Pain Management Tables and Guidelines

Dana-Farber Cancer Institute/Brigham & Women's Hospital

Benjamin S. Kematick, PharmD, Iman Suliman, PharmD, Molly Bacon, PharmD, L. Diana Ardeljan, PharmD, Mary Dube, PharmD, Allyson Beechy, PharmD, Clark Cassone, NP, Jose Zeballos, MD, Kevin M. Dube, PharmD, Victor Phantumvanit, PharmD, Elizabeth Rickerson, MD, Mark Zhang, DO, MMSc, Addison Sember, PharmD, Lida Nabati, MD, Linda Drury, PA-C, Courtney Moller, PA-C, Lyns Hercule, NP, Inna Zinger, NP, and Bridget Scullion, PharmD

2024

The BWH/DFCI Pain Management Tables and Guidelines Committee would like to acknowledge the following people for their contributions to past versions of these tables: Christopher J. Scott, PharmD, Cherlynn Griffin, PharmD, Amanda Dietzek, PharmD, Janet Abrahm, MD, Hallie S. Greenberg, MS-PREP, RN, BC, Elaine Robbins, ANP, ACNP, CCRN, Barbara Reville, DNP, Maureen Lynch, NP

Revised by the BWH/DFCI Pain Management Tables and Guidelines Committee in March 2024

Past revisions: 1998, 2000, 2002, 2004, 2007, 2009, 2013, 2017, 2020

Dana-Farber Cancer Institute/Brigham and Women's Hospital Pain Management Tables and Guidelines (Pink Book) provides educational information for healthcare professionals at Dana-Farber and Brigham and Women's Hospital. This information is not medical advice. The Pink Book is not continually updated, and new safety information may emerge after the most recent publication date. Health care providers should always exercise their own independent clinical judgment and consult other relevant and up-to-date experts and resources. Official prescribing information should be consulted before any product is used or recommendation made.

Table of Contents

Pain Assessment

A simple acronym for use in pain assessment is: **OPQRSTU**

Onset – What were you doing when the pain started? Did it start suddenly or gradually get worse?

Provokes/**P**alliates – What makes the pain worse? What makes the pain better?
What medicines or non-medicines have been helpful? Were they and are they still effective?

Quality – How does the pain feel? What words can you use to describe the pain?
(sharp, stabbing, burning, shooting, dull, achy, throbbing, crampy)

Region/**R**adiates – Where is your pain primarily located? Does it travel anywhere?

Severity – What is the present and past intensity of the pain, at its worst and at its best? (See scales below)

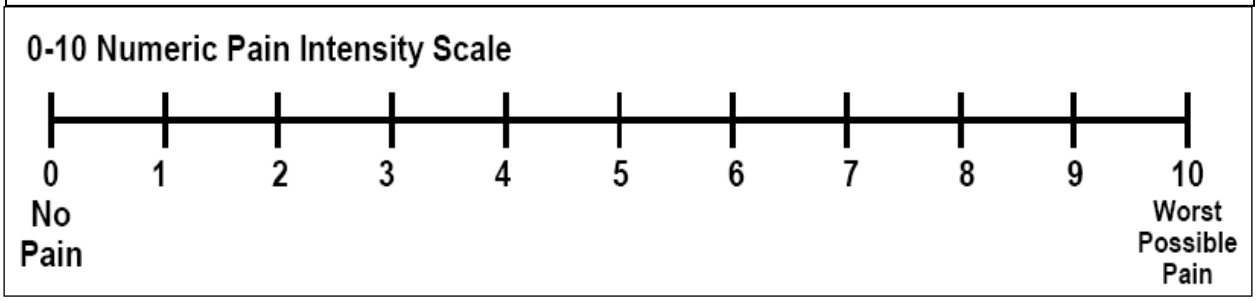
Time – How often does it occur? Is it constant or intermittent?

U – How is this pain affecting YOU and your life?

Verbal Numerical Scale

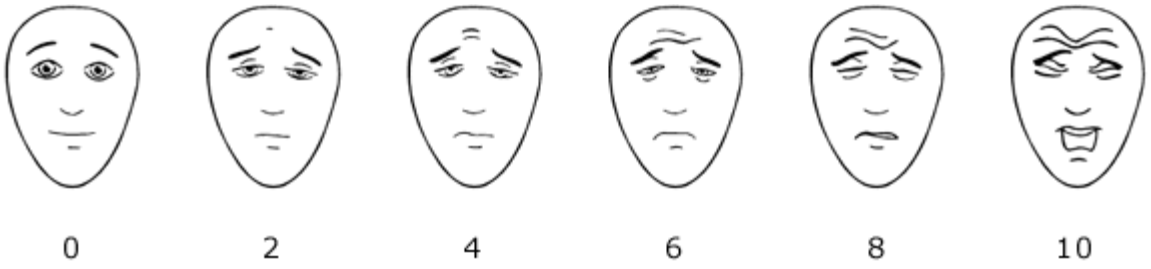
"If *0* is 'No Pain' and *10* is the 'Worst Pain Imaginable' what is your pain right now?"

Verbal Descriptor Scale



If used as a graphic rating scale, a 10 cm baseline is recommended

The Faces Pain Scale – Revised- Ask the patient which picture matches their pain.



Hicks CL, von Baeyer CL, Spafford P, van Korlaar I, Goodenough B. ã 2001 International Association for the Study of Pain.

Functional Pain Scale: First ask the patient if they have pain. Next ask the patient if their pain is "Tolerable" or "Intolerable". If Tolerable, ask if it interferes with any activities. If Intolerable, determine if pain is intense enough to prevent passive activities.

RATING	Description
0	No Pain
1	Tolerable, does not prevent ANY activity
2	Tolerable, prevents SOME activities
3	Intolerable, but can use phone, read or watch TV
4	Intolerable, and CANNOT use phone, read or watch TV
5	Non-verbal due to pain

For pain assessment in cognitively impaired/advanced dementia and in infants, see BWH pain management policy.

Guidelines for the Management of Pain

Important Terms	Definition
Pain	An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.
Nociceptive pain	Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors. • **Somatic pain** refers to pain receptors in the tissues (skin, muscle, joints and connective tissue). • **Visceral pain** which refers to pain from internal thoracic, pelvic or abdominal organs. • **Inflammatory pain** refers to tissue damage due to inflammatory process.
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system.
Nociplastic pain	Pain from a condition where the perception of pain is altered and occurs without discernible evidence of actual tissue damage or the activation of peripheral nociceptors.
Analgesia	Absence of pain in response to stimulation which would normally be painful.
Hyperalgesia	Abnormally elevated pain response from a stimulus that normally provokes pain.
Allodynia	Pain due to a stimulus that does not normally provoke pain.

I. General Pain Management:

- Pain management should begin with a differential diagnosis for pain etiology, and the pain should be categorized by its archetype (see table above). The best aspect of the assessment to help determine this is the **qualitative description** of the pain (see Pain Assessment).
- Based on the pain assessment, etiology and duration, the pain can be subcategorized into acute or chronic pain. **Acute pain** is often nociceptive pain that improves over time. If the pain persists longer than expected or more than 3 months, then it is often considered **chronic pain**.
- Pain may also be an **acute on chronic exacerbation** or there may be a new acute etiology on top of the chronic pain. Treat these cases as acute pain.
- Individualize each patient's regimen based on patient-specific factors including but not limited to age, organ function, other co-morbidities and using the opioid prescribing checklist on page 6 if considering opioids.
- The oral route is the preferred route of analgesic administration. It is the most convenient, and cost-effective method.

II. Acute Pain Management:

- Acute pain is caused by injury, trauma, illness, surgery, or painful medical procedures. It generally resolves after a short duration once the underlying cause has been treated or healed.
- Non-pharmacologic treatments should be incorporated as appropriate for all patients. This includes acknowledging the patient's experience, using distraction techniques, controlled breathing, using positioning or elevation and the use of ice/cold for acute inflammatory pain.
- Simple analgesics such as acetaminophen and NSAIDs should be part of every acute pain treatment regimen and opioids are reserved for patients with contraindications or unresolved pain with the simple analgesics.
    - Consider NSAIDs and steroids for inflammatory pain or bone pain.
    - Consider topical diclofenac for patients with musculoskeletal pain without open wounds if systemic NSAIDs cannot be used.
    - Muscle relaxants may be used for muscular pain or spasms, limit to short course and see **Adjuvant Analgesic Agents Table for the section on Select Muscle Relaxants** (Page 26) for considerations related to side effects.
- Consider local interventional procedures (e.g. nerve blocks) or systemic therapy (e.g. ketamine).

III. Chronic Pain Management:

- Chronic pain is defined as pain persisting beyond expected healing or sometimes defined as pain lasting more than 3 months. It may be nociceptive, neuropathic, nociplastic or a combination of these types.
- Non-pharmacologic treatments should be incorporated into the management plan for all chronic pain patients, as outlined in the acute pain section. These may include exercise, physical therapy, occupational therapy, massage, acupuncture, cognitive behavioral therapy (CBT), and interdisciplinary rehabilitation.
- Consider referral to social work to support access to both physical activities of daily living and emotional coping support.
- Treating underlying syndromes like depression and anxiety, which can exacerbate pain, can be effective methods of restoring patient function and quality of life.
- Consider pain management or palliative care consultations/referrals for interventional therapies like nerve blocks, corticosteroid injections, or systemic therapy with ketamine or lidocaine in patients who fail standard non-invasive therapies.
- **Optimize adjuvant pharmacologic therapy** based on the underlying pain etiology. A multi-modal approach may be beneficial but consider the risks of polypharmacy. See the **Adjuvant Analgesic Agents Table** (Pages 25-27)
- Patient counseling is essential to inform patients that adjuvant therapies may take time to reach optimal dosing and effectiveness. Discontinue any adjuvants that do not provide adequate improvement in pain control.

Guidelines for Prescribing Opioids

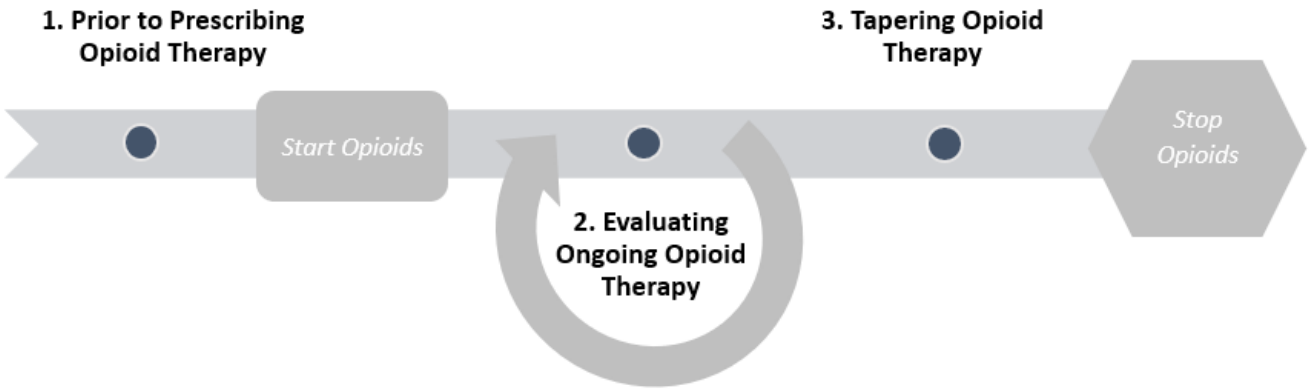
Short-Term Opioid Therapy:

- If non-opioid therapy is insufficient to provide adequate pain control, consider the benefits and risks to adding a short-acting opioid as needed to control pain.
- Single-agent, short-acting opioids are preferred over combination products for maximum flexibility in opioid dose.
- Parenteral opioids can be used for rapid relief of pain and then switched to oral opioids once pain is managed and patient can tolerate oral agents.
- Intramuscular administration of medications should be avoided. This route is painful, inconvenient, and is prone to erratic absorption rates. Subcutaneous or rectal routes may be considered if there is no intravenous access.

Acute Pain Crisis Opioid Dosing Pearls:

- Start with an initial dose based on patient's age, comorbid conditions impacting drug clearance, and current opioid dose if opioid tolerant.
    - For opioid tolerant patients: discuss with patient the last dose and time opioid agents were taken. May consider starting with equivalent IV dose of their home PRN agent or 10-15% of their daily OME.
- If an initial dose of IV opioid provides minimal or no improvement in pain, repeat the dose once after 15 minutes up to a total of 3 doses. Monitor sedation and respiratory rate before each dose.
- Avoid increasing the dose before drug has sufficient time to clear without specialist consultation.
- Consult specialty service if pain is not improved despite repeat doses.
- If possible, use a Patient Controlled Analgesia (PCA) for acute pain that requires frequent dosing. Refer to the PCA section on page 19.
- Do NOT increase long-acting opioids in an acute pain crisis without consulting pain or palliative care teams.
- Opioids do not have a maximum pharmacologic dose; however, dosing may be limited by side effects, primarily respiratory depression, sedation, hyperalgesia, and individual patient response.

Opioid Therapy Timeline & Checklist:



Opioid Prescribing Checklist	
Always assess acuity of pain to appropriately determine order of steps	
1. Prior to Initiating Opioid Therapy	
☐ Assess baseline pain & function	• Use a comprehensive pain assessment tool, see Pain Assessment on page 3
☐ Set realistic, function-based goals	• Goals: maximize the patient's function, pain control and ability to enjoy life.
☐ Optimize non-opioid therapy	• Optimize non-opioid therapy by maximizing non-pharmacologic and pharmacologic approaches, including adjuvants (see General Pain Management Section). • Encourage patients to maintain a pain diary noting daily pain scores, PRN medication use, side effects, and efficacy.

