Appendix D: Drug Tables

A. Short-acting, Orally Administered Opioids

Table D-1: Use of Short-acting, Orally Administered Opioids in Adults (243)

Short-acting Opioids[a]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Timing	Dosing In Special Populations	Other Considerations
Codeine (alone or in combination with APAP or ASA) • Codeine available as 15, 30, and 60 mg tablets • Combination products vary in codeine content from 15 to 60 mg/dose unit • Oral solution codeine/APAP 12/120 mg per 5 ml	• 15 to 30 mg • every 4 to 6 hr • Initial dose • based upon codeine component, maximum dose based upon non-opioid component	• Maximum APAP dose: 4000 mg/d (2000 mg/d in chronic alcoholics or in hepatic impairment) • Codeine alone is a weak analgesic; more effective alternatives are available (including codeine in combination with APAP or ASA)	• **Analgesic Onset (min):** 15 to 30 • **Peak (min):** 30 to 60 • **Duration (hr):** 4 to 6 • **t½ (hr):** ~3	• *Elderly or debilitated*: Use with caution • *Hepatic dysfunction:* Conversion to active metabolite (morphine) may be reduced in patients with cirrhosis; avoid use in patients with liver disease • *Renal dysfunction:* Use lower dosage or an alternative analgesic	• Codeine may be less effective in patients with decreased CYP- 2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[b]) because of decreased conversion to the active metabolite, morphine • CYP-2D6 ultra-rapid metabolizers[c] can have extensive conversion to morphine with increase in opioid-mediated effects
Hydrocodone (in combination with APAP, ASA, or IBU) • Hydrocodone/APAP available as oral elixir, solution, and tablets; hydrocodone/IBU available as tablets; combination products vary in hydrocodone content (2.5 to 10 mg per dosage unit)	• 5 to 10 mg • every 6 hr (hydrocodone component) • Initial dose • based upon hydrocodone component • Maximum dose based upon non-opioid component	• Maximum dose: • 60 mg/d (4000 ♦ mg/d APAP; 2000 mg/d APAP in chronic alcoholics or hepatic impairment) for hydrocodone + APAP combination OR ♦ 25 to 50 mg/d (1000 mg/d IBU) for hydrocodone + IBU combination	• **Analgesic Onset (min):** 10 to 20 • **Peak (min):** 60 to 100 • **Duration (hr):** 4 to 8 • **t½ (hr):** ~4	• *Elderly or debilitated*: Use with caution; start with reduced dose (2.5-5 mg) of hydrocodone component • *Hepatic dysfunction:* Use with caution	• 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[b]) • CYP-2D6 ultra-rapid metabolizers[c] can have extensive conversion to hydromorphone with potential increase in opioid-mediated effects

Short-acting Opioids[a]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Timing	Dosing In Special Populations	Other Considerations
Hydromorphone • Available as oral liquid 1 mg/ml; 2, 4, and 8 mg tablets; 0.2, 1, and 2 mg/ml solution for injection; and 3 mg rectal suppository	• 2 mg every 4 to 6 hr • May give an initial dose of 4 to 8 mg for severe pain	• There is no optimal or maximum dose of hydromorphone; patients on LOT are likely to become tolerant[d] and require doses higher than the usual dosage range to maintain the desired effect	• **Analgesic Onset (min):** 15 to 30 • **Peak (min):** 30 to 60 • **Duration (hr):** 3 to 4 • **t½ (hr):** 2 to 3	• *Elderly or debilitated*: Use with caution, start at 25% to 50% of usual dose at low end of dosing range • *Hepatic / Renal dysfunction*: Reduce initial dose by 25% to 50% of usual dose depending on degree of impairment	• Women appear to have a 25% higher Cmax than men • Hepatic metabolism via glucuronidation to inactive metabolites, mainly to hydro-morphone 3-glucuronide, a potentially neuroexcitatory metabolite which can accumulate in renal impairment
Morphine • Available as oral solution (10 or 20 mg/5 ml, or 100 mg/5 ml for opioid- tolerant patients only) or as 15 or 30 mg tablets; also available as a 5, 10, 20, and 30 mg rectal suppository and as a solution for injection in various concentrations	• 10 to 30 mg every 4 hr	• There is no optimal or maximum dose of morphine; patients on LOT are likely to become tolerant[d] and require doses higher than the usual dosage range to maintain the desired effect	• **Analgesic Onset (min):** 30 • **Peak (min):** 60 • **Duration (hr):** 3 to 5 • **t½ (hr):** 2 to 4 in adults	• *Elderly or debilitated*: Give with extreme caution; use lower dose • *Hepatic dysfunction*: Use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times; half-life may be doubled (3 to 4 hr) and bioavailability is increased • *Renal dysfunction*: Reduce dose or, if severe renal impairment exists, avoid use (see *Other Considerations*)	• M6G, an active metabolite, may accumulate in renal impairment • M3G, a metabolite without analgesic activity, may accumulate in renal impairment; this metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia

Short-acting Opioids[a]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Timing	Dosing In Special Populations	Other Considerations
Oxycodone (alone or in combination with APAP or ASA) • Single-agent oxycodone available as oral solution 5 mg/5 ml, 20 mg/1 ml, and oral tablet 5, 10, 15, 20, and 30 mg • Combination products vary in oxycodone content, 2.5 to 10 mg per dose unit	• 5 to 15 mg every 4 to 6 hr • Initial dose based upon oxycodone component • Maximum dose based upon non-opioid component	• For combination products, maximum dose is limited by APAP or ASA content (4000 mg/d for both; 2000 mg/d APAP in chronic alcoholics or patients with hepatic impairment) • There is no optimal or maximum dose of oxycodone; patients on LOT are likely to become tolerant d and require doses higher than the usual dosage range to maintain the desired effect	• **Analgesic Onset (min):** 10 to 15 • **Peak (min):** 30 to 60 • **Duration (hr):** 3 to 6 • **t½ (hr):** 3.2 to ~4	• *Elderly or debilitated*: Reduce dosage • *Hepatic / Renal*: Use with caution; consider reducing dose and increasing frequency of dosing	• Conversion to the active metabolite, oxymorphone (< 15% plasma concentration), may be decreased in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[b]) • Higher peak plasma oxycodone (50%) and noroxycodone (20%), higher AUC for oxycodone (60%), noroxycodone (50%), and oxymorphone (40%) in patients with CrCl < 60 ml/min • Higher oxycodone peak plasma concentration (50%) and AUC values (95%) in mild to moderate hepatic impairment; oxymorphone peak plasma concentration and AUC values are lower by 30% and 40%, respectively
Oxymorphone • Available as 5 or 10 mg tablets and 1mg/ml solution for injection	• 5 to 10 mg every 4 to 6 hr	• There is no optimal or maximum dose of oxymorphone; patients on LOT are likely to become tolerant and require doses higher than the usual dosage range to maintain the desired effect	• **Analgesic Onset (min):** 30 to 45 • **Peak (min):** N/A • **Duration (hr):** 4 • **t½ (hr):** 7 to 0	• *Elderly or debilitated*: Use with caution and start at low end of dosing range; levels are increased 40% in patients ≥65 years	• Food: When taken orally with a high-fat meal, food has been shown to increase peak levels of oxymorphone immediate-release are 38 to 50% greater; must be taken on an empty stomach at least 1 hr before or 2 hr after a meal

