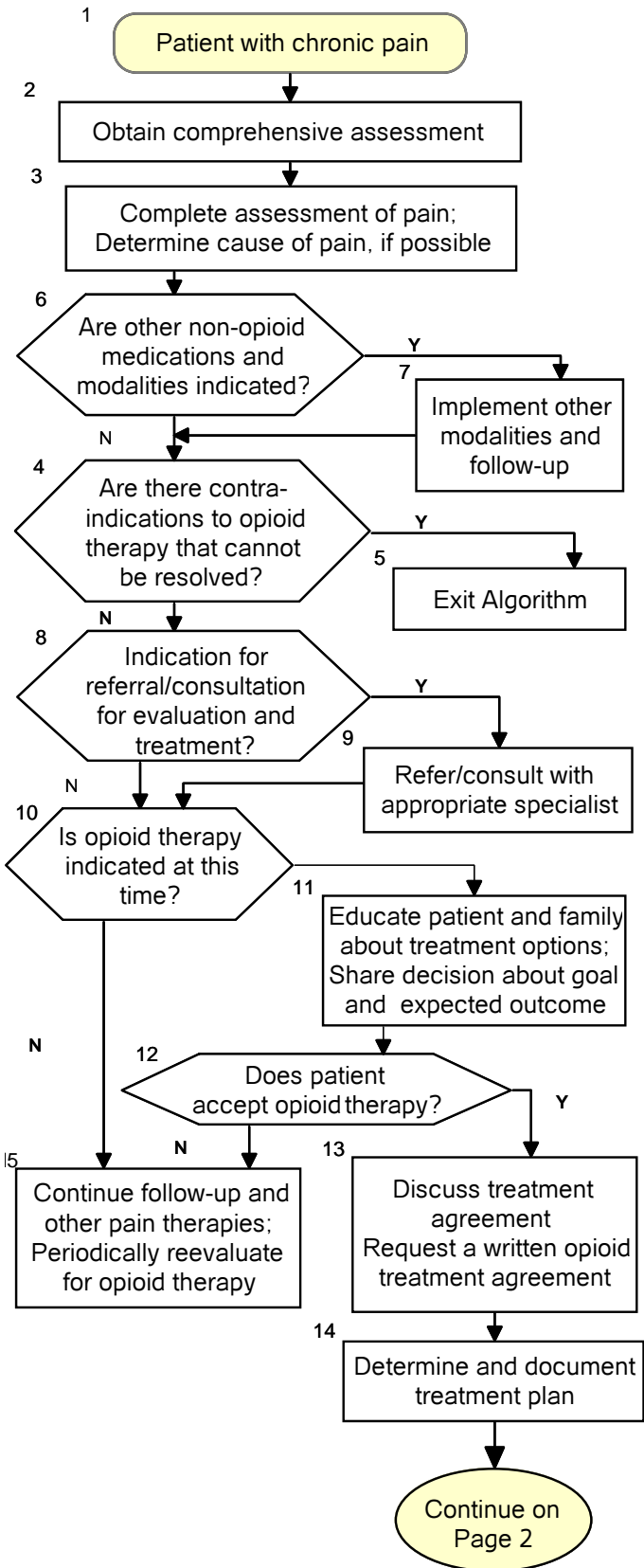
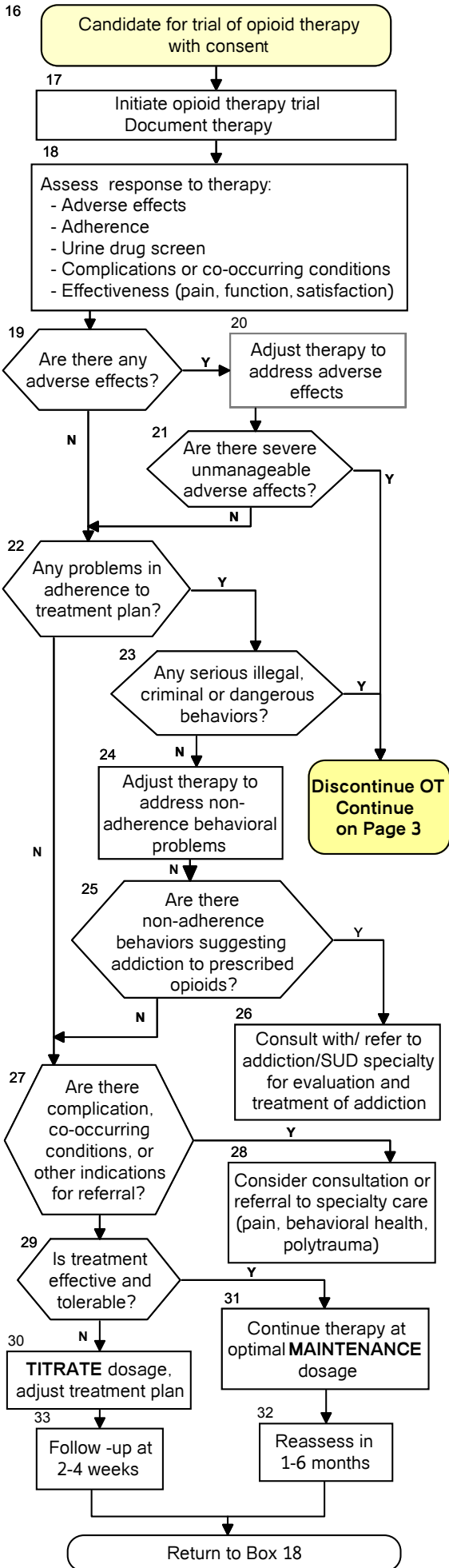