☐ Assess the risks of opioid therapy	• Identify patient risk factors for respiratory depression:
	  ○ History or risk of sleep apnea, pulmonary and cardiac history, renal or hepatic impairment, depression or other psychiatric conditions, and medications that increase sedation or respiratory depression.
	• Assess the risk of misuse and opioid use disorder using a validated tool: **Refer to Risk-related Definitions on page 8**
	  ○ Complete Opioid Risk Tool, or
	  ○ Consider SOAPP-R
	• Consider initial urine drug screen

☐ Discuss and mitigate Risk	• Check PDMP (see **Risk-related Definitions page 8)** • Complete an opioid medication agreement, see Appendix E • Prescribe naloxone and provide education to patient and a caregiver about how to use. • Set criteria for stopping or continuing opioids.
☐ Select initial regimen	• The appropriate dose is the one needed to control (not eliminate) the patient's pain with the fewest side effects. • Avoid combination opioid products (e.g. Percocet) to allow for individual titration. Dosing of opioid combination oral products is limited by the maximum dose of non-opioid ingredients. (e.g. acetaminophen) • Start with a low dose of short-acting opioid for the shortest amount of time anticipated for the pain to continue – often 7 days or less in non-cancer pain. Higher doses, longer courses, and long-acting medications should be initiated in a stepwise, logical manner. • Avoid meperidine for the treatment of pain; it has an active metabolite with a significantly longer half-life that can accumulate and cause CNS toxicity. • Exercise caution with codeine. Dosing is limited by constipation and nausea, and ≥10% of patients lack the enzyme necessary to convert codeine into active metabolites. Codeine is not preferred for the treatment of pain. • Caution using tramadol especially in older adults due to increased risk of falls and seizures related to its pharmacologic activity.

☐ Discuss adverse effects	• Respiratory Depression – Use naloxone in life-threatening respiratory depression. It reverses both respiratory depression and analgesia. See page 22 for instructions. • Constipation is a common adverse effect of opioid administration. It should be anticipated, treated prophylactically, and monitored carefully (see Management of Opioid Induced Constipation on page 21). • Counsel patient on additional side effects (See Management of Opioid Side Effects on page 20).
2. Evaluating Ongoing Opioid Therapy	
☐ Re-evaluate pain and function	• Use a pain assessment tool to compare current status with baseline and functional goals.
☐ Re-evaluate risk	• Observe for signs of over-sedation, withdrawal, misuse, and opioid use disorder. • Check PDMP with each opioid prescription (required by law). • Consider using the COMM assessment tool.
☐ Assess adverse effects	• Evaluate constipation management, risk of falls, mood changes, and other adverse events (see pages 20-21 for details). • Consider **switching opioids** for intolerable side effects, when a drug is not available by a new route, inadequate pain control despite dose escalation, or cost issues (refer to page 10 for dosing calculations).
☐ Re-evaluate regimen	• Decide whether to continue, adjust, taper, or stop opioids. • For pain requiring around-the-clock pain control with short-acting opioids, consider adding extended-release/long-acting opioids, which can be used alongside non-opioid and short-acting PRN therapy. • When prescribing long-acting opioids, assess the need for short-acting breakthrough pain medication (dosed as 10-20% of total OME). • Evaluate usage of short-acting/breakthrough medication for patients on both long-acting and short-acting opioids. Consider increasing the long-acting dose if more than 3-4 doses are used daily for persistent pain. • Incident pain related to specific activity (such as eating, defecation, socializing or walking) may not require an increase in baseline opioids. **Refer to the list of long-acting opioids on pages 23-24 and opioid dosing calculations on page 10**
☐ Mitigate risks of ongoing opioid therapy	• Complete an opioid agreement for chronic opioid therapy (required by MA and NH laws). • Check naloxone prescription expiration and renew as needed.
3. Tapering Opioid Therapy	
☐ Discuss tapering with patient	• Explain the reasons and benefits of opioid tapering. • Collaborate with the patient to address individualized timeline, goals, and concerns. Speed of taper should be inversely related to duration of opioid therapy. • Counsel patients on potential withdrawal symptoms and management.
☐ Set taper plan ☐ Reassess plan and support symptoms	• For **acute pain and short duration** (less than a week), opioid therapy can be stopped or tapered rapidly by 25-50% per dose and then spacing the doses out. • **Chronic opioid therapy** (treatment for longer than 2 months) requires a slower taper, see Weaning Chronic Opioid Therapy on page 21. • Follow up frequently to assess the patient and address concerns. • Consider referrals for additional support, such as CBT or interventional pain service.

MA Law on Opioid Agreements for Long-Acting Opioid Therapy

MGB Tapering Chronic Opioid Therapy Guidelines

Opioid Risk-Related Definitions

The risk of misuse or developing opioid use disorder is the most significant concern with opioids due to the associated morbidity and mortality risks. These risks increase with chronic use, and patients may have additional risk factors that further elevate their risk. Incorporating this risk assessment and patient education serves as a crucial risk mitigation strategy, as outlined in the checklist above.

Opioid Risk-Related Terms	Definition
Opioid Use Disorder	A diagnosis which is defined in the DSM-5. It is characterized by the compulsive use of opioids despite adverse events from continued use and signs of withdrawal when stopped.
Misuse	Use of a medication with therapeutic intent, but other than as directed, regardless of whether a harmful outcome occurs. Examples of misuse include taking an extra opioid when pain is worse even though they weren't specifically prescribed as such or altering the route of delivery.
Physical Dependence	An expected state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.
Tolerance	A state of adaptation in which exposure to a drug induces changes that result in an expected diminution of one or more of the drug's effects over time.
Opioid Tolerant	Patients who have been taking, for a week or longer, at least 60 mg of oral morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid.
Withdrawal	The symptoms that occur when opioids are stopped abruptly in a patient who has been chronically on opioids and has their dose stopped or reduced by greater than 50%. These symptoms include but are not limited to anxiety, agitation, muscle aches, sweating, diarrhea, nausea and vomiting.
Aberrant Behavior	Any behavior departing from the prescribed plan of care, ranging from mild (e.g., hoarding medications for times of severe pain) to significant (e.g., selling medications, obtaining drugs from other sources - including other prescribers)
Diversion	The redirection of a prescription drug from its lawful purpose to illicit use.
Prescription Drug Monitoring Program (PDMP)	All clinicians who prescribe controlled substances must register with their state PDMP. Checking the PDMP before issuing a prescription for schedule II, III and benzodiazepines may be required by the state. The online prescription monitoring program in • Massachusetts: https://massachusetts.pmpaware.net/login • New Hampshire: https://www.newhampshirepdmp.com/
Urine Drug Screen	Can be used when prescribing medications for chronic pain to monitor for misuse or diversion. When reading the results of urine drug screens, it is important to understand the metabolism of the drugs being tested. Please see opioid metabolism chart on page 16 for common opioid metabolites.
Validated Risk Assessment Tools	Useful tools to estimate risk of noncompliant opioid use. Scores from any tool are not a reason to deny opioids, but rather an estimate of level of risk and should be used alongside, not in lieu of, clinic judgement when prescribing opioids to a patient. Examples of assessment tools include SOAPP-R, ORT, and COMM-17. Copies of these tools can be found at pinkbook.dfci.org

Opioid Equianalgesic Doses		
Drug	**PO/PR (mg)**	**Subcut/IV (mg)**
Morphine	30	10
OxyCODONE	20	n/a
HYDROcodone	20	n/a
HYDROmorphone	7.5	1.5
Methadone	See pages 11-12 for conversion	
FentaNYL (See page #15 for transdermal conversions)	n/a	0.1 (100 mcg)
OxyMORphone	10	1

How to use the Opioid Equianalgesic Doses Table and other tables

The data in this table represents approximate equianalgesic doses of the most used opioids. It can be inferred that for an opioid-naïve patient that a 20 mg oral dose of oxyCODONE will provide a similar analgesic effect to 30 mg of oral morphine or 10 mg of IV morphine. **These estimations do not take into account the incomplete cross-tolerance that occurs with chronic dosing** and dosage adjustments must be considered when switching from one opioid to another. Different published equianalgesic tables may be used at other institutions. The table chosen in the DFCI/BWH Pink Book was chosen to avoid magnification of IV hydromorphone when converting from oral opioids. Please see the following for an alternative table- https://www.capc.org/documents/20/

Opioid Characteristics

Agonist	Route	Onset (min)	Peak Effect (min)	Duration of effect (hr)
Morphine	IV	5-10	10-30	3-5
	Oral	15-60	90-120	4
OxyCODONE	Oral	15-30	30-60	4-6
HYDROcodone	Oral	30	90	3-4
HYDROmorphone	IV	5-20	15-30	3-4
	Oral	15-30	90-120	4-6
Methadone (See pages 11-12)	IV	10-20	60-120	4-6
	Oral	30-60	90-120	4-12
FentaNYL (See page 15)	IV	under 1	5-7	0.75-2+
OxyMORphone	IV	5-10	30-60	3-6
	Oral	30-60	60	4-6

Common Conversions					
Morphine milligram (mg)		HYDROmorphone milligram (mg)		OxyCODONE milligram (mg)	FentaNYL **micro**gram (µg)
Oral (PO)	Intravenous (IV)	Oral (PO)	Intravenous (IV)	Oral (PO)	Intravenous (IV)
15	5	3.75	0.75	10	50
30	10	7.5	1.5	20	100
45	15	11.25	2.25	30	150
60	20	15	3	40	200
90	30	22.5	4.5	60	300
120	40	30	6	80	400
150	50	37.5	7.5	100	500

Opioid Conversion Calculations

EQUIANALGESIC CONVERSION EXAMPLE

A patient is on ER oxyCODONE 40 mg PO Q8H and oxyCODONE 15 mg (three 5 mg tablets) PO Q3H PRN for breakthrough pain. The patient's pain has been well controlled on this regimen, requiring only one rescue dose of 15 mg each day. You wish to convert to a continuous IV infusion of morphine.

STEP I	**Calculate the patient's total daily dose (TDD) of opioids.** $oxyCODONE\ ER\ TDD\ =\ 40\ mg\ x\ 3\ doses\ =\ 120\ mg$ $oxyCODONE\ IR\ TDD\ =\ 15\ mg\ x\ 1\ dose\ =\ 15\ mg$ $oxyCODONE\ TDD\ =\ 120\ mg\ ER\ +\ 15\ mg\ IR\ =\ 135\ mg$
STEP II	**Convert the TDD of the old opioid to the new opioid using the conversion table** $20\ \text{mg PO oxyCODONE} = 10\ \text{mg IV morphine}$ $\frac{20\ mg\ PO\ oxycodone}{10\ mg\ IV\ morphine} = \frac{135\ mg\ PO\ oxycodone}{\boldsymbol{X}\ mg\ IV\ morphine}$ $\boldsymbol{X} = 135\ PO\ oxycodone\ X \frac{10mg\ IV\ Morphine}{20\ mg\ PO\ Oxycodone}$ $\boldsymbol{X} = 67.5\ mg\ IV\ morphine$ 67.5 mg IV morphine/day is equianalgesic to 135 mg PO oxyCODONE/day
STEP III (if needed)	**When switching from one opioid to another, dose reduce by 25-50% for incomplete cross tolerance. (Exceptions see Fentanyl (pg 15) and Methadone (pgs 11-12))** $Reduce\ dose\ by\ 25\%\ for\ incomplete\ cross\ tolerance\ =\ \sim 50\ mg\ IV\ morphine/day$
STEP IV	**Select the new long-acting opioid regimen based on available formulations.** $50\ mg/day,\ 24\ hours/day\ =\ \sim 2\ mg\ of\ IV\ morphine/hour$
STEP V	**Calculate a breakthrough dose. Each breakthrough opioid dose should equal 10-20% of the total daily long-acting regimen** $50\ mg/day\ X\ 10\%\ =\ 5\ mg\ IV\ Q2H\ PRN$

Continuous Opioid Infusions

1. Continuous opioid infusion may be needed if no other routes of administration are available, and around-the-clock opioid therapy is required to manage pain and/or dyspnea. Please also refer to policies available on the BWH Intranet for more information on continuous opioid infusions and intensive comfort measures.
2. "Titrate to comfort" is neither a clear nor acceptable order. Acute symptoms must be managed with a bolus dose, infusions are slowly infused over time and should not be expected to relieve acute symptoms.
3. For patients already on opioids when initiating a continuous opioid infusion, calculate the approximate total daily dose and provide a continuous rate of infusion to approximate previously established opioid requirement.
4. PRN boluses of opioids should be made available on an every 1 or 2 hour basis for acute symptom exacerbations, and should be dosed at 10-20% of total daily infusion amount or 50-150% of hourly infusion rate.
5. Dose ranges for boluses should be specific and provide clear parameters for the interval of available boluses and a narrow parameter (not more than a 1:3 ratio) for the dose per bolus.
    - Morphine Sulfate IV 2-4mg every 2 hours → OK
    - Morphine Sulfate IV 2-30mg every 2-3 hours → NOT OK
6. Infusion rate should only be titrated based on symptom severity and frequency of boluses needed to maintain comfort from pain and/ or dyspnea. Infusion rate for continuous infusions should not be titrated more frequently than every 8 hours outside of an ICU.
7. Titrating the continuous infusion rate without the use of PRN boluses may provide inadequate or delayed symptom relief and increase the risk of undesirable side effects such as myoclonus and respiratory depression.
8. Patients should be closely monitored for side effects such as myoclonus or delirium.
9. Judicious use of opioids for pain or dyspnea in actively-dying patients has not been shown to hasten death.
10. If the patient is not on opioids and is not in pain and does not have dyspnea, initiation of an opioid infusion at the end-of-life is unnecessary. Opioids should only be used to treat symptoms of pain and dyspnea.