Short-acting Opioids[a]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Timing	Dosing In Special Populations	Other Considerations
Oxymorphone (cont.)				• *Hepatic dysfunction* ♦ *Mild hepatic impairment:* Use cautiously, start at low end of dosing range ♦ *Moderate and severe hepatic impairment:* Contraindicated • *Renal dysfunction*: Bioavailability is increased 57 – 65% in moderate and severe impairment; start at lower doses and adjust slowly	• Must NOT be taken concomitantly with alcohol; alcohol (240 ml of 4% to 40% ethanol) can cause highly variable effects on peak drug levels, ranging from a decrease of 50% to an increase of 270% (demonstrated with ER oxymorphone)
Tapentadol • Available as 50, 75, or 100 mg tablets	• 50 mg every 4 to 6 hr • For diabetic peripheral neuropathy (DPN): 50 mg every 12 hrs	• Subsequent dose is 50, 75, or 100 mg every 4 to 6 hr, adjusted to analgesia and tolerability • Second dose may be given 1 hr after the first dose if necessary • Max recommended dose: 700 mg on first day, 600 mg on subsequent days • Use tapentadol only under careful medical supervision at lowest effective dose • Patients on LOT are likely to become tolerant [d] and require doses higher than the usual dosage range to maintain the desired effect	• **Analgesic Onset (min):** N/A (rapid) • **Peak (min):** 60 • **Duration (hr):** 4 to 6 • **t½ (hr):** ~4	• *Elderly*: Consider starting at the lowest recommended dose • *Hepatic dysfunction:* ♦ *Mild hepatic impairment:* No dosage adjustment ♦ *Moderate hepatic impairment:* Start at 50 mg and give subsequent doses at least 8 hr apart (max. 3 doses in 24 hr) • *Severe hepatic impairment:* Use is not recommended • *Renal dysfunction:* No dosage adjustment for mild or moderate renal impairment; not recommended in severe renal impairment (CrCl < 30 ml/min)	• Must NOT be taken concomitantly with alcohol which can increase serum tapentadol concentration • Food: When administered after a high fat/calorie meal, the AUC and Cmax increased by 25% and 16% respectively; management: may administer without regards to meals • If used in combination with other CNS depressants, consider dose reduction of one or both agents • Use with or within 14 days of MAOIs is contraindicated • Monitor for signs and symptoms of serotonin syndrome when used in combination with serotonergic agents

Short-acting Opioids[a]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Timing	Dosing In Special Populations	Other Considerations
Tapentadol (cont.)		• For DPN: Titrate in increments of 50 mg no more-frequently than twice daily every 3 days to effective dose (therapeutic range: 100 to 250 mg every 12 hrs)		• *Respiratory dysfunction:* Use with caution because of respiratory depressant effects; consider non–mu opioid agonist analgesics	
Tramadol (alone or in combination with APAP) • Tramadol available as 50 mg and 100 mg tablets, a 5 mg/ml oral solution, and as a tablet in combination with APAP (325 mg APAP, 37.5 mg tramadol)	• 25 mg every morning	• May increase by 25 mg per day every 3 days to 100 mg tramadol/d (25 mg every 6 hr) • Subsequent increments of 50 mg/d may then be made every 3 days to 200 mg/d (50 mg every 6 hr) • After titration, may give 50 to 100 mg every 4 to 6 hr • Maximum daily dose of tramadol: 400 mg/d • Combination product: maximum 4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics or in hepatic impairment	• **Analgesic Onset (min):** <60 • **Peak (min):** ~120 to 180 • **Duration (hr):** 6 • **t½ (hr):** 6.3 ± 1.4	• *Elderly or debilitated:* In elderly patients >75 years: give <300 mg/d in divided dose; use with caution in debilitated patients • *Hepatic dysfunction:* Decrease dosage to 50 mg once every 12 hr in patients with cirrhosis • *Renal dysfunction*: ♦ *CrCl >30 ml/min:* No *change in dose or frequency required* ♦ *CrCl <30 ml/min: Increase* dosing interval to 12 hr and decrease maximum daily dose to 200 mg • *Dialysis patients*: Can receive their regular dose on the day of dialysis (<7% of a dose is removed by hemodialysis)	• Slower initiation and titration improves tolerability • Inhibits reuptake of serotonin and norepinephrine; concomitant use with MAOIs or SSRIs may increase risk of seizures, serotonin syndrome • Dose carefully or use another agent in patients on serotonergic agents • Seizures reported within the recommended dosage range; increased risk above recommended dosage range and in patient with seizure disorder, history of seizures, in conditions with increased risk of seizures, or with other drugs that increase seizure risk; observe maximum dose limits

Short-acting Opioids[a]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Timing	Dosing In Special Populations	Other Considerations
Tramadol (alone or in combination with APAP) (cont.)					• Serious anaphylactoid reactions reported, often following first dose; patients with a history of anaphylactoid reaction to codeine and other opioids may be at increased risk

[a] Check local formulary for available formulations

[b] 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), miscellaneous compounds (clomipramine, ketoconazole, ticlopidine)

[c] CYP-2D6 ultra-rapid metabolizers include 1% of Asian and Hispanic, 1-10% of Caucasians, 3% of African-Americans, and 16-28% of N. African and Arabic populations

[d] Opioid tolerance is assumed in patients already taking fentanyl 25 mcg/hr OR daily doses of the following oral agents for ≥ 1 week: ≥ 60 mg oral morphine, 30 mg oxycodone, 8 mg hydromorphone, 25 mg of oxymorphone, or an equianalgesic dose of another opioid

Abbreviations: APAP: acetaminophen; ASA: acetylsalicylic acid; CNS: central nervous system; CrCl: creatinine clearance; d: day(s); ER: extended-release; hr: hour(s); IBU: ibuprofen; LOT: long-term opioid therapy; M3G: morphine-3-glucuronide; M6G: morphine-6-glucuronide; MAOIs: monoamine oxidase inhibitors; mg: milligram(s); min: minute(s); mL: milliliter(s); SSRIs: selective serotonin reuptake inhibitors

B. Long-acting/Extended-release Opioids

Table D-2. Use of Long-acting/Extended-release Opioids in Adults (243)

- Long-acting/ER opioids expose patients and other users to the risks of opioid misuse and OUD, which can lead to overdose and death, even when used at recommended dosages. Long-acting/ER opioids should be reserved for patients for whom alternative analgesic treatment options (e.g., non-opioid analgesics or immediate-release opioid analgesics) are ineffective, not tolerated, or provide inadequate control of pain. Assess each patient's risk prior to prescribing long-acting/ER opioids and institute risk mitigation strategies.
- The FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) program (see http://www.er-la-opioidrems.com/IwgUI/rems/home.action) is necessary for all opioid analgesics intended for outpatient use to manage known or potential serious risks associated with their use.(244)
- Most abuse deterrent technologies have been designed to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. Despite these efforts, no opioid formulation prevents consumption of a large number of intact capsules or tablets, which continues to be the most common method of abuse.