VA/DoD Clinical Practice Guideline Management of Opioid Therapy for Chronic Pain



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



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

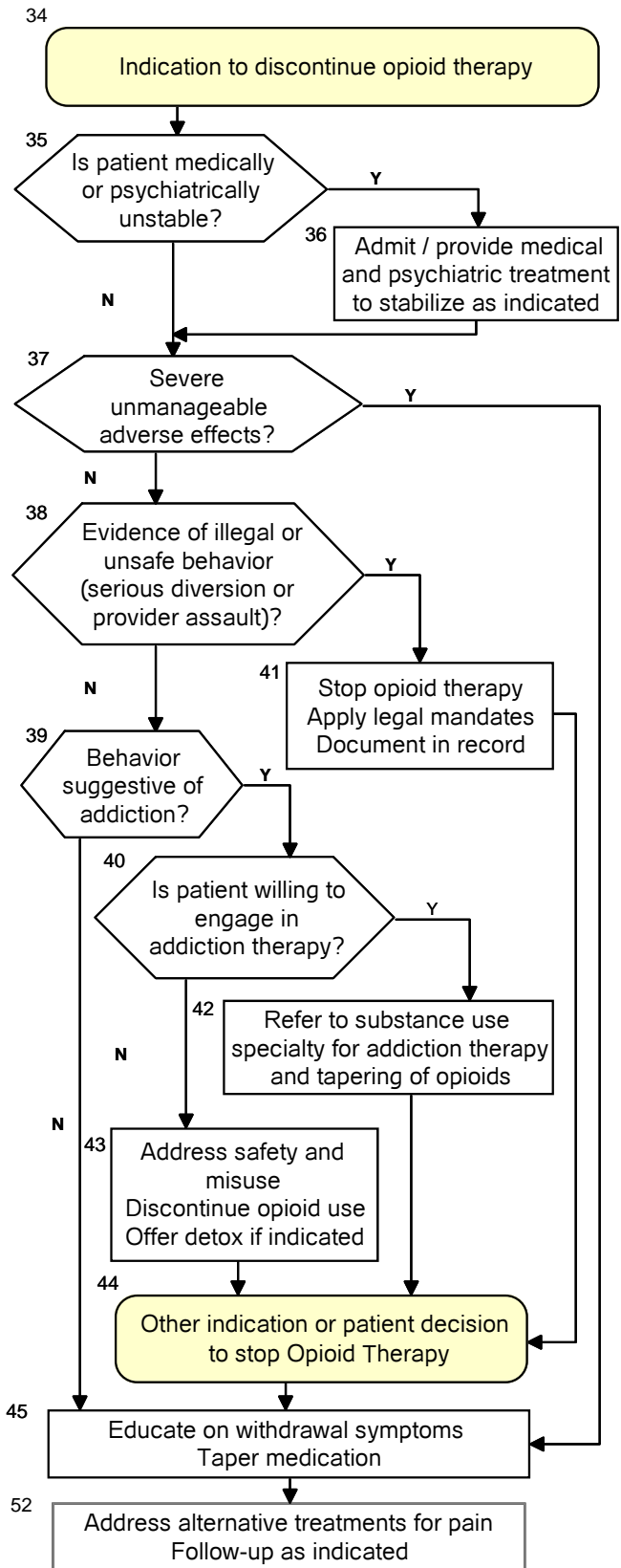


Table 1: Classes of Opioid Medications ^a

Phenanthrenes	Diphenylheptanes	Phenylpiperidine	Other
Codeine Hydrocodone Hydromorphone Morphine Oxycodone Oxymorphone	Methadone Propoxyphene	Fentanyl	Tramadol Tapentadol

^a for contraindication regarding specific medications (See [Appendix E](#))

Table 2: Risks for Misuse of Opioid Therapy and Preferred Treatment

Risk opioid misuse	Condition/situation	Treatment Setting for OT
Low	<ul style="list-style-type: none"> - No history of SUD - No psychiatric co-morbidity - Prior good adherence to treatments with the primary care provider - Existence of social support system 	<ul style="list-style-type: none"> - Provide OT in primary care setting
Moderate	<ul style="list-style-type: none"> - History of substance use - History or co-occurring psychiatric disorder - History of suicide attempt - Any positive UDT - Any history of legal problems - Young age (less than 25) 	<ul style="list-style-type: none"> - Primary care with escalated monitoring and caution - Consider consultation with SUD or Behavioral health specialty
High	<ul style="list-style-type: none"> - Unstable or untreated substance use or mental health disorder - Persistent or repeated troublesome aberrant behavior or history of ADRB 	<ul style="list-style-type: none"> - Advanced structured pain clinic/ program - Co-managed with Substance Use Disorder or Mental Health Specialty

Table 3 | Types of Serious and Dangerous Behaviors

Illegal or Criminal behavior
