

VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain

Medications Pocket Guide

Equianalgesic Opioid Conversion Ratios for Patients Previously Receiving Other Opioids

Opioid Agent	Equianalgesic Dose (Mg)	Initial Conversion Dose (Not Equianalgesic) [†]
Codeine	180 to 200 p.o. [‡]	30 mg q 4 to 6 h
Fentanyl	— (transdermal)	For converting ONLY to fentanyl from another opioid, use about 25 mcg/h fentanyl transdermally for every 90 mg of oral morphine or equivalent (see Initial Fentanyl Transdermal Dosage below)
Hydrocodone	30 p.o.	50% to 67% of estimated oral equianalgesic dose
Hydromorphone	7.5 p.o.	50% to 67% of estimated oral equianalgesic dose
Levorphanol	4 p.o. acute 1 p.o. chronic	50% to 67% of estimated oral equianalgesic dose
Methadone	20 p.o. acute 2 to 4 p.o. chronic	Methadone-to-morphine dosage proportion (%) is dependent on morphine-equivalent dose of previous opioid For gradual conversion to methadone: Oral morphine Methadone < 200 mg/d 5 mg q 8 h 200 to 500 mg/d ~7% of oral morphine-equivalent dose, given in divided doses q 8 h > 500 mg/d Consider consultation with a pain specialist, clinical pharmacist, or other practitioner who has experience with using methadone for chronic pain
Morphine	30 p.o.	50% to 67% of estimated oral equianalgesic dose
Oxycodone	15 to 20 p.o. [§]	50% to 67% of estimated oral equianalgesic dose
Propoxyphene	100 to 130 p.o. [‡]	HCl: 65 mg q 6 to 8 h Napsylate: 100 mg q 6 to 8 h
Tramadol	100 to 150 p.o. [‡]	25 mg q.a.m.

[†] The initial dose of the new drug applies to patients who are not tolerant to the new opioid and should be given at 50% to 67% of the calculated dose for all potent opioids except fentanyl and methadone to allow for incomplete cross-tolerance (the new drug may have more relative analgesic efficacy and more adverse effects). For methadone, use dosage proportions (%) based on the morphine-equivalent dose of previous opioid. Initial 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.

[‡] When converting from weak opioid analgesics to stronger opioids, use the recommended initial doses of the new opioid for opioid-naïve patients. Dose of tramadol should NOT be considered equianalgesic to the doses of pure agonists.

[§] Exceeds recommended initial dose (oxycodone 5 mg)

OPIOID CONVERSION INSTRUCTIONS

- Determine the total 24-h dose of the current opioid.
- Using the estimated equianalgesic dose, calculate the equivalent dose of new analgesic for the desired route of administration.
- When converting to a different opioid, for most agents, the starting conversion dose of the new opioid should be 50% to 67% of the equianalgesic dose because of incomplete cross-tolerance.
- Divide the 24-h starting dose of the new opioid by the frequency of administration to give the new dose for the new route.
- Consider rescue opioid therapy during the conversion process.

Example: Conversion to methadone

Patient receives a total of 360 mg /d oral morphine.

- From the equianalgesic table, we determine that the initial conversion dose of methadone is about 7% of the oral morphine-equivalent dose. The initial conversion dose would be $360 \times 7\% =$ about 25 mg per day.
- The recommended frequency of administration for methadone is q 6-8 h (3 doses per day).
- Consulting the local drug formulary, we find that methadone is available in 5-mg scored tablets. The starting dose of methadone would be 7.5 mg q 6-8 h (22.5 mg/d).
- Titrate dose at appropriate intervals depending on response and adverse effect.

Recommendations for Supplemental Opioid Therapy

Type Of Therapy	Description Of Pain Episode	Recommendation	General Guidelines For Supplemental Opioid Therapy
Rescue	Insufficient analgesia during dosage titration	In patients being started on a new opioid, consider giving rescue medication Rescue therapy is often used when pain is severe or escalating	Use supplemental short-acting opioid, non-opioid, or a combination of both agents on an as-needed basis When using short-acting pure agonist opioids (alone or in combination with non-opioid analgesics) for supplemental therapy, give opioid doses equivalent to about 10% of the daily opioid dose as needed When using combination products, do not exceed maximum recommended doses of acetaminophen (4000 mg), aspirin (4000 mg), or ibuprofen (1000 mg) Encourage the use of nonpharmacologic modalities Avoid the use of mixed agonist-antagonist opioids, as these agents may precipitate withdrawal in patients who have physical opioid dependence
Breakthrough pain	Unpredictable exacerbation of chronic pain otherwise controlled on stable maintenance doses of opioid	Controversial, not routinely recommended If necessary, use breakthrough pain medications sparingly	
Incident pain	Predictable, activity-related exacerbation of chronic pain otherwise controlled on stable maintenance doses of opioid	Many patients taking long-acting opioid analgesics may need supplemental analgesia for incident pain (e.g., 8 to 12 doses per month of short-acting opioid preparation)	