- Long-acting/ER opioids should not be used for management of acute pain (with exception of oxycodone/acetaminophen ER tablets), as an as-needed medication, or on initiation of long-term opioids (see Recommendation 11)

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Buprenorphine buccal film • Available in strengths of 75, 150, 300, 450, 600, 750 and 900 mcg/film for twice daily administration	• 75 mcg once or twice daily for at least 4 days, then increase dose to 150 mcg every 12 hr • There is potential for buprenorphine buccal film to precipitate withdrawal in patients already on opioids; to reduce risk, the dose of other opioids should be tapered to ≤30 mg MEDD before initiating buprenorphine buccal film • See Section E. Additional Buprenorphine Guidance for alternate dosing instructions	• After initial dosing, dosing changes as necessary can proceed in increments of 150 mcg every 12 hr, no more frequently than every 4 days • Patients on prior dose of opioid 30 to 89 mg MEDD may initiate buprenorphine film at 150 mcg every 12 hr, 90 to 160 mg MEDD may initiate at 300 mcg every 12 hr; if prior opioid is >160 mg MEDD – consider an alternative analgesic • Time to steady state ~3 days with every 12 hr dosing	• *Elderly:* Initiation at the low end of the dosing range is recommended • *Renal dysfunction:* No dose adjustment recommended • *Hepatic dysfunction:* Patients with severe hepatic impairment should have starting and titration doses reduced by half that of patients with normal liver function	• QTc prolongation reported with recommended doses of buprenorphine; maximum dose of 900 mcg every 12 hr established due to the potential for this adverse effect; avoid in patients with long QT syndrome, family history of long QT syndrome, or those taking Class IA or Class III antiarrhythmic drugs • Buprenorphine buccal film is a potential treatment option for patients with significant renal impairment and those with gastrointestinal structural or functional abnormality that interferes with swallowing or absorption of orally administered medications
Buprenorphine TDS • Available in every 7 day patch formulation that delivers transdermal buprenorphine at the following rates: 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr	• In opioid-naïve or in patients on <30 mg MEDD of alternate agent: Initiate treatment with 5 mcg/hr patch • There is potential for buprenorphine to precipitate withdrawal in patients already on opioids; to reduce risk, the dose of other opioid should be tapered to ≤30 mg MEDD before initiating buprenorphine; the 10 mcg/hr patch may then be initiated at the next dosing interval	• Initial buprenorphine TDS dose based on previous oral morphine equivalent: 5mcg/hr for <30mg MEDD, 10 mcg/hr for 30-80mg MEDD • The maximum dose of buprenorphine TDS 20 mcg/hr may not provide adequate analgesia for patients requiring greater than 80 mg MEDD; an alternate analgesic should be considered	• Dosage does not need to be adjusted in patients with mild or moderate hepatic impairment, renal impairment, or in the elderly	• Dose of one 20 mcg/hr patch per week should not be exceeded due to risk of QTc prolongation • Avoid use in patients with long QT syndrome, family history of long QT syndrome, or those taking Class IA or Class III antiarrhythmic medications • Advise patients that application of external heat (e.g., hot baths, sunbathing, saunas, heating pads) increases maximum plasma concentration of buprenorphine and risk of fatal overdose

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Buprenorphine TDS (cont.)		• Because steady-state plasma concentrations are achieved within 72 hours, buprenorphine TDS dosage may be adjusted every 3 days		• Potential treatment option for patients with significant renal impairment or those with gastrointestinal structural or functional abnormality that interferes with swallowing or absorption of oral medications
Buprenorphine and Buprenorphine/ Naloxone • Buprenorphine is available in 2 mg and 8 mg SL tabs • Buprenorphine/ naloxone is available in 2-0.5 and 8-2 mg/ SL tablets and 2-0.5, 4-1, 8-2, and 12-3 mg film	• **Used off-label for pain management:** FDA approved for the treatment of opioid dependence or OUD • 2 to 4 mg of buprenorphine or 2**/**0.5 mg to 4/1 mg of buprenorphine/ naloxone in divided doses should be adequate for most patients	• For patients who are on buprenorphine or buprenorphine naloxone for OUD, the current 24-hour dose could be split and divided for BID or TID dosing for pain management • To avoid precipitating withdrawal in patients that are being converted from other opioids, initiation with buprenorphine/naloxone SL tablet should be undertaken when objective and clear signs of mild withdrawal are evident; 2 to 4 mg of buprenorphine or 2**/**0.5 mg to 4/1 mg of buprenorphine/ naloxone in divided doses should be adequate for most patients	• *Elderly:* Use cautiously and monitor closely • Dosage does not need to be adjusted in patients with mild or moderate hepatic impairment or renal impairment; avoid in patients with severe hepatic impairment	• BUP sublingual tablet contains no naloxone and may be preferred during pregnancy • Buprenorphine/naloxone may be the preferred opioid in patients with comorbid pain and OUD

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Buprenorphine and Buprenorphine/ Naloxone (cont.)		• A buprenorphine dosing strategy designed to avoid precipitated withdrawal during the conversion is the low dose buprenorphine initiation (LDBI) strategy. This method introduces small incremental doses of buprenorphine while: simultaneously slowly reducing the dose of the full opioid agonist over time; or maintaining the current full agonist opioid dose and subsequently, stopping the full agonist once buprenorphine dose is sufficient to mitigate withdrawal symptoms. • Given that currently there is no consensus regarding a particular LDI approach or clinical trials comparing the proposed LDBI schedules or comparing traditional vs LDBI protocols, we cannot recommend and specific LDPI protocol at this time. • May titrate dose to 16 to 24 mg/day in divided doses if needed		