<ul style="list-style-type: none"> - Active diversion (selling or provision of drugs to others) - Prescription forgery - Stealing, "borrowing", or buying drugs from others
Dangerous behavior
<ul style="list-style-type: none"> - Motor vehicle crash /arrest related to opioid or illicit drug or alcohol intoxication or effects - Intentional or unintentional overdose or suicide attempt - Assaultive behaviors - Aggressive/threatening/belligerent behavior in the clinic

Table 4 | Predictors of Opioid Misuse

Strong predictors	Moderate predictors	Weak predictors	Inconsistent predictors
History of alcohol and illicit substance abuse	<ul style="list-style-type: none"> - Younger age - History of legal problems - Positive UDT 	<ul style="list-style-type: none"> - Family history of drug abuse - History of childhood sexual abuse - History of DUIs or drug convictions - Lost or stolen prescriptions - Obtaining opioids from alternate sources - High SOAPP or SOAPP-R scores 	<ul style="list-style-type: none"> - Male sex - History of an anxiety disorder - History of prescribed drug misuse - Race (nonwhite) - Education - History of MVAs - History of schizophrenia

UDT = Urine Drug Test; MVAs = Motor Vehicles Accidents;
 SOAPP-R = Screener and Opioid Assessment for Patients with Pain (Revised)

Table 5 | Time Drugs of Abuse Can Be Detected in Urine

Drug	Time
Alcohol	7-12 h
Amphetamine	48 h
Methamphetamine	48 h
Barbiturate	
Short-acting (eg, pentobarbital)	24 h
Long-acting (eg, phenobarbital)	3 wk
Benzodiazepine	
Short-acting (eg, lorazepam)	3 d
Long-acting (eg, diazepam)	30 d
Cocaine metabolites	2-4 d
Marijuana	
Single use	3 d
Moderate use (4 times/wk)	5-7 d
Daily use	10-15 d
Long-term heavy smoker	>30 d
Opioids	
Codeine	48 h
Heroin (morphine)	48 h
Hydromorphone	2-4 d
Methadone	3 d
Morphine	48-72 h
Oxycodone	2-4 d
Propoxyphene	6-48 h
Phencyclidine	8 d