METHADONE

Methadone is a synthetic opioid indicated for the treatment of pain and/or opioid use disorder. Methadone has many characteristics which make it both an extremely useful drug when used for pain, and a challenging drug to use safely. Highlights of methadone properties are as follows:

- Methadone is classified as a diphenylheptane opioid, structurally distinct from other opioids.
- Methadone has a unique dual mechanism of action as a mu-opioid receptor agonist and an NMDA receptor antagonist.
- Methadone use can prolong the QTc interval and has several interactions, see charts below.
- Methadone has a highly variable pharmacokinetic profile and dosing needs to be patient specific.
    - Terminal half-life of methadone ranges from 6-150 hours, while the analgesic effect lasts for 4-12 hours when dosed chronically.
    - Accumulation of methadone in the body will occur after repeated doses, making titration to effect a much slower process, ranging from days to weeks.
- Methadone **cannot** be converted linearly from other opioids, refer to chart below.

Notable Interactions (not comprehensive)	
Increase methadone concentrations	Strong CYP3A4 inhibitors: azole antifungals (ketoconazole, fluconazole, voriconazole, posaconazole), macrolide antibiotics (erythromycin, azithromycin, clarithromycin), ciprofloxacin, isoniazid, cimetidine, verapamil, diltiazem, nefazodone
Increase methadone concentration AND **prolong QT** interval	Azole antifungals (as above), macrolide antibiotics (as above), fluvoxamine, paroxetine, fluoxetine, sertraline
Decrease methadone concentrations	Strong CYP 3A4 inducers: carbamazepine, phenobarbital, phenytoin, nevirapine, nelfinavir, rifampin [α] ritonavir, Paxlovid (ritonavir containing)
Prolong QT interval	Chlorobutanol (preservative in IV methadone), ondansetron, palonosetron, granisetron, haloperidol, quetiapine, olanzapine, metoclopramide, chlorpromazine, amitriptyline, nortriptyline, desipramine, imipramine

[α] ritonavir is a strong CYP3A4 inhibitor; however, during co-administration with methadone, decreased methadone concentrations are seen

For a more thorough review of drug interactions please utilize the following:
Lexi-Comp: Interactions - Lexicomp
Flockhart table: https://drug-interactions.medicine.iu.edu/MainTable.aspx
Liverpool Covid-19 Drug interaction checker: https://www.covid19-druginteractions.org/checker

ECG Monitoring with Methadone		
Goals of care	**Baseline ECG**	**Follow-up ECG**
Curative, life-prolonging	Obtain baseline ECG if: • Has risk factors* • Prior QTc >450 ms • History of ventricular arrhythmia Consider baseline ECG if: • No risk factors* • QTc <450 ms in the previous year **Recommendation:** • QTc >500 ms – do not initiate • QTc 450-499 – consider alternative (or correct reversible causes and reassess)	Obtain ECG within 2-4 weeks if: • New risk factors* • Prior ECG QTc >450 ms • History of syncope Obtain additional or more frequent ECG: • New risk factors* or signs/symptoms arrhythmia • TDD methadone ≥30-40 mg and when ≥100 mg **Recommendation**: • QTc >500 ms – switch to alternative or reduce dose • QTc 450-499 – consider alternative or reduce dose • Discuss risks/benefits if goals of care change
Comfort focused, limited prognosis	• No ECG unless compelling indication • If ECG obtained, follow recommendations above	• No ECG unless compelling indication • If ECG obtained, follow recommendations above
* **Risk factors**: hypokalemia, hypomagnesemia, impaired liver function, structural heart disease (congenital heart defects, history of endocarditis, or heart failure), and genetic predisposition including patient or family history of congenital QTc syndrome, use of QTc-prolonging medications		

Equianalgesic Conversion TO Methadone Dose-dependent potency changes well-established in the literature.		
Oral Morphine Equivalent	**Mg of oral Methadone**	**Mg of oral Morphine**
under 60 mg/day	Do not start higher than 7.5 mg methadone per day	
61-200 mg/day*	1	10
over 200 mg/day	1	20
IV methadone is twice as potent as oral methadone; Reduce by 50% when converting to IV from PO Doses above 2000 mg oral morphine have not been studied for conversion to methadone – please use caution in these circumstances *May consider 1:20 conversion ratio in patients older than 65 or with other comorbidities		

Determining the starting dose of methadone:

- Convert all opioids taken by patient to PO morphine equivalents.
- Calculate total daily dose (TDD) of morphine equivalents to determine ratio.
- Calculate methadone dose using appropriate conversion ratio.
- Divide the total daily dose by 3 for an 8 hour dosing interval or 2 for a 12 hour dosing interval.
    - **Further dose reduction is not needed.**
- **Prior to starting methadone contact appropriate outpatient provider to coordinate ongoing prescribing and monitoring,** if expected to continue methadone after discharge from hospital.
- When prescribing methadone for pain, "for pain" must appear clearly on the face of the prescription.
- **Do NOT start oral methadone at higher than 30-40 mg daily (15-20 mg IV daily)** without consultation from appropriate Palliative Care or Non-Operative Pain service.
- Initial dose increases of methadone should not be more than 10 mg per day every 5-7 days.
- *Strongly consider rotating to methadone **only after** consulting the appropriate Pain or Palliative Care team.*

Experience converting patients **FROM methadone TO another opioid** is limited and may be difficult. Estimated equianalgesic conversion ranges from 3-5 mg oral morphine equivalents for 1 mg of oral methadone. **Strongly consider** consulting the Pain or Palliative Care services in these cases.

Methadone as a Co-Analgesic:

Low dose methadone may be considered as a co-analgesic adjuvant for patients on other long acting-opioids.

- Typically start between 1-5 mg BID or Q8H (usually <10 mg/24 hr total) to reduce overall breakthrough needs, and/or start transition to full rotation.
- **Strongly consider** consulting Pain or Palliative Care services in these patients for guidance.

Opioid Use Disorder:

Methadone maintenance for opioid use disorder is limited to specialized clinics and cannot be prescribed or filled at a pharmacy for this indication.

- Confirm patient's clinic dose with their clinics whenever possible.
    - If you cannot confirm the dose with their clinic, a max dose of 30 mg may be ordered.
- Managed with one large dose in the morning, usually liquid formulation.
- Methadone's extremely long terminal half-life allows for continued receptor occupancy, reducing cravings long after the end of analgesic effect, allowing for once daily dosing for OUD.
- Typically dosed between 60-120mg to prevent opioid withdrawal symptoms and cravings but avoid euphoria.
    - Sometimes this dose can be divided if additional pain control is required in a hospital setting.

BUPRENORPHINE

Buprenorphine is a mixed opioid agonist antagonist that is indicated for both pain management and as a Medication for Opioid Use Disorder (MOUD).

- Buprenorphine is a partial agonist at the μ-opioid receptor, and an antagonist at the κ-opioid receptor.
- At doses used for MOUD, buprenorphine will bind to opioid receptors more tightly than other opioids, increasing opioid requirements if administering full agonists for pain.
- Patients on buprenorphine for MOUD and experiencing or expected to experience pain (procedures, new painful diagnoses) require consult to an appropriate Pain, Palliative Care, or Addiction Psychiatry service.
- When used for MOUD, patients might not need to be in mild withdrawal for induction to high dose buprenorphine. Please refer to BWH Guideline for low-dose buprenorphine initiation.

Pain Management

- Buprenorphine can be considered when selecting a long-acting opioid in patients who are opioid naïve or have low PRN opioid doses and are requiring around-the-clock coverage given its unique safety profile coupled with potent analgesic effect.
- 300 mcg (0.3mg) of IV buprenorphine produces similar analgesia to 10mg of IV morphine (30 OME)
    - This ratio is not an opioid conversion due to effects of partial agonism at higher doses
- Buprenorphine is not an appropriate initial choice for acute pain without specialty pain service consultation.
- Doses used for pain management are typically lower than doses used for MOUD.
- At low doses (<2 mg SL,<1mg IV, <40 mcg/hr TD) buprenorphine acts similarly to a full μ-agonist.
- Buprenorphine is very poorly absorbed enterally (PO/PR), but due to high lipophilicity is more easily absorbed through transmucosal routes.
- Full agonist short-acting opioids **can** be used concurrently with buprenorphine products for breakthrough pain relief. Always consult with an appropriate pain management or palliative care team when using buprenorphine for pain.
    - If a patient is taking higher doses of buprenorphine (>8 mg SL/day), consider using agents with greater receptor affinity such as hydromorphone or fentanyl to treat breakthrough pain.
- If inadequate analgesia with higher doses of short-acting opioids in patients on higher than 16 mg SL buprenorphine/day, consult an appropriate pain management or palliative care service.
- Due to the long half-life of buprenorphine products, when stopping a buprenorphine product it may continue to occupy opioid receptors for an extended period. Consult a specialty pain service for guidance with pain management around buprenorphine transitions.
- At BWH, Belbuca products may need to be ordered by a clinical pharmacist given its role in low dose induction.

Safety

- When high dose buprenorphine (>~8mg SL, ~4mg IV) is given to an opioid tolerant patient currently on full agonist opioids, it may precipitate severe opioid withdrawal.
- Buprenorphine has a similar adverse effect profile to most other opioids (pages 20-21).
    - Compared to other opioids, buprenorphine shows a lower risk of respiratory depression with increasing doses.
- Buprenorphine can cause QT prolongation at higher doses, however the risk of torsades des pointes when used for MOUD is low.

Pharmacokinetics of selected buprenorphine formulations				
Formulation	Route	Bioavailability	Dosing interval for pain	Elimination T½
Buprenex	IV/IM	100%	6-8 hours	1.5- 7 hours
Butrans	TD	100% (effective)	7 days	26 Hours
Belbuca	Buccal	46-65%	12 Hours	27 Hours
Subutex	SL	~30%	6-8 hours	31-35 Hours

Starting Dose Selection in Pain Management

Products indicated for pain management						
Product	**Total Daily OME[1]:**					**Comments**
	0 – 30	**30 – 80**	**80 – 90**	**90 – 160**	**> 160**	
Butrans (transdermal patch)	5 mcg/hr	10 mcg/hr		Consider Alternative Product		Onset of effect: 18-24 Hours Titrate no more than: Every 3 days Increase by up to: 10 mcg/hr Maximum labeled dose: 20 mcg/hr
Belbuca (buccal film)	75 mcg Q12-24h	150 mcg Q12H		300 mcg Q12H	Consider Alternative Product	Onset of effect: 2-4 Hours Titrate no more than: Every 4 days Increase by up to: 150 mcg Q12H Maximum dose: 900 mcg Q12H

Products not indicated for pain management (requires consult for pain)			
Product	Available Strengths	Caution	Comments
Suboxone (Buprenorphine-naloxone tab and film)	2 mg – 0.5 mg 4 mg – 1 mg 8 mg – 2 mg 12 mg – 3 mg	Do not start for pain management in a patient who is currently on full agonist opioids and not already on higher dose buprenorphine. (Risk of precipitated withdrawal)	Lower doses are needed for pain (often 2-10mg total in a day) than OUD treatment and the total daily dose should be split into 2-3 doses when using for pain
Subutex (Buprenorphine tab)	2 mg 8 mg		Subutex is only recommended for use during induction phase when initiating treatment for OUD and is NOT commonly used in chronic pain treatment unless patients have a sensitivity to naloxone
Zubsolv (Buprenorphine-naloxone film)	0.5 mg – 0.18 mg 1.4 mg – 0.36 mg 2.9 mg – 0.71 mg 5.7 mg – 1.4 mg 8.6 mg – 2.1 mg 11.4 mg – 2.9 mg		Zubsolv strength is NOT equivalent to Suboxone/Subutex and requires conversion. Zubsolv dose in mg X 1.4 = Suboxone dose in mg

Notes:
[1]The current total daily OME needs of the patient including both long-acting and short-acting

Acute Pain Management in Patients Already Taking Buprenorphine

- Buprenorphine **should NOT be automatically held in the setting of unplanned surgery, acute pain, or injury.** Consider the patient's current buprenorphine dose and anticipated pain needs prior to tapering or holding buprenorphine.
- Refer to the BWH Perioperative Management of Opioid Tolerant Patients and Patients Treated with Medications for Opioid Use Disorder
- Short-acting opioids with higher potency and greater receptor affinity, such as hydromorphone and fentanyl, may be more effective for acute pain than other opioids in patients taking buprenorphine.