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Fentanyl TDS • Available in every 3 day patch formulation that delivers transdermal fentanyl at the following rates: 12 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr	• The initial dose of fentanyl TDS in opioid- tolerant patients[2] is 25 mcg/hr, applied every 72 hr; the 12 mcg/hr dose has not been evaluated as an initial dose • Fentanyl TDS is contraindicated in non-opioid-tolerant patients • Fentanyl TDS is contraindicated in the management of mild or post-operative pain, and as an "as-needed" analgesic	• Fentanyl TDS must be used only on intact skin • Dose change increments should be based on supplemental opioid doses, using a ratio of fentanyl TDS 12 mcg/hr for every 45 mg/ 24 hr of supplemental oral MEDD • Dosing changes, as necessary, should occur at least 3 days after the initial dose; thereafter, not more often than every 6 days	• *Elderly:* Twice as sensitive to fentanyl as younger patients; avoid initiation at doses >25 mcg/hr unless patient is already taking >135 mg oral morphine or equivalent • *Hepatic impairment:* Reduce dose by 50% in mild- moderate impairment and avoid use if impairment is severe • *Renal Impairment:* ♦ CrCl >50 ml/minute: no dosage adjustment necessary ♦ CrCl 10 to 50 ml/ minute: 75% of normal dose ♦ CrCl < 10 ml/minute: 50% of normal dose	• Consider fentanyl TDS in patients with persistent, moderate-to- severe pain who cannot take oral ER morphine or oral ER oxycodone • Avoid application of external heat sources (e.g., heating pads, electric blankets, heat lamps, saunas, hot tubs, hot baths, sunbathing, heated water beds) to the application site while the patch is worn as heat may increase release and speed absorption of fentanyl • *Patients with fever*: Increased body temperature may increase release of fentanyl from the TDS; monitor patients for opioid adverse effects and modify dosage as necessary • Using damaged or cut fentanyl TDS patches can lead to rapid release of the contents of the patch and fatal overdose • Use of fentanyl TDS with CYP3A4 inhibitors[3] can result in increased fentanyl plasma concentrations, increased or prolonged opioid effects, including fatal respiratory depression; use extreme caution and frequent monitoring in patients receiving these combinations • CYP 3A4 inducers may increase fentanyl clearance

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Hydrocodone ER • **ER tablets** contain 20, 30, 40, 60, 80, 100 or 120 mg hydrocodone for once daily administration • **ER capsules** contain 10, 15, 20, 30, 40 or 50 mg hydrocodone for every 12 hr administration	• *Opioid-naïve patients:* 20 mg ER tablet once daily • *Opioid-naïve patients:* 10 mg ER capsule every 12 hr • *Opioid tolerant[b] patients:* Convert current opioid to equianalgesic daily dose of hydromorphone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	• *For opioid-experienced, both ER tablets and capsules:* Convert current opioid to equianalgesic hydrocodone dose then reduce that dose by 33-50%; initiate at nearest whole-tablet or capsule strength, rounding down as necessary • *For both tablets and capsules:* Dose change increments of 20 mg per day may be made every 3 to 5 days • Steady state achieved in ~3 days of dosing	• *Elderly:* No significant pharmacokinetic differences • *Patients with renal impairment:* Hydrocodone plasma concentrations are increased in moderate or severe impairment; use low initial dose and monitor closely for AEs such as excessive sedation and respiratory depression • *Patients with hepatic impairment:* No dosage adjustment is required in mild or moderate hepatic impairment; start with the lowest dose, 10 mg, in patients with severe hepatic impairment, and monitor closely	• CYP3A4 inhibitors[c] may decrease clearance of hydrocodone, increase plasma concentrations, and increase risk of overdose; CYP3A4 inducers[d] may increase clearance and reduce opioid effect • Both ER tablets and ER capsules are formulated with polyethylene oxide which imparts ER properties • Hydrocodone ER tablets or capsules must be swallowed intact and should not be cut, broken, chewed, crushed or dissolved due to risk of fatal overdose • ER tablet has abuse deterrent labeling related to resistance to crushing and high viscosity when dissolved in aqueous solution • ER capsule has abuse deterrent properties but is not FDA-labeled as an abuse deterrent formulation

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Hydromorphone ER Tablets • Available as 8, 12, 16, and 32 mg tablets for once daily administration	• Not indicated in opioid – naïve patients due to the risk of respiratory depression • *Opioid tolerant[b] patients:* Convert current MEDD to equianalgesic daily dose of hydromorphone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	• Dosage adjustments may be made in increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia • Steady state reached after 3 to 4 days of once-daily dosing	• *Elderly:* Initiate at low dose and titrate slowly; monitor closely • *Patients with renal impairment:* Start patients with moderate impairment at 50% of usual dose, and patients with severe impairment at 25% of usual dose • *Patients with hepatic impairment:* Start patients with moderate impairment at 25% of usual dose in non-impaired patients	• Hydromorphone ER tablets must be swallowed intact and should not be cut, broken, chewed, crushed or dissolved due to risk of fatal overdose • Hydromorphone ER contains sulfites • Hydromorphone ER has abuse deterrent properties but is not FDA-labeled as an abuse deterrent formulation
Methadone • Available as 5 and 10 mg tablets and oral solution, 5 or 10 mg/ 5 ml, for every 8 to 12 hr administration	• Start low and go slow • Should not be used for as-needed supplemental OT • *Initial dose:* 2.5 to 5 mg orally every 8 to 12 hr; more frequent administration (every 6 hr) may be necessary during initiation to maintain analgesia • See Section D. Methadone Dosing Guidance for detailed dosing information including dosing recommendations in patients previously exposed to opioids • Monitor patients carefully during initiation, conversions to and from other opioids, and dose titration	Dose change increments of 2.5 mg every 8 hr may be made every 5 to 7 days • Delayed analgesia or toxicity may occur because of drug accumulation after repeated doses, e.g., on days 2 to 5; if patient has excessive sedation during this timeframe, consider temporarily holding dose(s), lowering the dose, and/or slowing the titration rate • Once a stable analgesic dose is reached, the dosing interval may be extended to every 8 to 12 hr or longer	• *Elderly or debilitated*: Consider reduced dosing in elderly or debilitated patients who may be more sensitive to opioid adverse effects • *Hepatic dysfunction*: No dosage adjustments required in patients with stable chronic liver disease or mild-to-moderate hepatic dysfunction; avoid in severe liver disease • *Renal dysfunction*: Methadone and its metabolites do not accumulate in patients with renal failure; however, dosage reduction by up to 50- 75% is recommended in patients with CrCl <10 mL/ min	• Prescribers of methadone should be thoroughly familiar with its complex pharmacokinetic and pharmacodynamic properties or consult a clinician with experience in dosing methadone • Plasma half-life (22 to 128 hr short- term; 24 to 48 hr at steady-state) may be longer than the analgesic duration • Methadone has little cross-tolerance with other opioids; therefore, even patients with a high degree of opioid tolerance may be at risk for overdose when switched to methadone • Methadone is the only long-acting opioid available as an oral solution