Table E1. Use of Short-acting, Orally Administered Opioids in Adults

Short-Acting Opioid †	Initial Oral Dosage	Dosage Titration	Analgesic Onset (Min) Peak (Min) Duration (H)
Codeine (alone or in combination with APAP or ASA)	30 mg q 4 to 6 h	Increase dose as needed and tolerated to a maximum of 360 mg/d (4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics) Ceiling effect occurs at doses > 60 mg/dose	15 to 30 30 to 60 4 to 6
Hydrocodone (in combination with APAP, ASA, or IBU)	5 to 10 mg q 4 to 6 h	Increase dose as needed and tolerated Maximum dose: 60 mg/d (4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics) for hydrocodone + APAP combination, or 37.5 mg/d (1000 mg/d IBU) for hydrocodone + IBU combination	15 to 30 30 to 60 4 to 8
Hydromorphone	2 mg q 4 to 6 h	Individually titrate as needed and tolerated; doses \geq 4 mg q 4 to 6 h may be necessary	15 to 30 30 to 60 4 to 6
Morphine	10 to 30 mg q 4 h	Individually titrate as needed and tolerated	15 to 60 60 to 90 2 to 6
Oxycodone (alone or in combination with APAP or ASA)	5 mg q 6 h	Increase dose as needed and tolerated For combination products, maximum dose is limited by APAP or ASA content (4000 mg/d for both; 2000 mg/d APAP in chronic alcoholics)	10 to 15 30 to 60 3 to 6
Oxymorphone	10 to 20 mg q 4 to 6 h (may start at 5 mg to improve tolerability)	Individually titrate as needed and tolerated	34 to 45 — 4
Propoxyphene (alone or in combination with APAP)	HCl: 65 mg q 6 to 8 hours Napsylate: 100 mg q 6 to 8 hours	Increase dose as tolerated Maximum daily dose is 390 mg/d for HCl salt and 600 mg/d for napsylate salt (Maximum daily dose of APAP: 4000 mg/day APAP; 2000 mg/day APAP in chronic alcoholics)	15 to 60 120 to 180 4 to 6
Tapentadol	50 mg q4–6hours	Subsequent dose is 50, 75, or 100 mg q4–6h, adjusted to analgesia and tolerability. Second dose may be given 1 h after the first dose if necessary. Max recommended dose: 700 mg on first day, 600 mg on subsequent days.	— 60 4 to 6
Tramadol (alone or in combination with APAP)	25 mg every morning	Increase by 25 mg as separate doses every 3 d to 100 mg/d (25 mg q 6 h) Subsequent increments of 50 mg/d may be made every 3 d to 200 mg/d (50 mg q 6 h) After titration, may give 50 to 100 mg q 4 to 6 h Maximum daily dose: 400 mg/d (Maximum 4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics)	< 60 ~120 to 240 3 to 6

Table E2. Use of Long-acting, Opioids in Adults

Long-Acting Opioid †	Initial Dosage	Dosage Titration	Analgesic Onset (Min) Peak (Min) Duration (H)
Fentanyl Transdermal System	25 mcg/h transdermally. q 72 h CONTRAINDICATE D in non-opioid-tolerant patients 12 mcg/h dose has not been evaluated as an initial dose	Increments should be based on supplemental opioid doses, using a ratio of 12 mcg/h t.d. fentanyl for every 45 mg/24 h of supplemental oral morphine equivalent Make increments at least 3 d after initial dose then not more often than q 6 d thereafter as necessary	12 to 18 (h) 24 to 72 (h) 48 to 72
Methadone	2.5 to 10 mg orally. q 8 to 12 h More frequent administration (q 6 h) may be necessary during initiation to maintain analgesia—use extreme caution to avoid overdosage due to long plasma half-life	Increments of 2.5 mg q 8 h may be made every 5 to 7 days START LOW AND GO SLOW	30 to 60 — 4 to 12 Analgesic duration increases with continued use and cumulative effects
Morphine Controlled Release (CR) / Sustained Release (SR) and Extended Release (ER)	15 mg q 8 to 12 h (CR / SR) to 30 mg q 24 h (ER)	Total daily increments of < 30 to 40 mg/d may be made q 2 d	30 to 60 30 to 60 Varies by product; overall range is 8 to 24
Oxycodone Controlled Release	10 mg orally q 12 h	May increase to 20 mg q 12 h after 1 or 2 d Thereafter, the total daily dose may be increased by 25% to 50% of the current dose every 1 or 2 d	30 to 60 90 to 180 8 to 12
Oxymorphone Extended Release	5 mg orally every 12 h	May increase by 5 to 10 mg every 12 h every 3–7 days	— 1 (fasted state) —
Tramadol ER	100 mg once daily If converting from tramadol IR, start at 24-h dosage equivalent rounded down to closest 100 -mg increment	Increase by 100 mg every 5 days based on analgesia and tolerability. Max dose: 300 mg/day	— 12 h 24 h

