria should be assessed on a case-by-case basis. On occasion, a patient may require opioid rotation. Oxycodone CR offers another alternative and may be considered on a case-by-case basis in these situations.

[c] For more information on general principles of pain management, recognizing patients with aberrant drug-related behavior, identifying patients who should be referred to a pain specialist or pain clinic, and dosing methadone, see the Web-based educational program for VA employees entitled *Opioids in the Management of Acute and Chronic Pain*; available at: http://vaww.sites.lrn.va.gov/pain/opioids/).

Table 1 Approximate equianalgesic doses for pure agonist opioids (American Pain Society)

Opioid agent	Estimated equianalgesic dose (mg) Oral	Parenteral
Fentanyl	—	0.1
Hydromorphone	7.5	1.5
Levorphanol	4 acute	2 acute
	1 chronic	1 chronic
Meperidine	300	75
Methadone	20 acute†	10 acute†
	2 to 4 chronic†	2 to 4 chronic†
Morphine	30	10
Oxycodone	20‡	—
Oxymorphone	—	1

† Alternative methods of converting between methadone and other opioids have been described[d]; see Gouldin, *et al.*[12]; *Opioids in the Management of Acute and Chronic Pain,* section on chronic noncancer pain[c]; and *Methadone Dosing Recommendations for Treatment of Chronic Pain* available at: http://vapbm.org.

‡ To obtain the amount of oral oxycodone CR to be given q 12 h, divide the total daily equivalent dose by 2. This amount should be rounded down to the closest tablet size available (10, 20, 40, or 80 mg). The 80-mg tablet of oxycodone CR is intended for use only in opioid-tolerant patients who require the equivalent daily dose of 160 mg oxycodone. Starting doses should be individualized. The patient's medical condition, the potency, dose, and type of previous opioid, the patient's degree of opioid exposure and tolerance, the patient's past analgesic response and adverse experiences, and the accuracy and reliability of opioid conversion factors may all influence the choice of starting dose.

Sources: Principles of analgesic use in the treatment of acute pain and cancer pain, 4th ed.[13]; OxyContin® package insert.[14]

Transdermal fentanyl-to-oxycodone CR conversions should use conservative equianalgesic dosage estimates because there is limited information on such a conversion (Table 2). As noted above, practitioners are encouraged to use a conversion scheme that they are familiar with and have successfully used to convert between different opioid analgesics.

Table 2 Guidelines for converting ONLY from transdermal fentanyl to oxycodone CR

Fentanyl TTS Dose (µg/h)	Content (mg)	Recommended starting dose of oxycodone CR (10 mg q 12 h for each 25 µg/h of fentanyl TTS)†
25	2.5	10 mg q 12 h
50	5.0	20 mg q 12 h
75	7.5	30 mg q 12 h
100	10.0	40 mg q 12 h

Source: OxyContin® package insert.[14]

NOTE: Do not use these guidelines to convert from oxycodone CR to fentanyl TTS. *This conversion is conservative. If it is used to switch from oxycodone CR to fentanyl TTS, the dosage of fentanyl TTS may be overestimated and fentanyl toxicity may occur.*

† Start oxycodone CR 18 h after removing fentanyl TTS patch. Use caution when converting from transdermal fentanyl to oxycodone CR. There is limited clinical experience and no systematic evaluation of this conversion.
TTS = Transdermal therapeutic system.

When titrating opioids or converting between drug formulations or opioid agents, dosing requirements should be monitored and individualized to patient response. For all conversions, closely monitor the patient and make frequent dosage adjustments to ensure a satisfactory, stable response is obtained.

Rescue doses of oxycodone IR or other short-acting analgesic, either alone or in combination with acetaminophen, aspirin, or NSAIDs, may be given for breakthrough pain as needed or about 1 h before anticipated incident pain. The dose of supplemental oxycodone IR may be about one fourth to one third of the 12-h dose of oxycodone CR.