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Methadone (cont.)				• Methadone may be subject to drug interactions with agents that can influence CYP2B6 (e.g., ticlopidine) • May prolong QTc intervals on ECG; risk of torsade de pointes; see Appendix D for detailed QTc monitoring information
Morphine CR or SR • Available in 15, 30, 60, 100, and 200 mg strengths for every 8 to 12 hr administration • Morphine ER capsules available in 10, 20, 30, 40, 50, 60, 75, 80, 90, 100, 120, and 200 mg capsule strengths for once daily administration **Morphine and Naltrexone ER Capsule** • Available as 20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2, and 100/4 capsule strengths (mg morphine/mg naltrexone) for once or twice-daily administration	• *Opioid-naïve patients:* Morphine CR or SR 15 mg every 8 to 12 hr • Total daily increments of <30 to 40 mg/d may be made every 2 days • *Opioid-naïve patients:* Morphine ER capsules are not indicated in opioid-naïve patients • *Patients who are not opioid tolerant:* Start morphine ER at 30 mg daily, may adjust every 1 to 2 days • *Opioid-naïve patients:* Initiate at the lowest dose, 20 mg/ 0.8 mg once daily • *Opioid tolerant[b] patients:* Convert current opioid to equianalgesic daily dose of morphine; reduce the calculated amount by 33-50% for initial start dose (see Table D-3) • Dose may be up titrated no more frequent than every 1 to 2 days	• Morphine CR or SR 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 may be sprinkled onto a small amount of soft food (for administration without chewing) or administered via 16F gastrostomy tube • Steady state achieved with morphine ER within 24 to 36 hr • Morphine/naltrexone must be swallowed whole or the contents of the capsules sprinkled on apple sauce; crushing, dissolving, or chewing pellets may cause a fatal overdose (particularly in the opioid-naïve patient) and the absorption of naltrexone could increase the risk of precipitating withdrawal in opioid tolerant patients	*Information applies to all formulations of morphine listed* • *Elderly:* Use with caution and at lower dose • *Patients with renal dysfunction:* Bioavailability is increased and clearance is decreased; metabolites M3G and M6G accumulate significantly • Reduce dose for CrCl of 30 to ≤ 60 ml/min by 50 to 75%, For CrCl of 15% to 30% reduce dose by 25% to 50% or avoid use. *Patients with hepatic dysfunction:* Clearance decreases and half-life increases; M3G and M6G to morphine ratios are reduced; use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times	• Morphine SR is preferred first-line long-acting agent because of similar efficacy to other long-acting opioids, comparable safety profile, provider familiarity with use, and lower cost • M6G, an active metabolite, may accumulate in renal impairment and contribute to excessive opioid effects • M3G, a metabolite without analgesic activity, may accumulate in renal impairment; this metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia • Morphine/naltrexone ER capsule has abuse deterrent labeling related to potential to precipitate withdrawal if drug is taken by other than oral route

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Morphine CR or SR and Morphine and Naltrexone ER Capsule (cont.)		• Morphine/naltrexone: If once daily administration results in inadequate analgesia, may switch to twice daily dosing		
Oxycodone ER • **Tablets** available in 10, 15, 20, 30, 40, 60, and 80 mg strengths for every 12 hr administration • **Capsules** available in 9, 13.5, 18, 27 and 36 mg strengths for every 12 hr administration	• *Opioid-naïve patients:* 10 mg (tablets) or 9 mg (capsules) orally every 12 hr • *Opioid tolerant*[b] *patients:* Convert current opioid to equianalgesic daily dose of oxycodone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	• *Dose change increments:* May increase to 20 mg (tablets) or 18 mg (capsules) every 12 hr after 1 or 2 days; thereafter, the total daily dose may be increased by 25-50% of the current dose every 1 or 2 days • ER tablets are not bioequivalent to ER capsules; 10 mg oxycodone HCl (ER tablet) = 9 mg oxycodone base (ER capsule) • Steady state achieved with tablets or capsules in 24 to 36 hr with repeat dosing	• *Elderly*: Plasma concentrations of oxycodone are increased ~15% in the elderly; however, usual dosing and dosing intervals may be appropriate • *Patients with renal dysfunction*: Plasma concentrations of oxycodone are increased ~50% in patients with CrCl <60 ml/min; dose conservatively and adjust according to clinical situation • *Patients with hepatic dysfunction*: Reduce initial dose to 1/3 to 1/2 of the usual dose and monitor closely	• Recommended for patients who experience intolerable, unmanageable adverse effects to long- acting morphine • Both ER tablets and ER capsules have abuse deterrent labeling related to resistance to abuse by intranasal and intravenous means • ER tablets should be swallowed whole, not broken, chewed, or crushed • ER capsules may be opened and sprinkled on soft food or administered via feeding tube

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxycodone/APAP ER • Available as tablets containing oxycodone 7.5 mg and APAP 325 mg for every 12 hr administration	• *Opioid-naïve patients:* May initiate therapy with the standard dose of 2 tablets every 12 hr • A standard, single dose consists of 2 tablets totaling 15 mg oxycodone/650 mg APAP • This is the only long-acting/ER opioid to have an acute pain indication	• The polyethylene oxide content causes the tablet to swell and become sticky when wet. This has the potential to cause obstruction of the airway or GI obstruction • Steady state concentration of both components are reached within 24 hr of product initiation	• *Elderly:* Take precautions when determining the dosing amount and frequency in geriatric patients since a greater sensitivity to oxycodone may be observed in this patient population when compared to younger patients • *Patients with renal or hepatic dysfunction:* Patients with renal dysfunction (CrCl <60 ml/min) or hepatic dysfunction should initiate therapy with 1 tablet every 12 hr and adjust as needed	• This long-acting/ER opioid is an exception to the REMS requirements due to the relatively low amount of oxycodone contained in each tablet • Oxycodone/APAP ER tablets are formulated with PEO which is responsible for its ER in addition to labeled abuse deterrent properties • Patients should be instructed not to pre-soak, lick, or otherwise wet tablets prior to swallowing and to take one tablet at a time with adequate water to insure complete and immediate swallowing • Breaking, chewing, crushing, cutting, dissolving, or splitting the tablets will result in uncontrolled release of oxycodone and can lead to overdose or death
Oxymorphone ER Tablets • Available as 5, 7.5, 10, 15, 20, 30 and 40 mg tablets for every 12 hr administration	• *Opioid-naïve patients:* Initiate at 5 mg every 12 hr • *Opioid tolerant[b] patients:* Convert current opioid to equianalgesic daily dose of oxycodone; reduce the calculated amount by 33-50% for initial daily start dose (see Table D-3)	• *Dose change increments:* May increase by 5 to 10 mg every 12 hr every 3 to 7 days • Oxymorphone ER tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth • Steady-state plasma levels are achieved after 3 days of multiple dose administration	• *Elderly:* Plasma drug levels are about 40% higher in elderly versus younger subjects; use caution, starting at the low end of dosing range and titrating slowly	• Must be taken on an empty stomach at least 1 hr before or 2 hr after a meal; food has been shown to increase peak levels of oxymorphone ER by 50% • Must NOT be taken concomitantly with alcohol, which can cause highly variable effects on peak drug levels, ranging from a decrease of 50% to an increase of 270%