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]); histamine2 receptor antagonists (cimetidine); neuroleptics (chlorpromazine, haloperidol, methotrimeprazine, perphenazine, thioridazine); protease inhibitors (ritonavir), quinine compounds (hydroxychloroquine, quinacrine, quinine); selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline), and miscellaneous compounds (clomipramine, ketoconazole, ticlopidine).

§ CYP-3A4 Inhibiting Drugs: Ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil

THIS GUIDELINE DOES NOT RECOMMEND THE USE OF LONG-ACTING OPIOID AGONISTS FOR AS-NEEDED (P.R.N.) ADMINISTRATION.

Table E4. Equianalgesic and conversion doses for patients previously receiving other opioids

Opioid Agent	Est. Oral Equianalgesic Dose (Mg) [*]	Initial Conversion Dose (Not Equianalgesic) [†]								
Codeine	180 to 200 [‡]	30 mg q 4 to 6 h								
Fentanyl	— (transdermal)	For converting ONLY to fentanyl from another opioid, use about 12 mcg/h fentanyl transdermally for every 45 mg of oral morphine or equivalent (see Table E5, <i>Initial Fentanyl Transdermal Dosage</i>)								
Hydrocodone	30	50% to 67% of estimated oral equianalgesic dose								
Hydromorphone	7.5	50% to 67% of estimated oral equianalgesic dose								
Methadone	20 acute 2 to 4 chronic	Methadone-to-morphine dosage proportion (%) is dependent on morphine-equivalent dose of previous opioid For gradual conversion to methadone: <table style="margin-left: 40px; border: none;"> <tr> <td style="padding-right: 20px;">Oral morphine</td> <td>Methadone</td> </tr> <tr> <td style="padding-right: 20px;">< 200 mg/d</td> <td>5 mg q 8 h</td> </tr> <tr> <td style="padding-right: 20px;">200 to 500 mg/d</td> <td>~7% of oral morphine-equivalent dose, given in divided doses q 8 h</td> </tr> <tr> <td style="padding-right: 20px;">> 500 mg/d</td> <td>See <i>Methadone Dosing Recommendations for Treatment of Chronic Pain</i></td> </tr> </table> Consider consultation with a pain specialist, clinical pharmacist, or other practitioner who has experience with using methadone for chronic pain	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	See <i>Methadone Dosing Recommendations for Treatment of Chronic Pain</i>
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	See <i>Methadone Dosing Recommendations for Treatment of Chronic Pain</i>									
Morphine	30	50% to 67% of estimated oral equianalgesic dose								
Oxycodone	15 to 20 [§]	50% to 67% of estimated oral equianalgesic dose								
Oxymorphone	10	50% to 67% of estimated oral equianalgesic dose								
Propoxyphene	100 to 130 [‡]	HCl: 65 mg q 6 to 8 h Napsylate: 100 mg q 6 to 8 h								
Tapentadol	<i>No data</i> (50 to 100 [‡])	50 to 100 mg q 4 to 6 h								
Tramadol	<i>No data</i> (100 to 150 [‡])	25 mg every morning								

Many other equianalgesic dosing tables are available that may provide equivalent doses different from those shown here.

[†] 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 (also see *Methadone Dosing Recommendations for Treatment of Chronic Pain*). 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. For fentanyl, see Table E5.

[‡] When converting from weak opioid analgesics to stronger opioids, use the recommended initial doses of the new opioid for opioid-naïve patients. Doses of tapentadol and tramadol should NOT be considered equianalgesic to the doses of pure agonists. Equianalgesic doses have not been established for conversions between either tapentadol or tramadol and pure opioid agonists.