There is anecdotal experience but no published clinical information on dosing intervals shorter than 12 h. Therefore, when adjusting the dosage of oxycodone CR, a trial of changing the q 12 h dose is recommended before considering a change in the dosing interval. Certain dosing schedules may be more conveniently prescribed q 8 h (e.g., 10 mg q 8 h vs. 20 mg q AM and 10 mg q HS). Dosage adjustments may be made every 1 to 2 d, as approximate steady-state concentrations are achieved in 24 to 36 h. In most cases (with the exception of increasing from 10 mg q 12 h to 20 mg q 12 h), the dose can be increased by 25% to 50% of the patient's current dose.

When doses are appropriately titrated to individual response, adequate analgesia is obtained with either morphine CR or oxycodone CR,[15-17] despite large interpatient variability in plasma concentrations of opioid.[18]

[d] The use of methadone requires cautious, *slow* dosage titration (e.g., every 5 to 7 days) and careful opioid conversions because of uncertain equianalgesic potency[8] and complex pharmacokinetic properties, including high interpatient variability in pharmacokinetic parameters[9,10] and a long, time-dependent half-life.[11]

Dosing in special populations and patients taking other CNS depressants

Low initial doses are indicated in special patient populations (age > 65 y, hepatic impaired, renal impaired [CrCl < 60 ml/min]) and in patients taking other CNS depressants (e.g., sedatives, hypnotics, general anesthetics, tranquilizers, and alcohol).

Oxycodone may have a theoretical advantage over morphine in patients with renal insufficiency because of limited drug accumulation, as compared with greater accumulation of morphine's active metabolites.[19,20] A literature search found no clinical trials addressing this issue. Methadone is another option to consider, as it lacks active metabolites.[9] Whatever opioid agent is used, it must be carefully titrated in these patients.

Adverse Effects

Oxycodone CR has been associated with lower[2,21] and similar[1,3,22] rates of adverse effects compared with the IR formulation, but studies have varied in methods and doses. Therefore, it is not clear whether the CR formulation offers any advantages over the IR formulation in terms of safety.

Overall, the adverse effect profile of oxycodone CR is similar to that of morphine CR in the management of patients with moderate to severe cancer pain.[15-17,23] One trial showed no statistically significant treatment differences in terms of the proportion of patients or physicians who expressed a preference for either treatment,[17] and another trial found no treatment difference in patient acceptability during the daytime and slightly greater overnight acceptability with morphine CR than with oxycodone CR.[16]

A literature search of the PubMed-Medline database (1966 to June 2003) found no double-blind, randomized controlled trials evaluating the use of these agents in other types of chronic pain, nor have there been such trials comparing methadone or transdermal fentanyl with oxycodone in the treatment of chronic pain.

Oxycodone CR and morphine CR have been shown to have some differences in their adverse effect profiles in a limited number of studies. Adverse effects reported to be more common with oxycodone CR than morphine CR include headache (12% to 13% vs. 2%; $p < 0.05$)[23] and constipation (18 of 27 patients, 66.7% vs. 14 of 27 patients, 51.8%; $p < 0.01$).[16] Hallucinations,[15,24] vomiting,[16] itching,[25] and histamine release[25] may be less common or less intense with oxycodone than morphine. Small sample sizes and low frequencies of adverse effects, however, may prohibit definite conclusions.

Although switching to oxycodone has been shown to reduce morphine-related delirium,[26] some patients may experience severe adverse effects (e.g., nausea or vomiting) upon switching from morphine CR to oxycodone CR.[16]

Overall, considering differences in individual responses and interpatient variation in the development and tolerability of adverse effects, oxycodone does not offer any consistent advantages over morphine in terms of safety or tolerability. In addition, as seen with other opioids, tolerance develops to the common opioid-related adverse effects, except for constipation, after a few days of therapy.[27] The frequencies of common opioid-related adverse effects decrease with continued therapy despite stable levels of analgesia.[28]

Diversion and abuse of oxycodone CR have been highlighted in recent national media reports. Iatrogenic addiction (a behavior pattern characterized as loss of control over drug use, compulsive drug use, and continued use of a drug despite harm[29]) is also a concern. It is important to note, however, that there is no known pharmacologic reason for one opioid to have a greater addictive potential than another, and factors other than drug exposure, such as situational, personality, and physiologic variables, may also play a role.[30]

At least partly because of differences in definitions and diagnostic criteria, the rates of drug abuse, addiction, and dependence have varied widely (ranging from less than 1% to 45%) in patients being treated for chronic pain.[30-37] A reliable estimate of the prevalence of these problems has not been validated in opioid-treated patients with chronic pain.