INITIAL FENTANYL TRANSDERMAL DOSAGE (only for converting another opioid to fentanyl)

Oral 24-Hour Morphine (mg/d)	Fentanyl Transdermal (mcg/h)
45–134	25
135–224	50
225–314	75
315–404	100
405–494	125
495–584	150
585–674	175
675–764	200
765–854	225
855–944	250
945–1034	275
1035–1124	300

Source: Drug Facts and Comparisons (2002)

Note: Do not use this table to convert from fentanyl transdermal system to other opioid analgesics because these conversion dosage recommendations are conservative. Use of this table for conversion from fentanyl to other opioids can overestimate the dose of the new agent and may result in overdosage of the new agent.

Use of Short-acting, Orally Administered Opioids in OPIOID-NAIVE Adults (70 kg)		Short-Acting Opioid [†]	Initial Dosage	Analgesic Onset (Min) Peak (Min) Duration (H)	Other Considerations/Side Effects
		Codeine (alone or in combination with APAP or ASA)	30 mg p.o. q 4 to 6 h	15 to 30 30 to 60 4 to 6	May be less effective in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6-inhibiting drugs [‡]) because of decreased conversion to the active metabolite, morphine. CODEINE ALONE IS A WEAK ANALGESIC, AND MORE EFFECTIVE ALTERNATIVES ARE AVAILABLE (INCLUDING CODEINE IN COMBINATION WITH APAP OR ASA).
		Hydrocodone (in combination with APAP, ASA, or IBU)	5 to 10 mg p.o. q 4 to 6 h	15 to 30 30 to 60 4 to 8	Conversion to the active metabolite, hydromorphone, may be decreased in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6-inhibiting drugs [‡]). Impact of decreased formation of hydromorphone on analgesic efficacy of hydrocodone is unknown.
		Hydromorphone	2 mg p.o. q 4 to 6 h	15 to 30 30 to 60 4 to 6	
		Morphine	10 to 30 mg p.o. q 4 h	15 to 60 60 to 90 2 to 6	M6G, an active metabolite, may accumulate in renal impairment and contribute to toxic effects. M3G, a metabolite without analgesic activity, may accumulate in renal impairment. This metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia.
		Oxycodone (alone or in combination with APAP or ASA)	5 mg p.o. q 6 h	10 to 15 30 to 60 3 to 6	Conversion to the active metabolite, oxymorphone, may be decreased in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6-inhibiting drugs [‡]). Impact of decreased formation of oxymorphone on analgesic efficacy of oxycodone is unknown.
		Propoxyphene (alone or in combination with APAP)	HCl: 65 mg p.o. q 6 to 8 h Napsylate: 100 mg p.o. q 6 to 8 h	15 to 60 120 to 180 4 to 6	Seizures and cardiac arrhythmias may occur with the use of high doses or with renal failure. Equianalgesic doses for propoxyphene salts: 65 mg HCl ≅ 100 mg napsylate. Co-ingestion of alcohol or other CNS depressants with moderate (6 to 20 capsules or tablets) overdoses of propoxyphene has been associated with serious toxicity including death.
		Tramadol (alone or in combination with APAP)	25 mg p.o. q.a.m.	< 60 ~120 to 240 3 to 6	Slower initiation and titration improves tolerability. When converting to tramadol in patients who have physical opioid dependence and who are receiving substantial amounts of prior opioids, consider tapering the previous opioid to avoid inducing withdrawal symptoms. May be less effective in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6-inhibiting drugs [‡]) because of decreased conversion to the active metabolite, M1. Risk of seizures may be increased in the following patients: those taking MAOIs, SSRIs, tricyclic antidepressants, neuroleptics, or other drugs that reduce seizure threshold; patients with epilepsy; patients with risk factors for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections); or patients who take overdoses of tramadol (≥ 500 mg p.o.).
Use of Long-acting Opioids in OPIOID-NAIVE Adults (70 kg)		Long-Acting Opioid [†]	Initial Dosage	Analgesic Onset (Min) Peak (Min) Duration (H)	Other Considerations/Side Effects
		Fentanyl Transdermal System	25 mcg/h t.d. q 72 h	12 to 18 (h) 24 to 72 (h) 48 to 72	Consider t.d. fentanyl in patients who cannot take oral long-acting morphine and methadone. After application of t.d. fentanyl, continued absorption of fentanyl may occur from intradermal depots of drug. Steady-state is reached after several 72-h sequential applications. Application of external heat sources (e.g., heating pads, electric blankets, heat lamps, saunas, hot tubs, or heated water beds) to the application site while the patch is worn may increase release of fentanyl from the t.d. system; monitor for opioid adverse effects and adjust dosage as necessary.
		Levorphanol	2 mg p.o. q 6 to 8 h Longer initial dosing intervals (e.g., q 12 h) may be possible	30 to 60 60 to 120 4 to 14 (dose-dependent)	Like methadone, levorphanol has a plasma half-life that is longer than the duration of analgesia. Therefore, delayed analgesia or toxicity is possible due to accumulation of levorphanol (e.g., on about days 2 to 3).
		Methadone	2.5 mg p.o. q 6 to 8 h	30 to 60 — 4 to 12 Analgesic duration increases with continued use and cumulative effects	Recommended first- or second-line long-acting agent. Some evidence suggests methadone may be beneficial in neuropathic pain. The only long-acting opioid available as an oral solution. Once a stable analgesic dose is reached (in about 4 to 5 d), the dosing interval may be extended to q 8 to 12 h or longer. Plasma half-life (22 to 128 h short-term; 24 to 48 h at steady-state) may be longer than the analgesic duration. Delayed analgesia or toxicity may occur because of drug accumulation after repeated doses (e.g., on days 2 to 5).
		Morphine Controlled-Release [CR]	15 mg p.o. q 12 h	30 to 60 30 to 60 8 to 12 (CR); 8 to 24 (SR)	Preferred first-line long-acting agent because of similar efficacy to other long-acting opioids, comparable safety profile, provider familiarity with its use, and lower cost. M6G, an active metabolite, may accumulate in renal impairment and contribute to toxic effects.
		Morphine Sustained Release [SR]	15 mg p.o. q 12 h 20 mg p.o. q 24 h		M3G, a metabolite without analgesic activity, may accumulate in renal impairment. This metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia. Controlled-release tablets should be swallowed whole, not broken, chewed, or crushed. For patients who have difficulty swallowing, SR and ER capsules may be opened and the pellets sprinkled onto a small amount of soft food (such as apple sauce). The mixture should be taken immediately. The pellets must not be chewed or crushed, and the mouth should be rinsed to ensure that all pellets have been swallowed.
		Morphine Extended Release [ER]	30 mg q 24 h		
		Oxycodone Controlled Release [CR]	10 mg p.o. q 12 h	30 to 60 90 to 180 8 to 12	Recommended for patients who experience intolerable, unmanageable adverse effects to long-acting morphine and to methadone. Controlled-release tablets should be swallowed whole, not broken, chewed, or crushed. Conversion to the active metabolite, oxymorphone, may be decreased in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6-inhibiting drugs [‡]). Impact of decreased formation of oxymorphone on analgesic efficacy of oxycodone is unknown.
THIS GUIDELINE DOES NOT RECOMMEND THE USE OF LONG-ACTING OPIOID AGONISTS FOR AS-NEEDED (P.R.N.) ADMINISTRATION					