BWH Low dose induction guidelines

BWH Perioperative management of buprenorphine guidelines

FENTANYL

Dose Conversion Table for Selected Opioids to Transdermal FentaNYL

OxyCODONE (mg/day)	HYDROmorphone (mg/day)		Morphine (mg/day)		→	FentaNYL transdermal patch
PO	IV	PO	IV/IM	**PO**	Equivalent to	(mcg/hr)
15	1.25	6.25	8.5	**25**	→	**12**
30	2.5	12.5	17	**50**	→	**25**
65	5	25	33	**100**	→	**50**
100	7.5	37.5	50	**150**	→	**75**
130	10	50	67	**200**	→	**100**

- This chart is based on equianalgesic studies conducted on conversion of *oral morphine to transdermal fentaNYL patch*.
  - A dose reduction when converting was taken into account.
  - Generally speaking, a dose reduction is unnecessary. However, for patients with special considerations like in the elderly or in patients with reduced renal or hepatic function a dose reduction may be appropriate.
- There is also potential interpatient variability in *absorption* of transdermal fentaNYL.
- Starting a patch in an opioid-naïve patient is inappropriate.
- There is limited data on conversions **FROM** the patch to any oral opioid.
  - **Clinicians should dose reduce by 25-33% when converting a patient *from a patch to another opioid*.**
- Fentanyl is metabolized by CYP3A4 – use caution when administering concomitantly with CYP3A4 inhibitors such as antifungals (ketoconazole, voriconazole, etc.)
- Transdermal fentaNYL releases from the subcutaneous fat.
  - When removing the patch from a patient in order to switch to another opioid, it is important to consider that fentanyl will remain in the system for 6-18 hours after removal of the patch.
  - Fentanyl patches will take 12-18 hours to develop initial effect.

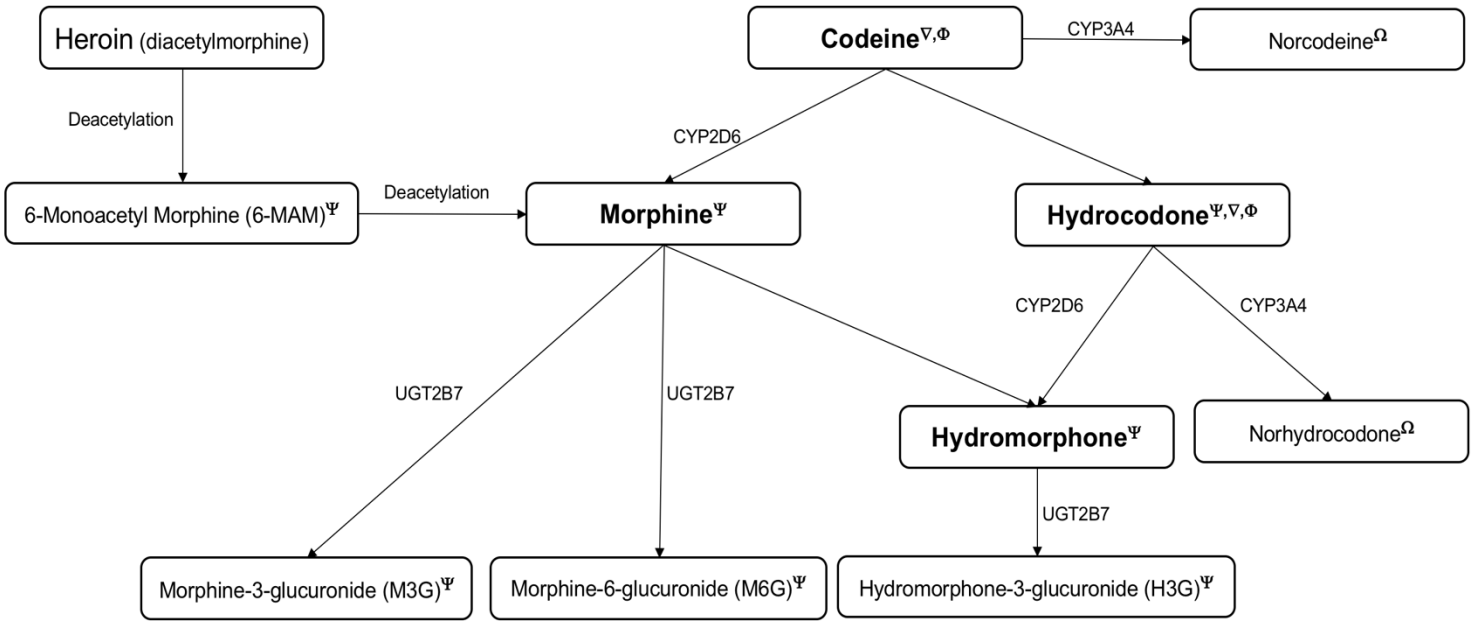
Transmucosal Immediate-Release FentaNYL (TIRF)

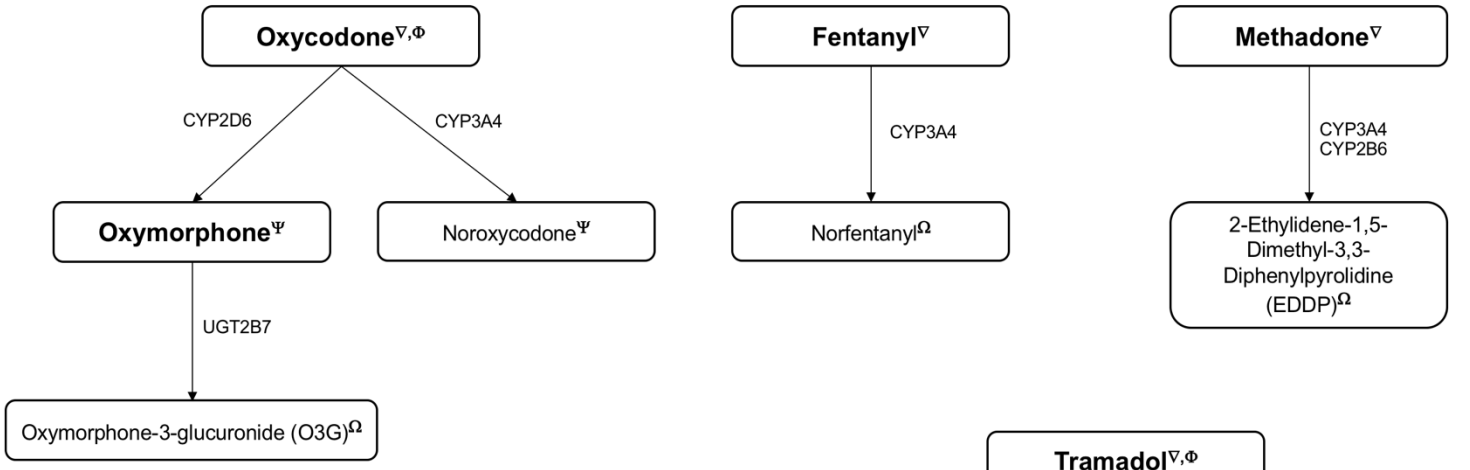
- Transmucosal Immediate-Release FentaNYL products are indicated only for the management of breakthrough pain in adult patients with cancer 18 years of age and older who are on long-acting opioids and who are tolerant to regular opioid therapy for underlying persistent cancer pain.
- TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at ANY dose in patients not taking chronic long-acting opioids.
- Prior to prescribing a TIRF medication, prescribers must be enrolled in the TIRF REMS program.
- TIRF medications should not be initiated as an inpatient if there is no plan to follow up with a TIRF prescriber.

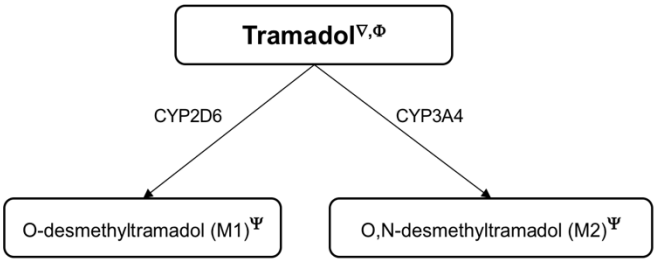
TIRF REMS Transmucosal Immediate-Release FentaNYL (e.g. Actiq, Fentora, Abstral, Lazanda, Subsys) **R**isk **E**valuation and **M**itigation **S**trategies programs are in place when prescribing any of these products. When initiating therapy with these products, use the lowest recommended dose and titrate upward according to manufacturer instructions and patient response. See website www.TIRFREMSaccess.com or call TIRF REMS Access program at 1-866-822-1483.

Opioid Metabolism Pathway

- Opioid metabolism takes place primarily in the liver as opioids undergo phase 1 metabolism by the CYP pathway and phase 2 metabolism by conjugation (glucuronidation).
    - The cytochrome P450 (CYP) metabolism enzyme, primarily via CYP3A4 and CYP2D6, influences possible drug-drug interactions when opioids are used concurrently with CYP inducers or inhibitors. See page 11 for examples of drug interactions.
- Accumulation of the M3G & H3G metabolites can lead to neuroexcitatory effects. The M6G metabolite exerts analgesic effects.
- Opioid metabolism pathways play a key role in the appropriate interpretation of urine toxicology screening.







Legend:

Bold = parent drug (commercially available)

Ψ = active metabolite

Ω = inactive metabolite

∇ = CYP3A4 drug interaction caution

Φ = CYP2D6 drug interaction caution

Opioid Dosing Considerations in Hepatic and Renal Impairment

- Recommendations for dosage adjustment are a part of individualized patient care along with clinical judgement and appropriate monitoring.
- When titrating any opioid in patients with hepatic and renal impairment, they should be titrated slowly and cautiously.
- Refer to the opioid metabolism pathway on page 16 for CYP enzyme metabolism and active/inactive metabolites.
- Practical clinical guidance for the hepatic and renal impairment tables has been provided in the comments section, where each opioid is assigned to one of four designations: **Most Safe, Less Safe, Avoid Use, Do Not Use**

Opioid Dosing in Hepatic Impairment

- The degree of hepatic impairment is defined utilizing the Child Pugh Score:
  - Mild Impairment: Child Pugh A, Moderate Impairment: Child Pugh B, Severe Impairment: Child Pugh C (See Appendix C on Child Pugh Scoring page 33)
- Recommendations for hepatic dosage adjustments should be considered alongside evaluating the degree and duration (acute vs. chronic) of hepatic impairment.

Opioid Dosing in Hepatic Impairment				
Agent	**Degree of Hepatic Impairment**			**Comments**
	Mild	**Moderate**	**Severe**	
Codeine	Avoid use			**Avoid Use**
Morphine	Prolong dosage interval or reduce doses, titrate slowly		Avoid use	**Avoid Use** ↑ bioavailability, ↑ T ½, ↓ clearance
OxyCODONE	Reduce dose by 25-50%, prolong dosage interval		Avoid use	**Less Safe** ↑ T ½, ↓ clearance Unpredictable serum levels
HYDROcodone	No adjustment required		Initiate at 50% dose	**Less Safe**
HYDROmorphone*	No adjustment required	Reduce dose by 25-50%	Reduce dose by 50%, prolong dosage interval	**Most Safe**
Methadone*	No adjustment required	No adjustment required	Avoid use – if needed, careful titration	**Safety considerations vary** Low 1st pass metabolism → significant absorption from GI tract ↑ T ½, ↓ clearance
Buprenorphine	TD: Start with lowest dose (5 mcg/hr) SL: No adjustment required		TD: Avoid use SL: Reduce dose by 50%	**Less Safe** Acute hepatitis has been reported with buprenorphine
FentaNYL*	TD: Reduce dose by 50% IV bolus: No dose adjustments required		TD: Use with caution IV bolus: No dose adjustments required	**Most Safe via IV bolus** **Less Safe via IV infusion** IV infusion: ↑T ½ due to lipophilicity & ↑ active drug due to decreased metabolism to inactive drug
Meperidine*	Do not use (see page #6)			**Do Not Use**
Tapentadol	No adjustment required	Reduce doses	Avoid use	**Less Safe** Extensive 1st pass metabolism (32% bioavailability)
TraMADol	Prolong dosage interval to Q12H		Avoid long-acting tramadol	**Less Safe** 3.2-fold ↑ AUC, 2.6-fold ↑ T ½
* Heavily protein bound (>70%); serum levels may be increased in low albumin states.				

Opioid Dosing in Renal Impairment

- The degree to which renal impairment affects analgesia, side effects, and toxicity of opioids is not well understood due to the lack of sufficient evidence.
- Glomerular filtration rate (GFR) recommendations have been provided to correlate with literature; however, creatinine clearance (CrCl) should also be assessed for dose adjustments.

Opioid Dosing in Renal Impairment

Agent	Renal Impairment		Dialysis	Renal Excretion Percentage	Comments
	GFR 10 – 50 mL/min*	GFR < 10 mL/min*			
Codeine	Do not use				**Do Not Use**
Morphine	Reduce dose by 25 – 50% if used	Avoid use; reduce dose by 50 – 75% if necessary	Use cautiously Dialyzable	~ 90% Not recommended in ESRD due to accumulation of drug & metabolites	**Avoid Use** If must be used, monitor closely for side effects and neurotoxicity
HYDROmorphone ——— HYDROcodone	Reduce dose by 25 – 50% if used; prolong dosage interval	Reduce dose by 50% if used; prolong dosage interval	Dialyzable ——— Use cautiously	Hydromorphone:75% ——— Hydrocodone: 6.5% Inactive metabolites may accumulate in renal insufficiency	**Less Safe** IV hydromorphone is **commonly used** in renal insufficiency in clinical practice Side effects typically occur over prolonged exposure
OxyCODONE	Reduce dose by 50% if used	Use cautiously & prolong dosing interval	Use cautiously & prolong dosing interval Partially dialyzable	75 – 85% ↓ excretion of metabolites & ↑ T ½ in uremia	**Less Safe** Insufficient evidence for safety in renal impairment
FentaNYL	May reduce dose by 25%	Reduce dose by 50%	Overall not dialyzable May be dialyzable by some filters	75 % No clinically active metabolites	**Most Safe**
Meperidine	Do not use (see page 6)				**Do Not Use**
Methadone	Dose reduction may be required alongside clinical assessment.		Not dialyzable	21% as unmetabolized No clinically active metabolites	**Safety considerations vary** Methadone is commonly used in renal insufficiency in clinical practice
Buprenorphine	Insufficient evidence for recommendations in renal insufficiency		Not dialyzable	27 – 30%	**Less Safe** Eliminated through the biliary system
Tapentadol	No dose adjustment	Do not use	Partially dialyzable		**Less Safe**
TraMADol	Reduce initial dose; prolong dosage interval to Q12H; max 200 mg/day	Do not use in GFR < 30 mL/min	7% of drug and active metabolite removed by dialysis	90% (30% as unmetabolized) ↑ T ½ in renal insufficiency	**Less Safe** Do not use long-acting tramadol Risk for seizures high with ↑↑ uremia & drugs that ↓ seizure threshold

***Glomerular filtration rate (GFR) recommendation interpretation should be coupled with evaluating the degree and duration of renal dysfunction, such as AKI, CKD, vs. acute on chronic CKD.