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxymorphone ER Tablets (cont.)			• *Patients with renal dysfunction:* Bioavailability is increased by 57% in moderate impairment and by 65% in severe impairment; in patients with CrCl <50 mL/min, oxymorphone should be started with the lowest dose and titrated slowly • *Patients with hepatic dysfunction:* Use with caution in patients with mild hepatic impairment, starting with lowest dose and titrating slowly • Contraindicated in patients with moderate or severe hepatic impairment	
Tapentadol ER • Available as tablets containing 50, 100, 150, 200, or 250 mg tapentadol fortwice daily dosing	• *In opioid-naïve and non-tolerant patients:* Initiate therapy with 50 mg twice daily; use of higher starting doses in patients who • are not opioid tolerant may cause fatal respiratory depression • There are no established conversion ratios for conversion from other opioid to tapentadol ER; convert current opioid to an estimated equianalgesic daily dose of tapentadol; reduce the calculated amount by 33-50% for initial daily start dose (see Table D-3)	• *Dose change increments:* May increase dose by no more than 50 mg twice daily every 3 days • *Maximum daily dose*: 500 mg daily • Tapentadol ER tablets must be taken whole; crushing, chewing, or dissolving tablets will result in uncontrolled delivery of tapentadol and can lead to overdose or death • Steady state is attained after the third dose (24 hr after the first twice daily multiple dose administration)	• *Elderly:* No dosing adjustment needed, consider starting at lowest recommended dosage • *Patients with renal dysfunction:* No dosage adjustment for mild or moderate renal impairment; not recommended in severe renal impairment • *Patients with hepatic dysfunction:* Use not recommended in severe hepatic impairment	• Must NOT be taken concomitantly with alcohol which can increase serum tapentadol concentration and cause fatal overdose • Use with or within 14 days of MAOIs is contraindicated

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Tramadol ER • Available as 100, 200 and 300 mg tablets and capsules for once daily administration	• Patients not currently on tramadol: 100 mg once daily • Converting from tramadol IR: Start at 24 hr dosage equivalent rounded down to closest 100 mg increment	• Dose change increments: May increase by 100 mg every 5 days based on analgesia and tolerability • Maximum dose: 300 mg/day	• Elderly: Start at low end of dosing range; use particular caution, especially in patients >75 years • Renal dysfunction: Avoid use if CrCl <30 ml/min • Hepatic dysfunction: Avoid use in severe hepatic impairment (Child-Pugh Class C)	• Must be swallowed whole and must not be chewed, crushed, or split • See warnings and precautions under Other Considerations for tramadol IR (Table D-1)

[a] Check local formulary for available formulations

[b] Opioid tolerance is assumed in patients already taking fentanyl 25 mcg/hr OR daily doses of the following oral agents for ≥ 1 week: ≥ 60 mg oral morphine, 30 mg oxycodone, 8 mg hydromorphone, 25 mg of oxymorphone or equianalgesic dose of another opioid

[c] CYP3A4 inhibiting agents include: ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil

[d] CYP3A4 inducing agents include: carbamazepine, phenobarbital, phenytoin, primidone, rifampin

Abbreviations: APAP: acetaminophen; CR: morphine controlled; CrCl: creatinine clearance; CYP2B6: cytochrome P450 2B6; CYP3A4: cytochrome P450 3A4; ECG: electrocardiogram; ER: extended-release; GI: gastrointestinal; HCl: hydrochloride; hr: hour(s); IR: immediate release; M3G: morphine-3-glucuronide; M6G: morphine-6-glucuronide; MAOIs: monoamine oxidase inhibitors; mcg: microgram(s); MEDD: morphine equivalent daily dose; mg: milligram(s); min: minute(s); mL: milliliter(s); OT: opioid therapy; PEO: polyethylene oxide; TDS: transdermal system; QTc: the heart rate's corrected time interval from the start of the Q wave to the end of the T wave; REMS: Risk Evaluation and Mitigation Strategy; SR: sustained release

C. Morphine Milligram Equivalent Doses

Table D-3: Morphine Milligram Equivalent Doses for Commonly Prescribed Full Opioid Receptor Agonist (17)

- All doses in mg/d except for fentanyl.
- Multiply the daily dosage for each opioid by the conversion factor to determine the equianalgesic dose in MME. Equianalgesic dose conversions are only estimates and cannot account for individual variability in genetics and pharmacokinetics.
- Do not use the calculated dose in MME to determine the doses to use when converting one opioid to another. When converting opioids, the new opioid is typically dosed at substantially lower than the calculated MME dose (33-50% less) to avoid accidental overdose due to incomplete cross-tolerance and individual variability in opioid pharmacokinetics.
- Use particular caution with fentanyl because it is dosed in mcg/hr instead of mg/d, and absorption is affected by heat and other factors.
- See Table D-2 for conversion guidance for buprenorphine-containing agents.

Morphine Milligrams Equivalent Doses (MME)[a]	
Opioid Agent	**Conversion Factor**
Codeine[b]	0.15
Tapentadol[c]	0.4
Morphine	1
Hydrocodone	1
Oxycodone	1.5
Oxymorphone	3
Hydromorphone	4

[a] The U.S. Department of Health and Human Services (HHS) *Opioid Oral Morphine Equivalent (MME) Conversion Factors Table for Prescription Drug Coverage* does not have an associated MME conversion factor for buprenorphine products. As a partial opioid agonist, buprenorphine is not expected to be associated with overdose risk in the same dose-dependent manner as doses for full agonist opioids. Given the wide variability in the recommended dose equivalencies between buprenorphine and morphine, the Work Group is unable to make any recommendations for equianalgesic dosing.

[b] When converting from weak opioid analgesics to more potent opioids, use the recommended initial doses of the new opioid for opioid-naïve patients

[c] The conversion factor estimate for tapentadol is based upon μ-receptor agonist activity in animal models where tapentadol has been shown to be 2-3 times less potent than morphine

Abbreviations: d: day(s); hr: hour(s); mcg: microgram(s); mg: milligrams; MME: morphine milligram equivalent dose

D. Methadone Dosing Guidance

a. Summary

- Methadone is not a first-line agent for the treatment of chronic pain.(17) It is an alternative long-acting opioid analgesic that may be useful in managing pain severe enough to require continuous daily treatment for which alternative treatment options are inadequate.
- In general, as with other opioids, methadone should be used as one aspect of a comprehensive pain management plan, as agreed upon by the practitioner and the patient.