Sources: Ortho-McNeil, Tylenol with codeine package insert (2000)(Ortho-McNeil 2000); Ortho-McNeil, Ultram package insert (2001)(Ortho-McNeil 2001); Drug Facts and Comparisons (2002)(Anonymous 2002); Endo, Percocet, Percodan and Zydone package inserts (2001) (Endo 2001),(Endo 2001),(Endo 2001); Purdue, MSIR package insert (2001)(Purdue 2001) and OxyIR package insert (2000)(Purdue 2000; Purdue 2001); Michalets (1998)(Michalets 1998); Davis and Homs (2001)(Davis and Homs 2001)

APAP = Acetaminophen; ASA = Aspirin (acetylsalicylic acid); IBU = Ibuprofen; MAOI = Monoamine oxidase inhibitor; P.o. = Per os (orally); t.d. = Transdermally

[†] Check local formulary for available formulations.

[‡] **CYP-2D6-Inhibiting Drugs:** *Antiarrhythmics* (amiodarone, propafenone, quinidine [strong inhibitor]); *analgesics* (methadone [weak inhibitor], propoxyphene); *antihistamines* (diphenhydramine, chlorpheniramine [in vitro], brompheniramine [in vitro], triprolidine [in vitro]); *histamine receptor antagonists* (cimetidine); *neuroleptics* (chlorpromazine, haloperidol, methotrimeprazine, perphenazine, thioridazine); *protease inhibitors* (ritonavir); *quinine compounds* (hydroxychloroquine, quinacrine, quinidine); *selective serotonin reuptake inhibitors* (fluoxetine, fluvoxamine, paroxetine, sertraline), and *miscellaneous compounds* (clomipramine, ketoconazole, ticlopidine).