Appendix D: Drug Tables

A. Short-acting, Orally Administered Opioids

Table D-1: Use of Short-acting, Orally Administered Opioids in Adults [198]

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	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	▪ 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) ▪ Analgesic ceiling effect occurs with codeine at doses >60 mg/dose ▪ Codeine alone is a weak analgesic; more effective alternatives are available (including codeine in combination with APAP or ASA)	15 to 30 30 to 60 4 to 6	▪ *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[2]) because of decreased conversion to the active metabolite, morphine ▪ CYP-2D6 ultra-rapid metabolizers[3] can have extensive conversion to morphine with increase in opioid-mediated effects

Source: https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPGProviderSummary022817.pdf

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Hydrocodone (in combination with APAP, ASA, or IBU) ▪ 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 • 37.5 to 50 mg/d (1000 mg/d IBU) for hydrocodone + IBU combination	10 to 20 60 to 100 4 to 8	▪ *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[2]) ▪ CYP-2D6 ultra-rapid metabolizers[3] can have extensive conversion to hydromorphone with potential increase in opioid-mediated effects
Hydromorphone ▪ Available as oral liquid 1 mg/ml, and 2, 4, and 8 mg tablets	▪ 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[4] and require doses higher than the usual dosage range to maintain the desired effect	15 to 30 30 to 60 3 to 4	▪ *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 for moderate impairment, more with severe impairment	

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
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	▪ 10 to 30 mg every 4 hr	▪ There is no optimal or maximum dose of morphine; patients on LOT are likely to become tolerant [4] and require doses higher than the usual dosage range to maintain the desired effect	30 60 3 to 5	▪ *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[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	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 [4] and require doses higher than the usual dosage range to maintain the desired effect	10 to 15 30 to 60 3 to 6	▪ *Elderly or debilitated*: reduce dosage ▪ *Hepatic / Renal*: Use with caution; consider reducing dose and increasing frequency of dosing	▪ 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[2])

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Oxymorphone ▪ Available as 5 or 10 mg tablets	▪ 5 mg every 4 to 6 hr	▪ There is no optimal or maximum dose of oxymorphone; patients on LOT are likely to become tolerant[4] and require doses higher than the usual dosage range to maintain the desired effect	30 to 45 N/A 4	▪ *Elderly or debilitated*: Use with caution and start at low end of dosing range; levels are increased 40% in patients ≥65 years ▪ *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	▪ Food has been shown to increase peak levels of oxymorphone immediate-release by 38%; must be taken on an empty stomach at least 1 hr before or 2 hr after a meal ▪ 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)

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Tapentadol ▪ Available as 50, 75, or 100 mg tablets	▪ 50 mg every 4 to 6 hr	▪ 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[4] and require doses higher than the usual dosage range to maintain the desired effect	N/A (rapid) 60 4 to 6	▪ *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 ▪ *Respiratory dysfunction:* Use with caution because of respiratory depressant effects; consider non–mu opioid agonist analgesics	▪ Must NOT be taken concomitantly with alcohol which can increase serum tapentadol concentration ▪ 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

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Tramadol (alone or in combination with APAP) ▪ Tramadol available as 50 mg tablet, or in tablet 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	<60 ~120 to 240 6	▪ *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 ▪ 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

[1] Check local formulary for available formulations.

[2] 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)

[3] 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.