Patient-Controlled Analgesia (PCA)

1. Patient-controlled analgesia (PCA) may be used in patients requiring IV opioids who are alert, oriented, and able to use the equipment appropriately.
2. PCA pumps can be programmed to give bolus doses, a continuous infusion, or both.
3. Family or health care professional use of the PCA (PCA by proxy) is **not permitted in this institution**.
4. PCA dosing is recorded as:
   PCA bolus dose/lockout interval/1-hour limit/continuous infusion rate.

The following charts may be used as a reference for the default order sets at BWH. Patients who are already on opioids need additional dosing considerations such as higher bolus doses, addition of a continuous infusion and non-standard concentrations; consult the appropriate pain management or palliative care service. Please refer to PCA Drug Library for each individual order set. PCA pumps are limited by a minimum volume of 0.1 mL for delivery of doses. Refer to Assessing Opioid Therapy Risks on page 6 for descriptions of patients at risk for respiratory depression.

General PCA Default Dosing

	Morphine	HYDROmorphone	FentaNYL
PCA dose	1.5 mg	0.2 mg	20 mcg
PCA lockout interval	10 minutes	6 minutes	6 minutes
Continuous dose	0 mg/hr	0 mg/hr	0 mg/hr
Nursing bolus dose	2 mg	0.3 mg	25 mcg

High Risk PCA Default Dosing (e.g. age >65, morbid obesity, sleep apnea, RASS ≤ -2)

	Morphine	HYDROmorphone	FentaNYL
PCA dose	0.5 mg	0.1 mg	15 mcg
PCA lockout interval	10 minutes	10 minutes	6 minutes
Continuous dose	Not allowed	Not allowed	Not allowed
Nursing bolus dose	1 mg	0.2 mg	20 mcg

Opioid-Tolerant Default PCA Dosing

	Morphine	HYDROmorphone	FentaNYL	Methadone
PCA dose	3 mg	0.5 mg	40 mcg	A consult with an appropriate Pain Service is required for the use of a Methadone PCA
PCA lockout interval	6 minutes	6 minutes	6 minutes	
Continuous dose	0 mg/hr	0 mg/hr	0 mg/hr	
Nursing bolus dose	5 mg	0.8 mg	60 mcg	

There is also a “Palliative Care” order set which does not have presets, only to use under a Palliative Care or Pain team.

Management of Opioid Side Effects*

<table>
<tr><th>Adverse Effect</th><th>Management Considerations</th></tr>
<tr><td>Allergic Reaction</td><td>True allergic reactions are rare (i.e., IgE involvement). Selection of another opioid class (by chemical structure) is usually necessary only if the patient has had a true allergic reaction (e.g. rash, hives, difficulty breathing) and not simply a sensitivity to histamine release. Symptoms are usually secondary to mast cell activation and subsequent histamine release.

<table>
<tr><th>Chemical Structure</th><th>Opioids in class</th></tr>
<tr><td>Phenanthrene</td><td>codeine, HYDROcodone, HYDROmorphone, levorphanol, morphine, oxyCODONE, oxyMORphone</td></tr>
<tr><td>Phenylpiperidine</td><td>fentaNYL, meperidine, sufentanil</td></tr>
<tr><td>Diphenylheptane</td><td>methadone</td></tr>
</table>
</td></tr>
<tr><td>Delirium/ Confusion/ Hallucinations</td><td>Reduce dose or rotate opioid; consider neuroleptic therapy if agitation present (haloperidol 0.5-1 mg PO/IV Q6H-Q12H or OLANZapine 2.5-5 mg PO daily-BID)</td></tr>
<tr><td>Nausea/ Vomiting</td><td>Tolerance to N/V may develop, and it may be helpful to administer one antiemetic on a fixed schedule for a few days. After that time period, as-needed dosing is usually adequate.

Suggested:
Prochlorperazine 10 mg PO every 6-8 hours or 25 mg PR every 12 hours
Metoclopramide 10-20 mg PO/IV every 6 hours (for vomiting)
Haloperidol 0.5-2 mg PO/IV every 6-12 hours
Scopolamine 1.5 mg patch topically with changes every 3 days (esp. with h/o motion sickness, most effective when given prophylactically)

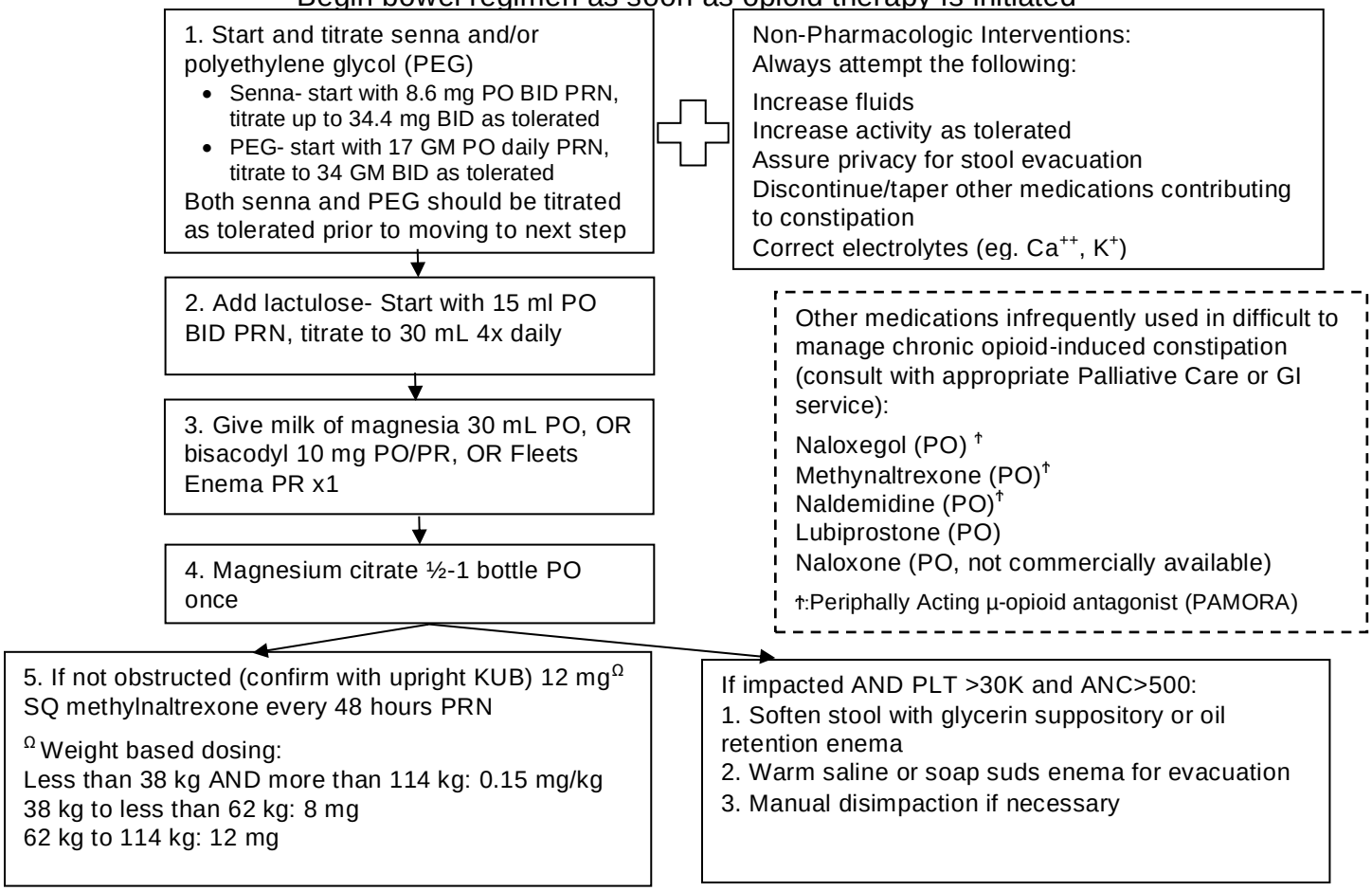
Ondansetron dosing for Post-Operative Nausea/Vomiting: 4 mg IV immediately prior to or following anesthesia induction</td></tr>
<tr><td>Pruritis</td><td>Pruritis in the absence of evidence of rash/allergic reaction is a central mu-related phenomenon (not histamine-related) and best treated with nalbuphine 5 mg IV Q6H prn and not an antihistamine. Consider switching opioids for refractory pruritus.</td></tr>
<tr><td>Respiratory Depression</td><td>Hold opioid; provide supportive measures; consider dilute naloxone. See page 22.</td></tr>
<tr><td>Myoclonic Jerking</td><td>Reduce dose or rotate opioid; hydration to enhance clearance of toxic metabolites.

Acute management may include: clonazePAM 0.25-0.5 mg PO TID; lorazepam 0.5-1 mg PO/IV 4x daily; baclofen 5-10 mg PO TID</td></tr>
<tr><td>Sedation</td><td>Tolerance typically develops; hold sedatives/anxiolytics; hold opioid; reduce dose; if persistent, consider CNS stimulants (e.g. increase caffeine intake, methylphenidate or dextroamphetamine 2.5-5 mg PO daily OR every morning and every day at noontime, or modafinil 100-200 mg PO daily).</td></tr>
</table>

*The above assumes that opioid therapy is a necessity. Non-opioid therapy options or alternative routes of administration should be considered. A thorough evaluation for other causes of the effect should always be done.

Management of Opioid-Induced Constipation

Begin bowel regimen as soon as opioid therapy is initiated



Weaning Chronic Opioid Therapy (COT)

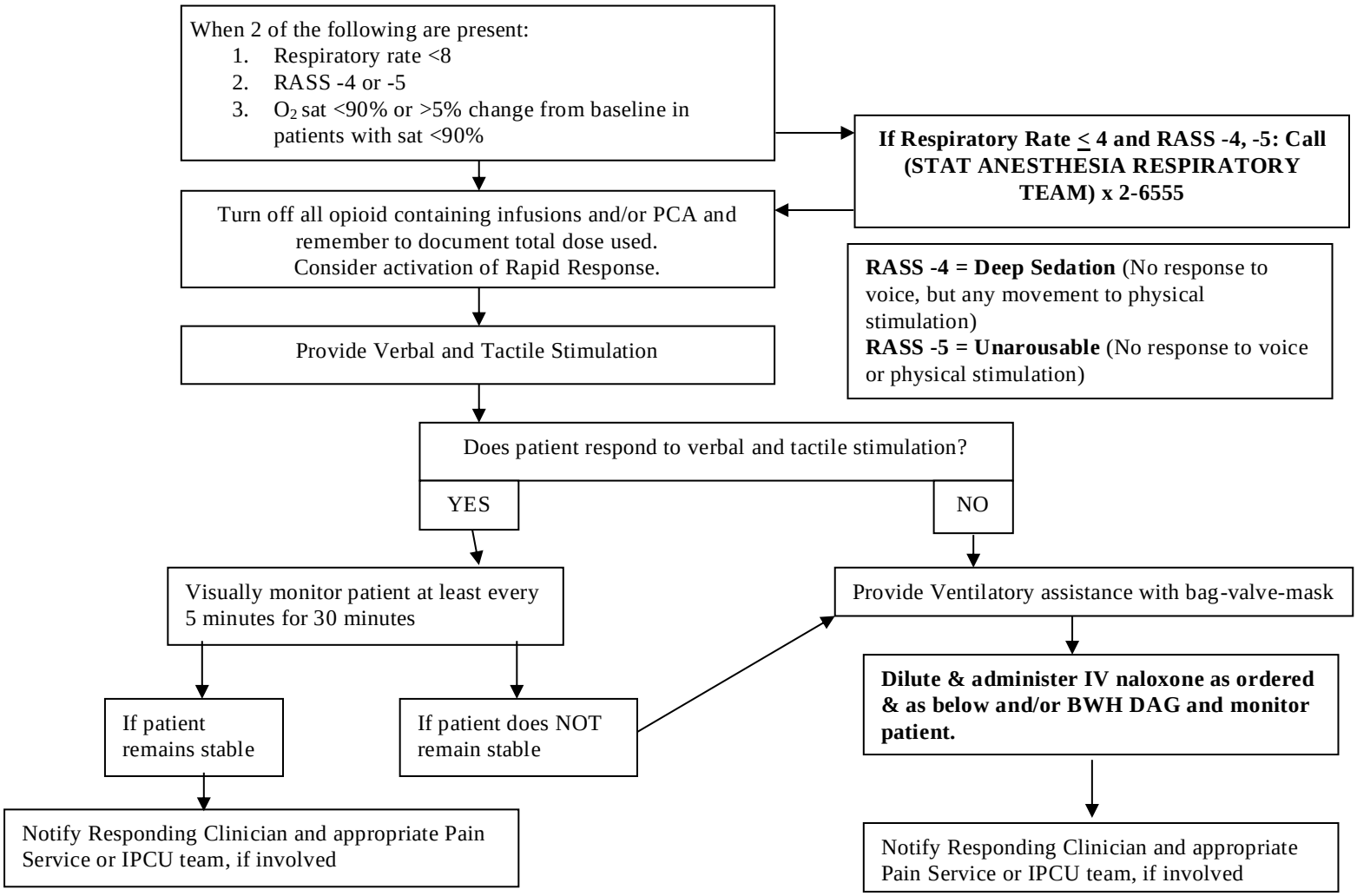
Long term use (≥2 months) of opioids for chronic non-malignant pain has been associated with harm, and has no clear evidence of benefit. Key points when considering tapering COT:

- The decision to taper COT should ideally be reached through shared decision making
  - Voluntary opioid tapers have been associated with improved function
  - No evidence to support involuntary tapers for patients who are not diverting medicines
- Individualized taper plans should ALWAYS be employed
- Speed of taper should be inversely proportional to length of COT
  - Time between dose changes and dosage reductions should be assessed on a regular basis
- Tapering can cause withdrawal related adverse events, and if severe enough, these can be managed medically

Symptom	Potential Treatment
Diarrhea	Loperamide 4mg PO X 1; then 2mg with each loose BM (max 16 mg/day)
HTN, tachycardia, anxiety	Clonidine 0.1-0.2 mg Q6H PRN
Insomnia	Trazodone 50-100 mg QHS, OR melatonin 3-6 mg QHS, OR mirtazapine 7.5 mg QHS
Nausea	Ondansetron 4 mg PO Q8H PRN, OR prochlorperazine 5-10 mg Q6H PRN
Abdominal cramping	Dicyclomine 10-20 mg Q6H PRN

- Decrease dose by 10-15% of original dose every 1-4 weeks
  - Faster tapers cause more intense adverse events over a shorter period of time, and slower tapers cause less intense adverse effects over a longer period of time
- Patients with Opioid Use Disorder should always be offered Medications for Opioid Use Disorder (MOUD)
- If more rapid weaning is required, please consult the Non-Operative Pain Service, Palliative Care Service or the Addiction Psychiatry Service.

Treatment of Suspected Opioid-Induced Respiratory Depression
When to Use Naloxone



Naloxone Dilution and Dosing

- Dilute 0.4 mg (1 mL) of naloxone in 9 mL of saline to yield 0.04 mg/mL.
- Administer to patient in 1-2 mL increments (0.04-0.08 mg) at 2-3 minute intervals until response.
- If no change in respiratory depression after 0.4 mg naloxone has been administered, consider another etiology other than opioid-induced.
- If there is some, but not enough, improvement after 0.4 mg of naloxone has been administered, continue titration.
- Naloxone's half-life is less than most of the opioid agents so be aware that respiratory depression may recur. Therefore, be prepared for the need to re-administer naloxone boluses or consider use of naloxone infusion in patients on long-acting opioids.

Naloxone Rescue Kits for Outpatients

Massachusetts law now allows for patients and caregivers to purchase naloxone rescue kits from community pharmacies without a prescription. Both BWH and DFCI Outpatient Pharmacy departments have naloxone available to purchase. Consider prescribing naloxone to all patients prescribed opioids.

Available Single Active Agent Opioid Formulations		
Drug	**Available Strengths and Dosage Forms**	**Comments**
Morphine	Tab: 15, 30 mg ER Tab Ψ: 15, 30, 60, 100, 200 mg ER Capsule: 10, 20, 30, 40, 50, 60, 70, 80, 100, 130, 150, 200 mg Liquid: 10 mg/5 mL, 20 mg/5 mL, 20 mg/mL Suppositories: 5, 10, 20, 30 mg Injectable solution: 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 4 mg/mL, 5 mg/mL, 8 mg/mL, 10 mg/mL, 15 mg/mL, 25 mg/mL, 50 mg/mL	ER Capsules- 24 hour capsule can be opened and sprinkled on food or via g-tube
HYDROcodone	ER Capsule Ψ: 10, 15, 20, 30, 40, 50 mg ER-24 Tablet Ψ: 20, 30, 40, 60, 80, 100 mg	Zohydro ER®: 12 hour capsule, reformulated into an abuse deterrent formulation after being pulled from the market Hysingla ER®: 24 hour tablet
HYDROmorphone	Tab: 2, 4, 8 mg ER (Exalgo®) Ψ: 8, 12, 16, 32 mg Liquid: 1 mg/mL Suppository: 3 mg Injectable solution: 0.2mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 4 mg/mL, 10 mg/mL	
OxyCODONE	HCl Tab: 5, 10, 15, 20, 30 mg HCl ER Tab Ψ: 10, 15, 20, 30, 40, 60, 80 mg Base ER Capsule (Xtampza)*** ,Ψ: 9, 18, 27, 36 mg HCl Oral Liquid: 5 mg/5mL, 20mg/mL	***Xtampza® is not a 1:1 conversion to other forms of oral oxycodone since it is formulated with oxycodone base. 10 mg HCl = 9 mg base. Should be administered with a high fat meal. Max of 288 mg of oxyCODONE base daily.
Oxymorphone	Tab: 5, 10 mg ER Tab (Opana ER®) Ψ: 5, 7.5, 10, 15, 20, 30, 40 mg Injectable solution: 1 mg/mL	Opana® is to be taken on empty stomach Branded Opana ER is available in a crush resistant formulation while Oxymorphone ER is not.
FentaNYL	Transdermal Patch (Duragesic®): 12, 25, 37.5, 50, 62.5, 75, 87.5,100 mcg/hr Injectable solution: 50 mcg/mL	TIRF REMS see page #15 A 25 mcg/hr transdermal patch is equianalgesic to ~ 50 mg of oral morphine per day.
Ψ Abuse Deterrent Formulation		

Available Single Active Agent Opioid Formulations (Continued)		
Methadone	Tab: 5, 10 mg Liquid: 5 mg/5mL, 10 mg/5 mL, 10 mg/mL Injectable solution: 10 mg/mL	Long half life; accumulates with repeated dosing; may require dose decrease on days 2-5 Methadone see page #11-12 **Please consult appropriate Pain or Palliative Care service for questions.**
TraMADol	Tab: 50, 100 mg ER Tab: 100, 200, 300 mg ER Capsule (Conzip®): 100, 150, 200, 300 mg	Not an Opioid – metabolite binds to opioid receptors. Ceiling dose 400 mg/d (300 mg/d for elderly) 50 mg of traMADol is equianalgesic to ~ 60 mg of oral codeine
Tapentadol	Tab: 50, 75, 100 mg ER Tab Ψ: 50, 100, 150, 200, 250 mg	Not an opioid – binds to opioid receptors Nucynta® IR – Max dose 600 mg/day Nucynta® ER – Max dose 500mg/day
Buprenorphine	Patch: 5, 7.5, 10, 15, 20 mcg/hr Film (Pain): 75, 150, 300, 450, 600, 750, 900mcg Injectable Solution: 0.3 mg/mL	Butrans® patch and Belbuca® film are indicated for treatment of chronic severe pain in patients who require daily, around-the-clock, long-term opioid treatment. Suboxone and Subutex are NOT indicated for the treatment of pain and are not included in this chart.
Ψ Abuse Deterrent Formulation		

Abuse Deterrent Formulations (ADF)

Abuse-deterrent properties make certain types of abuse, such as crushing a tablet in order to snort the contents or dissolving a capsule in order to inject its contents, more difficult or less rewarding. It **DOES NOT MEAN** the product is impossible to abuse or that these properties necessarily prevent addiction, overdose or death – notably, the FDA has not approved an opioid product with properties that are expected to deter abuse if the product is swallowed whole. If possible, it is considered good practice to preferably prescribe ADF of ER/LA opioids to mitigate risk of misuse and diversion.

Extended Release/Long-Acting Risk Evaluation and Mitigation Strategies Program

REMS (**R**isk **E**valuation and **M**itigation **S**trategies) are now in place for all long-acting and extended release opioid products. REMS will require opioid analgesic companies to make available training for health care professionals on proper prescribing practices and also to distribute educational materials to prescribers and patients on the safe use of these powerful pain medications.

Combination Opioid Analgesic Products

HYDROcodone, oxyCODONE, and traMADol are also available in various short-acting combination products. Dosing of combination products containing acetaminophen, aspirin or ibuprofen is limited by the maximum dose of the non-opioid ingredients. As such, single opioid agonist products are preferred for maximum flexibility when dosing opioids.

Adjuvant Analgesic Agents

Drug	*Clinical Indications*	*Usual Starting Dose and Interval*	*Common Dosage Range*	*Comments*
Anticonvulsants				
Gabapentin* (Neurontin®)	Neuropathic pain	100 mg PO TID, increase by 100 mg TID q 3 days	300-3600 mg/day in 3 divided doses	Adjust dose for renal dysfunction (CrCl < 60 mL/min)
Pregabalin* (Lyrica®)		150 mg PO divided BID or TID	300 mg in 2-3 divided doses	Significant increase in respiratory depressant effects of opioids Do not stop abruptly
OXcarbazepine (Trileptal®)		300 mg PO daily, then ↑ to 300 mg BID, then ↑ by 300 mg/day q 5 days	900 mg BID	Anecdotal data. Less adverse effects than carBAMazepine. Renal dose: start at 150 mg BID and titrate slowly
Lamotrigine (LaMICtal®)		25 mg every other day x 2 wks ↑ to 25 mg daily x 2 wks ↑ by 25-50 mg/d q 1-2 wks	50-400 mg/day	Do not stop abruptly
Topiramate (Topamax®)		25-50 mg daily ↑ by 25-50 mg q wk	100-400 mg/day Max dose 400mg	Limited data
Zonisamide (Zonegran®)		100 mg bedtime (↑ q 2 weeks)	200-400 mg bedtime	Cross sensitivity with sulfa allergy. Limited data. Wt. loss
Levetiracetam (Keppra®)		500 mg BID-TID ↑ q 2 weeks	1-3 gm/day	Dose reduce in renal insufficiency (CrCl < 80 mL/min)
CarBAMazepine (Tegretol®)		200-400 mg/day	600-800 mg/ day	Monitor serum levels (4-12 mcg/mL), CBC, LFTs Multiple drug-drug interactions via enzyme induction; levels increased by enzyme inhibitors; high plasma protein binding
Valproic Acid (Depakene®) Divalproex (Depakote®)		125 mg PO TID	500-1000 mg PO TID	Monitor levels (50-100 mcg/mL); potential ADRs: liver dysfunction, pancreatitis, thrombocytopenia, N/V; CYP-450 enzyme inhibitor
Phenytoin (Dilantin®)		300 mg PO daily or 100 mg PO TID	300-400 mg/day	Monitor serum levels (10-20 mcg/mL) ↓ efficacy vs other agents
SNRI Antidepressants				
DULoxetine* (Cymbalta®)	Peripheral Diabetic Neuropathy, Fibromyalgia	20 mg daily	20-60 mg/day (daily-BID)	Sweating is common side effect (~6% in adults)
Venlafaxine (Effexor®)	Neuropathic pain	37.5-75 mg daily ↑ by 75 mg/day q 4 days	75-225 mg/d (BID-TID)	Max dose 375mg/day for IR, 225mg/day for ER
Milnacipran (Savella®)	Fibromyalgia	12.5 mg PO day 1 12.5 mg BID days 2-3 25 mg BID days 4-7	50 mg PO BID (Max = 100 mg PO BID)	Monitor blood pressure

most commonly used for neuropathic pain

Adjuvant Analgesic Agents (continued)

Drug	Clinical Indications	Usual Starting Dose and Interval	Common Dosage Range	Comments
TCAs				
Amitriptyline (Elavil®)	Neuropathic pain	25 mg PO bedtime (10 mg in frail, elderly)	25-100 mg PO bedtime	Titrate dose every few days to minimize side effects; allow 1-2 weeks (up to 4) to see effect Side effects include drowsiness, orthostatic hypotension, wt gain, arrhythmias and anticholinergic effects may be increased in combo with SSRIs Avoid traMADol and TCA combo: ↑ seizure risk
Nortriptyline (Pamelor®)				
Desipramine (Norpramin®)				
Side effects greatest to least: amitriptyline>nortriptyline>desipramine				
Corticosteroids				
Dexamethasone Methylprednisolone	Acute spinal cord compression, Increased ICP#	Dex 10-20 mg IV Q6H or methylpred 40-80 mg IV Q6H	Dex 10-20 mg IV Q6H or methylpred 40-80 mg IV Q6H	High dose therapy should not exceed 72 hours; if no benefit, dose can be rapidly tapered; if pain improves, the initial maintenance dose should be tapered to the lowest effective and least toxic dose Usefulness limited to 2-3 months before steroid-induced side effects outweigh benefit
	Nerve compression, Visceral distension, Increased ICP#	Dex 4-8 mg PO Q8-12h or methylpred 20-40 mg PO Q8-12H	Minimum effective dose	
	Alleviation of nausea, anorexia, or bone pain	Dex 4-12 mg IV/PO per day or methylpred 5-10 mg IV/PO TID		
Selected Muscle Relaxants				
Baclofen (Lioresal®)	Muscle spasms	5-10 mg PO TID	15-80 mg/day (divided TID)	When stopping muscle relaxants after chronic use, it may be necessary to taper over 1-2 weeks. Methocarbamol may be given up to 8 gm/day for severe conditions
Metaxalone (Skelaxin®)		800 mg PO TID	800 mg TID-QID	
Methocarbamol (Robaxin®)		1.5 gm PO 3-4 times daily for 2-3 days. Then decrease to 750 mg-1.5 gm 3-4 times daily	750 mg TID-QID	
Tizanidine		4 mg TID	36 mg/day	
Miscellaneous Adjuvant Analgesic Agents				
Loratadine	Granulocyte colony stimulating factor related bone pain	10 mg PO daily for 7 days starting 1 day prior to chemo	10 mg PO daily for 7 days starting 1 day prior to chemo	Literature supports the use of loratadine in pegfilgrastim-related bone pain