Opioid Conversion Instructions

1. Determine the total 24-hour dose of the current opioid.
 2. Using the estimated equianalgesic dose, calculate the equivalent dose of new analgesic for the desired route of administration.
 3. 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. (For fentanyl, see conversion doses in Table E5).
 4. Take the 24-hour starting dose of the new opioid and divide by the frequency of administration to give the new dose for the new route.
- Consider rescue opioid therapy during the conversion process.

Examples

Conversion to methadone

Patient is receiving a total of 360 mg oral morphine in a 24-hour period.

1. 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 about 25 mg per day.
2. The recommended frequency of administration for methadone is q 8 h (3 doses per day).
3. 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 8 h (22.5 mg/d).

Titrate dose at appropriate intervals depending on response and adverse effects.

Conversion to oxycodone CR

Patient is receiving a total of 360 mg oral morphine in a 24-hour period.

1. From the equianalgesic table, we calculate that the estimated equianalgesic dose of oxycodone is 180 to 240 mg per day.
2. The initial conversion dose of oxycodone is 50% to 67% of 180 to 240 mg per day or about 90 to 160 mg per day.
3. The recommended frequency of administration for oxycodone is every 12 hours (2 doses per day).
4. Consulting the local drug formulary, we find that oxycodone is available in 10-, 20-, 40-, and 80-mg controlled-release tablets. The starting dose of oxycodone controlled-release would be 40 to 80 mg q 12 h. To be conservative, a dose of 40 mg q 12 h (80 mg/d) is selected.

Titrate dose at appropriate intervals depending on response and adverse effects.

E5. Fentanyl Transdermal Dosage (only for converting another opioid)

Oral 24-hour morphine (mg/d)	Fentanyl transdermal (mcg/h)
60–134	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

There are no FDA-approved dosing instructions on how to convert patients from fentanyl to other opioids. After discontinuing the fentanyl patch, titrate the new opioid according to the patient's level of pain relief and tolerability.

Do not use this table to convert from fentanyl transdermal system to other opioid analgesics because these conversion dosage recommendations are conservative. Use of table E5 for conversion from fentanyl to other opioids can overestimate the dose of the new agent and may result in overdosage of the new agent.

Take into consideration that serum fentanyl concentrations decline gradually after removal of the patch, decreasing about 50% in approximately 17 (range 13–22) hours.

Use conservative conversion doses and provide the patient with supplemental short-acting opioids to be taken as needed.

Table 6 Use of Opioid for Chronic Pain in Pregnancy

Medication	Pregnancy Risk Category (a)	Lactation (a)
Codeine	C*‡	D
Fentanyl transdermal	C†‡	UC
Hydrocodone	C†‡	PC
Hydromorphone	B†‡	PC
Methadone	B†‡	PC
Morphine	C†‡	PC
Morphine SR/CR (8-12h) ER (24h)		
Oxycodone	B†‡	PC
Oxycodone CR (12h)		
Oxymorphone	B†‡	PC
Oxymorphone ER (12h)		
Propoxyphene	C†‡	PC
Tapentadol	C†	X (f)
Tramadol	C†	PC
Tramadol ER (24h)		

A = Controlled studies show no risk

B = No evidence of risk in humans

C = Risk cannot be ruled out, but potential benefits may justify potential risk

D = Positive evidence of risk; however, potential benefits may outweigh potential risk

X = Contraindicated in pregnancy

UC = usually compatible; either not excreted into human breast milk in clinically significant amounts or not expected to cause toxicity in infant

PC = probably compatible; no or limited human data

* human data suggest risk

† human data suggest risk in 3rd trimester

‡ Risk category D if prolonged periods or high doses at term

(a) Estimates of risk of opioid therapy in pregnancy and while breastfeeding may be based on expectations of intermittent or short-term use; use of chronic opioid therapy during pregnancy or while breastfeeding should be approached with caution.