In a Purdue Pharma–sponsored analysis of oxycodone-related deaths based on the Drug Abuse Warning Network system, the majority (919, 90.8%) of 1014 evaluable fatalities have been related to drug abuse and 889 (96.7%) involved multiple drugs, while only 12 (1.3%) of the 919 drug abuse cases involved oxycodone CR as a single identifiable entity.[38] The abuse of *any* opioid is a high-risk activity. Fear of diversion, abuse, or addiction should not be a reason for preventing patients from receiving appropriate analgesic medication. Clinicians should take proper precautions to prevent opioid diversion and abuse, and should be able to recognize signs of possible drug misuse in patients.[e]

[e] See footnote "c" on page 2.

Cost

The monthly cost of opioids may vary considerably depending on the equianalgesic dosing factor used in cost calculations. Using the actual doses of opioids required to achieve adequate analgesia would be optimal when determining true differences in cost. In Table 3, the comparative costs of the long-duration opioids were calculated according to both the manufacturer-recommended initial doses for conversions from another opioid analgesic to oxycodone CR and the equianalgesic doses recommended by the American Pain Society.

Table 3 Lowest available VA costs of long-duration opioids

	Equianalgesic dose		Monthly cost		Cost factor‡	
Agent	**Mfr**	**APS**	**Mfr**	**APS**	**Mfr**	**APS**
Fentanyl TTS	50 µg/h q 3 d	25 µg/h q 3 d	$126.68	$76.18	1.53	0.92
Oxycodone CR	20 mg q 12 h	20 mg q 12 h	$82.76	$82.76	1.00	1.00
Levorphanol†	1 mg q 6 h	1 mg q 6 h	$25.89	$25.89	0.31	0.31
Morphine CR	45 mg q 12 h	30 mg q 12 h	$9.59	$7.86	0.12	0.10
Morphine ER	90 mg q 24 h	60 mg q 24 h	NA	$77.08	—	0.93
Morphine SR	45 mg q 12 h	30 mg q 12 h	$5.86	$3.87	0.07	0.05
Methadone	5 mg q 8 h	2.5 mg q 8 h	$3.83	$1.92	0.05	0.02

Costs to VA as of 24 June 2003

Source of equianalgesic dosage estimates: OxyContin® package insert[14] and Principles of analgesic use in the treatment of acute pain and cancer pain, 4th ed.[13]

APS = American Pain Society; CR = Controlled release; ER = Extended release; Mfr = Manufacturer (Purdue Pharma L.P.); NA = Not available; SR = Sustained release; TTS = Transdermal therapeutic system

† Nonformulary agent

‡ Cost factor in comparison with oxycodone CR; calculated by dividing the monthly cost of each opioid by the monthly cost of oxycodone CR.

Based on the estimated equianalgesic doses shown in Table 3, oxycodone CR is about 9 to 11 times more expensive than morphine CR. The least expensive agent is methadone (20 to 40 times less than oxycodone CR). Note that if methadone is dosed according to a 3:1 morphine-to-methadone conversion ratio,[39] then the cost of oxycodone CR would be about 7 times more expensive than methadone.

Conclusion

Because of similar efficacy, comparable adverse effects, and substantial cost savings, morphine CR / SR is the preferred long-duration opioid for VA patients. Oxycodone CR may be considered for patients who have intolerable adverse effects that prevent upward dosage titration and achievement of adequate analgesia on morphine CR / SR and on methadone. As a general rule, methadone titration should be done by practitioners with the relevant knowledge or after consultation with a pain specialist. If adequate pain management resources or consultants with expertise are not available for dosing methadone, then oxycodone CR or transdermal fentanyl may be used as the alternative long-duration opioid to morphine.

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