ICP = intracranial pressure **See "Systemic Equivalencies of Corticosteroids" page 29

Adjuvant Analgesic Agents (continued)

Drug	*Clinical Indications*	*Usual Starting Dose and Interval*	*Common Dosage Range*	*Comments*
Miscellaneous Adjuvant Analgesic Agents (continued)				
CloNIDine (Duraclon®)	Neuropathic pain	30 mcg/hr (epidural)	doses >40 mcg/h not well studied	FDA approved for epidural use; clinical experience supports intrathecal use
(Catapres®)	Analgesia; Opioid sparing effects	0.2 mg/day (patch lasts one wk)	0.1-0.3 mg/day	Usually only used for 1 week. If used for longer period, monitor for rebound HTN when d/c'd
Ketamine (Ketalar®)	Analgesia; Opioid-sparing effects	0.1-0.2 mg/kg bolus Followed by 1-5 mcg/kg/min infusion	Max dose: 15 mcg/kg/min	Restricted at BWH to pain services, ICUs and ED attendings – please refer to Drug Administration Guideline (DAG) Infusions > 5mcg/kg/min requires BWH Pain service consult
Lidocaine (Lidoderm®)	Post-herpetic neuralgia	1 patch applied to affected area 12 hours/day	1-3 patches	Clinical experience supports use in painful peripheral neuralgia
IV formulation (Xylocaine®)	Neuropathic pain	500 mg IV bolus over 30 min	0.5-2 mg/kg/hr	Requires consult to the appropriate pain service, special monitoring required (See BWH policy)
Memantine (Namenda)	Neuropathic pain	10 mg/day; increase by 10 mg/day q wk	30-60 mg/day studied	NMDA antagonist
Pamidronate (Aredia®)	Metastatic bone pain; delay of bone metastasis progression, hypercalcemia	90 mg IV q 4 wks	May decrease interval to every 3 weeks	Proven to decrease the impact of disease progression in patients with osteolytic lesions secondary to multiple myeloma, breast cancer, and prostate cancer. Doses reduced for renal dysfunction.
Zolendric Acid (Zometa®)		4 mg IV q 4 wks		
Denosumab (Xgeva®)	Prevention of skeletal-related events in pts w/ bone mets	120mg subcut q 4 wks	120mg subcut q 4 wks	Administer with calcium ≥ 500 mg/d and vitamin D ≥ 400 units/d
Radiopharmaceuticals				
Strontium chloride Sr-89	Metastatic bone pain	148 MBq, 4 mCi q3 months	148 MBq, 4 mCi q3 months	Typically reduces platelet count by ≈ 30%; nadir usually occurs 12-16 weeks after administration; degree of neutropenia varies; 2-3 days after administration, pain may transiently increase (flare) for 2-3 days
Samarium-153 (Quadramet)		1.0 mCi/kg once	1.0 mCi/kg	Pain flare after injection. Thrombocytopenia and neutropenia nadir 40-50% of baseline within 3-5 weeks; return to baseline 8 weeks.
Radium-223 Dichloride (Xofigo)	Symptomatic bone mets in prostate cancer	55 kBq/kg q 4 wks x 6 doses	55 kBq/kg q4weeks x 6 doses	Anemia, leukopenia and neutropenia are commonly seen. Nadir is usually after 2-4 weeks.

NON-ANALGESIC CNS ACTIVE AGENTS*

Drug	*Clinical Indications*	*Usual Starting Dose and Interval*	*Common Dosage Range*	Comments
Sedatives – Melatonin Receptor Agonist				
Ramelteon (Rozerem®)	Insomnia	8mg PO daily 2 hours before bedtime		Restricted at BWH. Requires Geriatrics, PMNR, or psychiatry consult
Dual Orexin Receptor Antagonist				
Suvorexant (Belsomra®)	Insomnia	10 mg PO 30 mins prior to bedtime		Restricted at BWH. Requires Geriatrics, PMNR, or psychiatry consult
Sedating Antidepressants				
TraZODone	Insomnia	50 mg PO bedtime		May start at 25 mg in elderly patients QTc prolongation concern
Mirtazapine (Remeron®)		7.5 mg PO bedtime	7.5 – 30 mg	15 mg, 30 mg, 45 mg are available in disintegrating tablets Mirtazapine is sedating at lower doses and activating at higher doses
Antipsychotics				
Haloperidol (Haldol)	Delirium, N/V, agitation	0.5 mg IV/PO Q6H PRN	0.5-2 mg IV/PO Q6H	Additive QTc prolongation is a concern with these agents, monitor Zydis ODT- 5 mg, 10 mg, 15 mg, 20 mg are available in disintegrating tablets
ChlorproMAZINE (Thorazine)	Delirium, Hiccups	12.5 mg IV/PO QHS	25-50 mg IV/PO Q6H	
Aripiprazole (Abilify®)	Insomnia, Delirium	5-15 mg PO QD		
Quetiapine (SEROquel®/SEROquel XR®)		25 mg PO bedtime	25-50 mg PO bedtime	
OLANZapine (Zyrexa®, Zydis®)		2.5-5 mg PO bedtime	2.5-10 mg PO QHS (MDD: 20 mg)	
Psychostimulants				
Dextroamphetamine (Dexedrine®)	Opioid-induced sedation	2.5 mg PO daily-BID	5-20 mg in divided doses (8am and 2pm)	For treatment of sedation, may increase delirium in confused patients Methylphenidate available in transdermal patch indicated for ADHD (10 mg/9h, 16 mg/9h, 20 mg/9h, 30 mg/9h)
Methylphenidate (Ritalin®)	Opioid-induced sedation, Depression	2.5-5 mg PO daily-BID	5-20 mg in divided doses (8am and 2pm)	
(Concerta®)		18 mg or 36 mg PO daily	Max dose = 72 mg/day	
(Metadate CD/ Ritalin LA®)		20 mg PO daily	Max dose = 60 mg/day	
Modafinil (Provigil®)	Opioid-induced sedation	100-200 mg PO QAM	200-400 mg/day	
Armodafinil (Nuvigil®)		150-250mg PO QAM	150 mg daily	

<u>These agents are not analgesics</u>

*These agents are not analgesic and are included in this reference so that clinicians can evaluate if these medications are contributing to any CNS depression.

NON-ANALGESIC CNS ACTIVE AGENTS (Continued)*

Drug	*Clinical Indications*	*Usual Starting Dose and Interval*	*Common Dosage Range*	Comments
Anxiolytics – Benzodiazepine Note: All benzodiazepines cause additive sedation and respiratory depression with opioids.				
LORazepam$^{\alpha}$ (Ativan®)	Anxiety, Insomnia	0.5-2 mg PO daily-TID	Use lowest effective dose	t½ = 10-20 h
ClonazePAM $^{\alpha}$ (KlonoPIN®)		0.25–0.5 mg PO BID		t½ = 19-50 h
Diazepam (Valium®)	Anxiety, Insomnia, Skeletal muscle spasm	5 mg PO daily-BID		t½ = 20-80 h t½ metabolite= 50-100 h
Oxazepam$^{\alpha}$ (Serax®)		10-15 mg PO daily-TID		t½ = 5-20 h
Temazepam$^{\alpha}$ (Restoril®)	Insomnia	15-30 mg PO bedtime		t½ = 10-40 h
ALPRAZolam$^{\alpha}$ (Xanax®)	Anxiety, Skeletal muscle spasm	0.25-0.5 mg PO daily-TID		t½ = 12-15 h, Very short acting with rebound anxiety.
Midazolam$^{\alpha}$ (Versed®)	Sedation	Doses vary depending on individual patient needs.		t½ = 2-5 h
α No active metabolites				
Sedatives – Imidazopyridines				
Zolpidem (Ambien®)	Insomnia	5-10 mg PO bedtime	5-10 mg	Short-term use is recommended. Adverse effects additive with opioids.
(Ambien CR®)		12.5 mg PO bedtime		
(Zolpimist®)		10 mg (2 sprays) over the tongue immediately at bedtime		
Zaleplon (Sonata®)		5 mg PO bedtime	5-20 mg	
Eszopiclone (Lunesta®)		2 mg PO bedtime	2-3 mg	

<u>These agents are not analgesics</u>

*These agents are not analgesic and are included in this reference so that clinicians can evaluate if these medications are contributing to any CNS depression.

<u>Systemic Equivalencies of Corticosteroids</u>

Drug	*Approximate Equivalent Dose*	*Relative Anti-Inflammatory Potency*	*Relative Mineralocorticoid Potency*
<u>Short-Acting</u>			
Cortisone	25 mg	0.8	2
Hydrocortisone	20 mg	1	2
<u>Intermediate-Acting</u>			
Prednisone	5 mg	4	1
Prednisolone	5 mg	4	1
Triamcinolone	4 mg	5	0
Methylprednisolone	4 mg	5	0
<u>Long-Acting</u>			
Dexamethasone	0.75 mg	25-30	0
Betamethasone	0.6-0.75 mg	25	0

Non-Opioid Analgesics: Available Dosage Forms and Selected Comments

NSAIDs and COX2 selective agents may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke. This risk may increase with duration of use. Patients with cardiovascular disease may be at greater risk.

Drug	***Suggested Maximum 24 hr Dose***	***Dosing Interval***	***Available Dosage Forms#***	***Comments*** ↓ - decreased incidence vs. other NSAIDs ↑ - increased incidence vs. other NSAIDs
Acetaminophen* (Tylenol®)	3000-4000 mg (for healthy adult)	4-6 hrs	Tab: 325, 500 mg ER Tab: 650 mg Elixir: 160 mg/5 mL Supp: 120, 325, 650 mg IV solution: varies	< 2 g/day appears to be well tolerated in patients with cirrhosis, monitor closely; **essentially no anti-inflammatory activity**; low risk of GI side effects; no effect on platelets IV is **restricted** on BWH formulary
Aspirin	3000 mg	4-6 hrs	Tab: 81, 325 mg Chew Tab: 81 mg EC Tab: 325, 650 mg Supp: 300, 600 mg	High risk of GI bleeding; use caution in preexisting liver disease and avoid in severe liver disease; least potent inhibitor of renal prostaglandins
Diclofenac (Voltaren® Zorvolex® Cataflam® Arthrotec® Flector®)	150 mg	12 hrs 24 hrs for SR	Tab: 25, 50, 75 mg Cap: 18, 35 mg SR Tab: 100 mg Patch: 1.3% Gel/Jelly: 1%(Voltaren®) 3%(Solaraze®) Solution: 1.5%, 2%	↑ dizziness, ↓ GI side effects**; possible ↑ nephrotoxicity Arthrotec® is a combination product containing either 50 or 75 mg of enteric-coated diclofenac and 200 mcg of misoprostol Flector® is a 1.3% patch (180 mg) applied topically to most painful site BID
Diflunisal (Dolobid®)	1000 mg	8-12 hrs	Tab: 500 mg	↓ nephrotoxicity; related to salicylates, may inhibit platelet function and prolong bleeding time
Etodolac (Lodine®)	1000 mg	6-8 hrs 24 hrs for ER	Cap: 200, 300, 500 mg ER Tab: 400, 500, 600 mg	↓ nephrotoxicity and GI bleeding complications; may be safer than other NSAIDs in patients with cirrhosis
Fenoprofen (Fenortho® Nalfon®)	2400 mg	4-8 hrs	Tab: 600 mg Cap: 200, 300, 400 mg	↑ incidence of headache, somnolence, dizziness; may cause genitourinary tract side effects
Flurbiprofen (Ansaid®)	300 mg	6-12 hrs	Tab: 50, 100 mg	↑ dizziness; use with caution in hepatic dysfunction
Ibuprofen (Advil® Motrin®)	2400 mg	4-8 hrs	Tab: 100, 200, 400, 600, 800 mg Chew Tab: 50, 100 mg Liquid: 100 mg/5 mL, 50 mg/1.25 mL Drops: 40 mg/mL Injectable (Neoprofen®): 10 mg/mL	Repeated studies have shown doses of 1500 mg/day or less have the lowest risk of inducing serious GI complications among non-salicylate NSAIDs; these studies did not include etodolac or nabumetone; low risk of inducing hepatotoxicity, but should be avoided in severe hepatic impairment; possible ↑ nephrotoxicity Neoprofen® is only indicated in patent ductus arteriosus
Indomethacin (Indocin®)	150 mg	8-12 hrs	Cap: 20, 25, 50 mg SR Cap: 75 mg Susp: 25 mg/5 mL Supp: 50 mg Injectable: 1 mg/mL	High risk of nephrotoxicity vs. other NSAIDs; ↑ headache, tinnitus, dizziness, GI side effects; may aggravate depression or other psychological disturbances secondary to CNS penetration