- Methadone should be initiated and adjusted by, or in consultation with, a practitioner who has the relevant knowledge and expertise;(17) if a provider with clinical experience is not available, then another long-acting opioid may be used until such consultation is obtained.
- The general principles utilized in the dosing of methadone are different than those of other opioids; these differences are due to methadone's unique pharmacokinetic and pharmacodynamic properties and include, but are not limited to:
    - Dose titration should occur after at least 5-7 days on a designated dose (in the large majority of cases)
    - Careful consideration must be given to potential drug interactions and to the potential for QT prolongation
- Methadone is considered to be safe in patients with renal and/or hepatic impairment but should be used with caution in end-stage disease cases of these conditions.
- There are a number of methods available that use conversion ratios to initiate or titrate methadone; no single method is considered superior to others. Titration should be based on patient response and not solely based on equianalgesic dosing tables.
- Monitoring ECG for QTc interval prolongation is recommended based upon certain clinical scenarios.

b. Overview

Methadone is indicated for persistent, moderate-to-severe chronic pain in patients requiring continuous, around-the-clock opioid administration over an extended time. Methadone's pharmacokinetic properties are complex and incompletely documented.(245, 246) It has a long elimination half-life that has wide inter-patient variability (mean or median half-life, depending on subject type, ranges from 3-128 hr) (247-259) and does not reflect duration of analgesia.(256, 260) Initially, methadone duration of analgesia ranges from 4-6 hr; however, with repeated dosing, duration of analgesia can extend to 8-12 hr. Accordingly, while initial dosing may require more frequent administration (three times per day [TID]) to achieve adequate analgesia,(261, 262) once steady-state levels are established, reducing dosing frequency to two times per day (BID) can be considered. In elderly and frail patients, consideration may be given to starting with BID dosing. Also, as a result of the dissociation between half-life and analgesic duration, tissue accumulation of methadone can occur. It may take ten days for plasma levels to stabilize; thus, as a general rule, dose titration should not be more frequent than every 5-7 days.(263) Patients should be reassessed more frequently (e.g., every few days) when methadone is initiated and when the dose is increased.(17) Once stable dosing is established, follow-up can be as clinically warranted.

While methadone is an alternative to ER morphine or oxycodone for treatment of moderate-to-severe pain, a number of authors have cautioned about the complexities of dosing and suggested the drug be prescribed by practitioners with relevant experience, in an adequately monitored setting.(17, 245, 261, 262, 264-269) Significant toxicity has occurred particularly when doses were increased too frequently, conversion doses were too high, or dosing intervals too close.(266, 270-272)

In 2014, a methadone safety guideline was developed by the American Pain Society and College of Problems of Drug Dependence, in collaboration with the Heart Rhythm Society, which made

recommendations for safer prescribing of methadone.(273) Table D-4 outlines baseline and monitoring recommendations based on categorization of patients for risk of QTc prolongation. Palliative care patients with the goal of comfort care may require less vigilance with ECG monitoring.

Table D-4: Baseline and Monitoring Recommendations Based on Categorization of Patients for Risk of QTc Prolongation (273)

Category	Baseline ECG	Follow Up ECGs[a]	Action
Patients with risk factors for QTc prolongation, any prior QTc >450, or history of syncope	Obtain baseline • ECG within last 3 months is sufficient • Strong recommendation • Low quality • evidence	• 2-4 weeks after initiation • With significant dose increases • When methadone dose reaches 30-40[b] mg/d • When methadone dose reaches 100 mg/d[b] • When new risk factors arise or signs or symptoms of suggestive arrhythmia	• Avoid use if QTc >500 ms[c] • Consider alternative to methadone for QTc 450-500[3] • Evaluate and correct reversible causes of QTc prolongation
Patients not known to be at higher risk of QTc prolongation	Consider baseline • ECG within the last 12 months is sufficient • Weak recommendation • Low quality • evidence	• When methadone dose reaches 30-40[b] mg/d • When dose reaches 100 mg/d[b] • When new risk factors arise or signs or symptoms of suggestive arrhythmia	• Avoid use if QTc >500 ms[c] • Consider alternative to methadone for QTc 450-500[3] • Evaluate and correct reversible causes of QTc prolongation

[a] Consider obtaining yearly ECGs once a stable dose is reached

[b] Doses this high are not recommended for chronic pain and are typically observed only for patients receiving methadone as MOUD

[c] For patients on stable doses of methadone in whom a prolonged QTc has been noted (QTc >450 ms), consider tapering the dose of methadone and repeating the ECG. Other QT prolonging medications should be evaluated, and cardiology specialty care should be consulted for expert opinion.

Abbreviations: d: day(s); ECG: electrocardiogram; MAT: medication assisted treatment; ms: millisecond(s); mg: milligram(s); OUD: opioid use disorder; QTc: QTc interval (the heart rate's corrected time interval from the start of the Q wave to the end of the T wave)

Special caution is recommended with concurrent benzodiazepines and drugs that prolong the QT interval. (274)

Methadone is primarily metabolized by CYP450 2B6to inactive/nontoxic metabolites.(275-280) CYP2B6 is a highly polymorphic gene (281) and may help to explain why the pharmacokinetics of methadone can be extremely variable from individual to individual. Currently, it is unclear whether cytochrome P450 3A has any influence on methadone metabolism and caution is encouraged when using drugs that interact with both enzymes.

c. Dosing Strategies

The dosing recommendations listed below (in Table D-5) are provided to offer guidance on using methadone in the treatment of patients with chronic pain, particularly when converting from another opioid to methadone. The use of methadone for pain should be done in the context of a pain clinic or with assistance of local pain management experts, including healthcare providers or pharmacists, who have

experience with methadone's use. If such resources are not readily available, other long-acting opioids should be considered (e.g., morphine sustained action [SA], or oxycodone SA).

Various methadone dosing strategies have been employed (268, 282, 283) and methods are still evolving. Older, prospective studies found no evidence to support the superiority of one dosing strategy over another.(284-286) The lack of prospective and comparative studies concerning methadone dosing strategies highlights the need to carefully individualize the dosing regimen of methadone.

For opioid tolerant patients, a number of different equianalgesic dose ratio tables can be used to determine the dose of methadone.(267, 286-290) This VA/DoD OT CPG includes one of the more conservative equianalgesic dose ratio tables as a reference for providers to discuss and/or consider (Table D-3).(289) Local subject matter experts may prefer, or be more familiar with, other accepted (evidence-based) equianalgesic dose ratio tables. No equianalgesic dose ratio table is considered superior and all have similar limitations. When converting to methadone, lower MEDDs have lower conversion ratios than higher MEDDs. As compared to lower MEDDs, higher MEDDs may convert to smaller methadone doses than one might expect. For example, 60 mg MEDD would be ~15 mg of methadone/day (a ratio of ~4:1); whereas 180 mg MEDD would be ~22.5 mg/day (a ratio of ~8:1). Methadone dose conversion is not a linear process. Furthermore, while the equianalgesic dose ratio tables account for cross-tolerance, (263) some subject matter experts feel the calculated methadone dose should be further decreased for incomplete cross-tolerance, especially for patients on higher MEDDs.(273, 291)

Table D-5: Dosing Recommendations for Patients Receiving Codeine Preparations or No Previous Opioids (292, 293)