Table 7 Opioid for Chronic Pain in Special Population

Medication	Prolonged QTc	Seizures	Elderly or debilitated	Decreased CYP-2D6 activity
Codeine (a)			Caution or Reduced Dose	Less effective
Fentanyl transdermal				
Hydrocodone				? Less effective
Hydromorphone				
Methadone (b)	Caution			
Morphine				
Morphine SR/CR (8-12h) ER (24h)				
Oxycodone				? Less effective
Oxycodone CR (12h)				
Oxymorphone				
Oxymorphone ER (12h)				
Propoxyphene		Caution		X
Tapentadol		Caution	Caution Reduced dose	
Tramadol		X		? less effective
Tramadol ER (24h)				

- a) Codeine is metabolized to morphine by CYP 2D6; both pass into breast milk in small amounts usually considered clinically insignificant; however, caution in known or suspected ultra rapid metabolizers of CYP 2D6 substrates; 2006 case report of death in a nursing infant of CYP 2D6 ultra rapid metabolizer mother associated with high morphine levels in breast milk (Koren et al., 2006).
- b) Methadone is the only long-acting opioid available as an oral solution. See full guideline for Dosing Recommendations for Treatment of Chronic Pain for further details and references.

Table 7 Opioid for Chronic Pain in Special Population

Medication	Swallowing difficulty	GI mal-absorption	Hepatic dysfunction	Renal dysfunction	Renal Dialysis
OS –oral solution RS—rectal suppository RBD = Removed by dialysis ND = no data ♦ = Use caution ↓ = reduce dose X = not recommended					
Codeine (a)			X		X
Fentanyl transdermal	+	+	♦ & ↓	♦ & ↓	♦
Hydrocodone					♦
Hydromorphone	+ OS RS	+ RS	♦ & ↓		♦ (RBD)
Methadone (b)	+ OS		♦ & ↓		♦
Morphine	+ OS RS	+ RS		↓ or X	♦ or X (RBD)
Morphine SR/CR (8-12h) ER (24h)					
Oxycodone	+ OS			♦ & ↓	X (RBD)
Oxycodone CR (12h)					
Oxymorphone				♦ & ↓	♦ (RBD)
Oxymorphone ER (12h)			X		
Propoxyphene			X	X	X
Tapentadol			♦	↓ or X	X (ND)
Tramadol				♦ & ↓	X (RBD)
Tramadol ER (24h)			♦ & ↓		

Table 8 Supplemental Therapy

TYPE OF THERAPY	DESCRIPTION OF PAIN EPISODE
Rescue	Insufficient analgesia during dosage titration
Breakthrough pain	Unpredictable exacerbation of chronic pain otherwise controlled on stable maintenance doses of opioid
Incident pain	Predictable, activity-related exacerbation of chronic pain otherwise controlled on stable maintenance doses of opioid

Opioid Therapy - Titrate to Effect

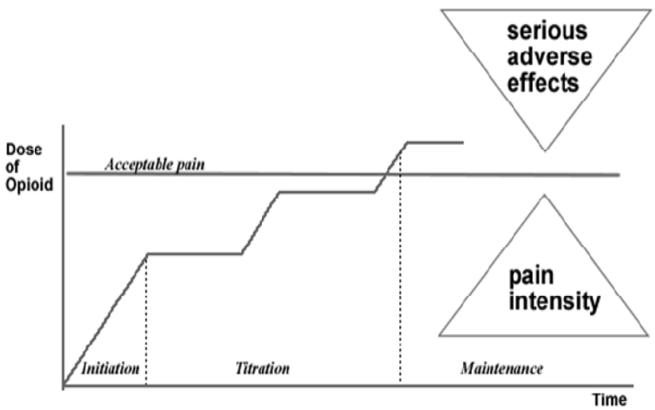


Table 9 | Indication for Referral to Specialty

- Consider consultation or referral to addiction specialty for evaluation and treatment in the following conditions:
- Demonstration of behaviors suggesting addiction to prescribed opioids or substance use disorders
- Patients with a significant chronic, or substantiated pain, who develop addiction behaviors in the context of chronic opioid therapy
- Uncontrolled substance use disorder (excluding nicotine)
- Behaviors characteristic of compulsive drug use (addiction) to either opioids or other drugs or alcohol should be referred to a addiction specialty
- Complex conditions who manifest behaviors characteristic of addiction with multiple co-occurring psychiatric disorders
- Need for tapering of opioids or unable to tolerate tapering after discontinuation of OT.
- Consider consultation with a SUD specialist to evaluate the risk of recurrent substance abuse or to assist with ongoing management.
- Refer patient for psychosocial treatments specific to prescription medication addiction/abuse. These can include addiction counselors comfortable with such topics, and self-help organizations (Pills Anonymous/PA, the National Chronic Pain Outreach association, and other similar organizations).