Dosing Strategy	Initial Methadone Dose	Increments	Comments
Gradual titration (For CNCP and situations necessitating less frequent monitoring)	2.5 mg every 12 hr or 8 hr	2.5 mg every 12 hr or 8 hr, no more often than every 5 to 7 d	As a general rule, *start low and go slow*
Faster titration (For cancer pain and situations where frequent monitoring is possible)	2.5-5 mg every 8 hr	2.5 to 5 mg every 8 hr as often as every third day	

Note: All doses refer to oral administration

Abbreviations: CNCP: chronic non-cancer pain; d: day(s); hr: hour(s); mg: milligram(s)

Table D-6: Equianalgesic Dose Ratios (289, 291)

Morphine Dose (mg/d)	<30	31-99	100-299	300-499	500-999	1000-1200	>1200
Morphine: Methadone	2:1	4:1	8:1	12:1	15:1	20:1	Consult

Note: The conversion ratio increases as the morphine equivalent dose increases (17, 265, 266, 286, 294)

Abbreviations: d: day(s); mg: milligram(s)

The equianalgesic dose ratio is only one component of the process for appropriate dosing of methadone and other opioids. Once the dose is determined, there are two different methods to make the switch: a

rapid conversion method and a stepwise/phased conversion. Again, no one conversion method has been determined to be superior to the others.

- For rapid conversion, the previous opioid is discontinued and the calculated methadone dose is started on day one.
- For the stepwise/phased conversion, the dose of the previous opioid is decreased by 1/3 and replaced with 1/3 of the calculated methadone dose (given in three divided doses). Then the previous opioid dose is decreased by an additional 1/3 and the methadone dose is increased by 1/3. Finally, the remaining 1/3 of the previous opioid dose is discontinued and the methadone dose is increased to the initial calculated dose. This can be done over several days or weeks.(263, 295)

For breakthrough pain, a short-acting opioid preparation (e.g., acetaminophen with hydrocodone, oxycodone with or without acetaminophen, or immediate-release morphine) may be used until steady state is achieved (i.e., 5-7 days). As-needed methadone has also been used in a palliative care setting;(268, 282, 284) however, it is generally discouraged to avoid drug accumulation. It is important to note that use of breakthrough pain medications in patients with CNCP is controversial. If opioid medications for breakthrough pain are indicated, following titration to a stable methadone dose in CNCP patients, they should be used sparingly.(285)

d. Converting from Methadone to Oral Morphine

Switching from methadone to another opioid is not simply the reverse process; the equianalgesic dose ratio tables previously mentioned are not bi-directional and cannot be used in reverse (i.e., the morphine to methadone conversion ratio may not be the same as the methadone to morphine ratio).(296) There is no widely accepted conversion strategy for switching from methadone to another opioid. A proposed safe and conservative approach is a 1:3 methadone to morphine ratio (10 mg methadone/day = 30 mg oral morphine/day).(263) However, literature suggests patients may end up on as high as 1:4.7 methadone to morphine ratio (10 mg methadone = 47 mg morphine).(297)

e. Special Patient Populations

Patients 65 years and older may have decreased clearance of methadone.(258) Dosage adjustments do not appear necessary in patients with stable chronic liver disease; in addition, methadone and its metabolites do not accumulate in patients with renal failure.(298) However, two prospective studies on methadone dosing strategies excluded patients with liver or renal disease,(284, 286) thus caution should be observed when dosing methadone in these populations. Dosage adjustments may be necessary in patients with end-stage liver or renal disease.

f. Patient Education

Discuss the following information with patients prior to and during treatment with methadone:(288)

- Methadone must be taken only as directed. Patients should never take extra doses without getting approval from the prescriber.
- Taking methadone as frequently as other opioids may produce a fatal overdose.

- Patients should use other CNS depressants (especially benzodiazepines) with caution and only as directed by a healthcare provider.
- Patients should only use methadone in combination with other opioids as prescribed by a healthcare provider.
- The use of illicit drugs and/or alcohol with methadone may be fatal.
- Pain relief builds gradually and usually takes 5-7 days to see the full effects of a particular dose.
- Patients should tell all medical providers that they are taking methadone. Adding medications or changing dosing of other medications can affect methadone and should be coordinated with the methadone prescriber.
- Patients should avoid activities requiring mental alertness or coordination (such as driving or using machinery) until the effects of methadone are realized, typically a week orlonger.
- Patients should rise slowly from a sitting/supine position, as methadone may causedizziness.
- Methadone, like other opioids, can cause significant constipation. Patients should take a prescribed laxative as directed.
- Patients should report any of the following symptoms immediately and/or seek urgent/emergent care: dizziness or lightheadedness, irregular heartbeat (palpitations), falls or near falls, chest pain/pressure, and shortness of breath.
- Patients should avoid abrupt discontinuation of methadone without first consulting a healthcare provider.

E. Additional Buprenorphine Guidance

Providers may consider an alternative initiation approach for patients with concern for/history of intolerable opioid withdrawal during buprenorphine initiation or otherwise unable to taper to 30 mg MEDD. It is recommended to either convert directly to an equivalent dose or cross-titrate for a short period of time. Provide a medication disposal bag for any remaining full agonist opioids.

Alternative initiation approach for a patient converting from full opioid agonist to buprenorphine buccal film:(299)

- For patients taking ≥80 mg MEDD, convert directly to an equivalent dose of buprenorphine buccal film:
    - **80 – 160 mg MEDD**: initiate 300 mcg 8 – 12 hours after last dose of full agonist opioids, q12 hr
    - **161 – 220 mg MEDD**: initiate 450 mcg 8 – 12 hours after last dose of full agonist opioids, q12 hr
- Alternatively, continue current full agonist opioids for 4 – 8 days while gradually up-titrating buprenorphine buccal film to the lowest effective dose. Once the buprenorphine dose is roughly an equianalgesic full agonist dose, stop the full agonist opioid (usually around day 4-8). For patients who stabilize (no withdrawal, tolerable pain) before reaching the proposed end dose, it is not necessary to proceed with further buprenorphine dose escalations.(300-305)

- For patients taking ≤80 mg MEDD, consider converting to buprenorphine transdermal delivery system (BTDS). When switching patients from oral MEDDs of 30 to 80 mg to BTDS, a patch strength of 10 mcg/h is recommended as a conservative initial conversion dose. The highest available BTDS strength of 20 mcg/h may be equianalgesic to an oral MEDD of 36 to 55 mg, whereas the product information states that the 20 mcg/h patch may not provide adequate analgesia for patients requiring greater than an oral MEDD of 80 mg.[a]

[a] For more information on BTDS, refer to the following guidance from VA PBM Services: https://www.pbm.va.gov/PBM/clinicalguidance/drugmonographs/Buprenorphine_Transdermal_System_BUTRANS_Monograph.pdf