#Supp = suppository; SR = sustained release; EC = enteric coated

*Included for comparison; has no anti-inflammatory activity

**Limited data versus COX 2 inhibitors

Non-Opioid Analgesics: Available Dosage Forms and Selected Comments

Drug	*Suggested Maximum 24 hr Dose*	*Dosing Interval*	*Available Dosage Forms#*	*Comments* ↓ - decreased incidence vs. other NSAIDs ↑ - increased incidence vs. other NSAIDs
Ketorolac (Toradol®)	120 mg IV 40 mg PO	6 hrs	Tab: 10 mg Injectable: 15, 30 mg/mL	Doses of 7.5-10 mg IV have been shown to have equal analgesia and less risk for side effects High incidence of headache, ↑ nephrotoxicity and GI complications; use no longer than 5 days; use 15 mg in patients > 65 years of age, < 50 kg, or with renal impairment
Ketoprofen (Orudis® Oruvail®)	300 mg	6-8 hrs 24 hrs for SR	Cap: 25, 50, 75 mg SR Cap: 200 mg	↓ dose in hepatic dysfunction; SR Cap allows for DAILY dosing; Occasionally compounded for topical use
Nabumetone (Relafen®)	1500 mg	12-24 hrs	Tab: 500, 750 mg	↓ GI bleeding** and side effects; reduce dose in hepatic dysfunction Daily-BID dosing
Naproxen (Naprosyn® Aleve® Anaprox®)	1500 mg	8-12 hrs 24 hrs for SR	Tab: 250, 275, 375, 500, 550 mg Tab(sodium): 220, 275, 550mg Cap: 220 mg SR Tab: 375, 500, 750 mg Susp: 25 mg/mL	↑ hepatotoxicity (↓ dose 50% in hepatic disease) and possible nephrotoxicity; high tissue penetration; potent inhibitor of leukocyte function Naproxen sodium (Aleve®, Anaprox®) sodium content is approximately 10%
Meclofenamate (Meclomen®)	300 mg	4-6 hrs	Cap: 50, 100 mg	High incidence of diarrhea, ↑ GI side effects; do not use for > 1 continuous week
Mefenamic Acid (Ponstel®)	1000 mg	6 hrs	Cap: 250 mg	↑ GI side effects
Meloxicam (Mobic®)	7.5 mg	24 hrs	Tabs: 7.5, 15 mg Susp: 7.5 mg/ 5 mL	↓ GI bleeding** and side effects
Oxaprozin (Daypro®)	1200 mg	12-24 hrs	Tab: 600 mg	Daily-BID dosing; use caution in severe hepatic impairment
Piroxicam (Feldene®)	20 mg	12-24 hrs	Cap: 10, 20 mg	High risk of serious GI adverse events vs. other NSAIDs; ↑ hepatotoxicity; daily-BID dosing
Sulindac (Clinoril®)	300 mg	12 hrs	Tab: 150, 200 mg	High risk of hepatotoxicity vs. other NSAIDs, use caution and low doses in cirrhosis; ↑ GI side effects; marketed as “renally sparing” but reports of renal failure exist; use caution in renal insufficiency
Tolmetin (Tolectin®)	1200 mg	6-8 hrs	Tab: 600 mg Cap: 400 mg	↑ incidence of auditory toxicity and GI adverse events

#SR = sustained release

** Limited data versus COX 2 inhibitors

Non-Opioid Analgesics: Available Dosing Forms and Selected Comments

Drug	*Suggested Maximum 24 hr Dose*	*Dosing Interval*	*Available Dosage Forms#*	*Comments* ↓ - decreased incidence vs. other NSAIDs ↑ - increased incidence vs. other NSAIDs
Non-Acetylated Salicylates				
Salsalate	3000 mg	8-12 hrs	Tab: 500, 750 mg	↓ rate of gastric erosions/lesions, lowest risk in GI toxicity Index vs. available NSAIDs, does not affect platelet aggregation
COX-2 Selective Agents				
Celecoxib (CeleBREX®)	200 mg	12 hrs	Tab: 50, 100, 200, 400 mg	↓ incidence of GI ulcerations; minimal to no inhibition of platelet function; cross-allergy with sulfonamides; similar renal effects to traditional NSAIDs; adverse CV effects with long term use

**Limited data versus COX 2 inhibitors

NSAID Selection*		
Situation or Patient Population	**Consider**	**Generally Avoid**
GI bleed, history of	Celecoxib, etodolac, ibuprofen, nabumetone, salsalate	Aspirin, indomethacin, ketoprofen, ketorolac, meclofenamate, tolmetin
Age > 65 years	Ibuprofen, celecoxib	Indomethacin, ketorolac, naproxen, piroxicam, oxaprozin
Hepatic dysfunction, current	Diclofenac, etodolac, ibuprofen	Aspirin, ibuprofen, piroxicam, sulindac
Hepatic dysfunction, high risk	Etodolac, ibuprofen	Naproxen, piroxicam, sulindac
Lactation	Diclofenac, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, ketorolac, naproxen, piroxicam, tolmetin	Aspirin, salsalate
Peptic ulcer	Celecoxib, salsalate	Aspirin, indomethacin, ketoprofen, ketorolac, meclofenamate, tolmetin
Renal dysfunction, current	Etodolac	Aspirin, salsalate, indomethacin
Renal dysfunction, pts. at risk for	Aspirin, etodolac, salsalate	Diclofenac, ibuprofen, indomethacin, piroxicam, naproxen
Thrombocytopenia	Celecoxib, salsalate	All other agents inhibit platelet function and prolong bleeding time to varying degrees.
Warfarin, concurrent use	Celecoxib, salsalate	
Pregnancy category B (1st and 2nd trimester only)	Sulindac, naproxen, ketoprofen, diclofenac	
Bariatric surgery, h/o	Non-NSAIDs (Acetaminophen)	Avoid all NSAIDs

* Assumes NSAID therapy is a necessity

Consider the non-NSAID acetaminophen when not contraindicated, especially in the following situations: history of GI bleed, age > 65 years, lactation, peptic ulcer, renal dysfunction, thrombocytopenia, warfarin use, and history of bariatric surgery.

Appendices:

Appendix A. Opioid Use Disorder Criteria

OUD Criteria: Check all boxes that apply	
	Opioids are often taken in larger amounts or over a longer period of time than intended.
	There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
	A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
	Craving, or a strong desire to use opioids.
	Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.
	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
	Important social, occupational or recreational activities are given up or reduced because of opioid use.
	Recurrent opioid use in situations in which it is physically hazardous.
	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.
	*****Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of an opioid
	*****Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome (b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms
***** These criteria are not considered to be met for those individuals taking opioids solely under medical supervision.	

Total Boxes Checked:_____
Severity: Mild 2-3, Moderate 4-5, Severe 6 or more

Appendix B. Selected GFR and Creatinine Clearance equations

Cockroft-Gault (mL/ min)**:**

$$CrCL = \left(\frac{(140 - Age)X\ Weight\ (Kg)}{SCr\ (mg/dL)X\ 72}\right) \times 0.85[if\ female]$$

Limitations: Assumes stable SCr, is an estimate that can differ from actual GFR by ±30%, validated only in white males

CKD-EPI (creatinine) (ml/min/1.73 m2)**:**

$$eGFR = 141 \times min(\frac{SCr}{\kappa}, 1)^{\alpha} \times max(\frac{SCr}{\kappa}, 1)^{-1.209} \times 0.993(Age) \times 1.018\ [if\ female] \times 1.159\ [if\ black],$$

κ=0.7 for women and 0.9 for men

α= −0.329 for women and −0.411 for men

min indicates the minimum of SCr/κ or 1

max indicates the maximum of SCr/κ or 1

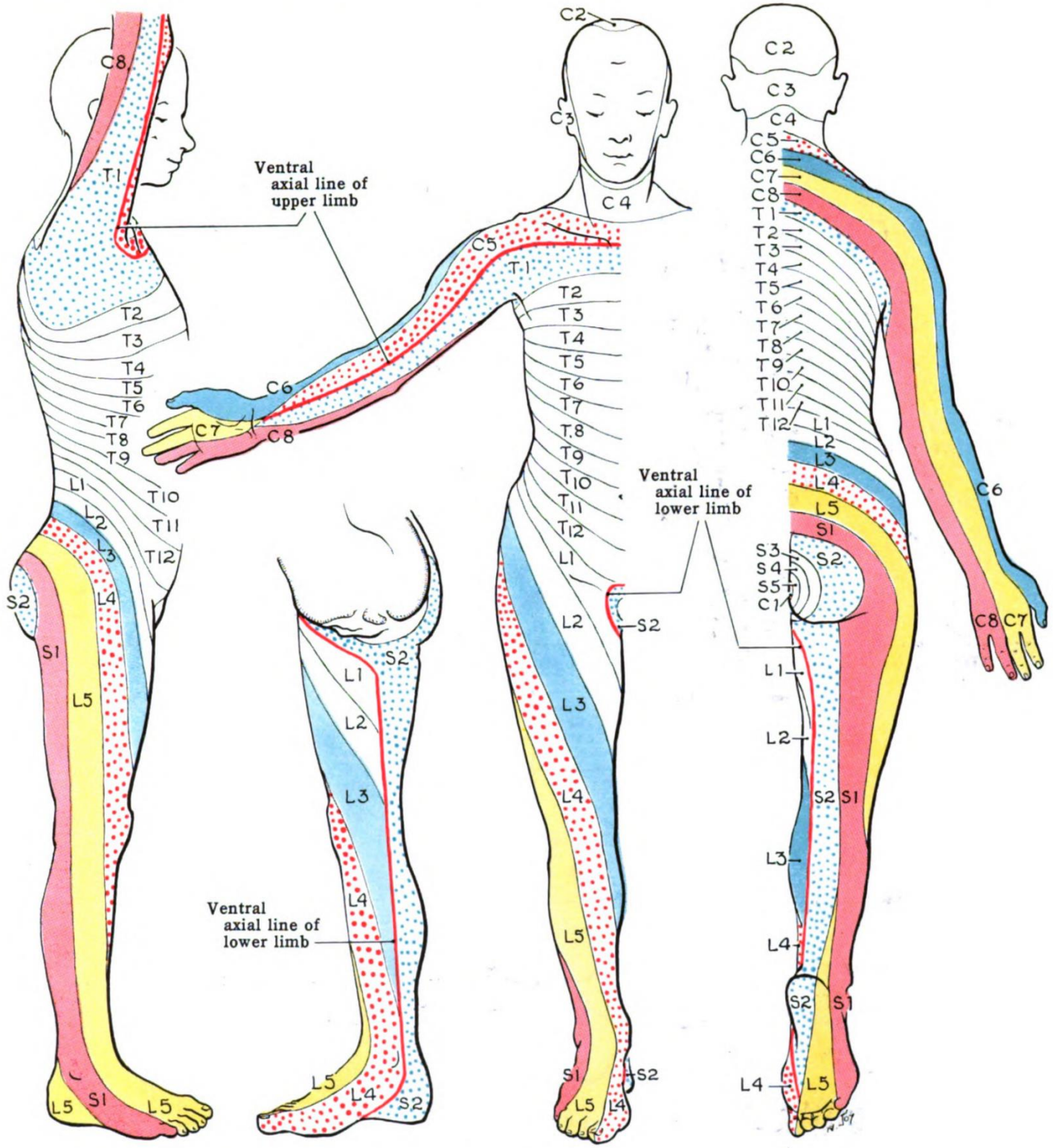
Limitations: Only for Chronic Kidney Disease, more accurately predicts GFR than MDRD in patients with preserved function. Online calculators available. Automatically calculated in Epic at Mass General Brigham, with assumption of non-Black race. If patient is Black, you will need to multiply by 1.159.

Appendix C: Child Pugh

The Child Pugh score is determined by scoring five clinical measures of liver disease: total bilirubin, serum albumin, INR (or prothrombin time), ascites, and liver encephalopathy.

Measure	**1 point**	**2 points**	**3 points**
Total bilirubin, (mg/dL)	< 2	2–3	> 3
Serum albumin, g/dL	> 3.5	2.8–3.5	< 2.8
INR	< 1.7	1.7–2.3	> 2.3
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grade I–II	Grade III–IV
Total Points:			
Scoring: Class A 5-6 points, Class B 7-9 points, Class C 10-15 points			

Appendix D: Dermatome Chart



By Grant, John Charles Boileau (An atlas of anatomy, / by regions 1962) [Public domain], via Wikimedia Commons

Appendix E: Opioid Agreement Quick Guide

Massachusetts regulations mandate Opioid Agreements for all long-acting opioid prescriptions.

Where to Find the Opioid Agreement

- Preferably through the e-consent activity tab in Epic
- In the exam room in the Opioid Info Folder
- Print from DFCI Intranet or MGB handbook (also available in 6 other languages)

Discussing the Opioid Agreement

Initiate an educational conversation with patients about the risks and benefits of opioid therapy.

Example Script

> "To manage your pain and enhance your quality of life, I recommend [opioid therapy]. Let's discuss potential risks and how we'll ensure your safety."

Six key points to discuss with patients:

Key Point	Description
Overdose and misuse risk	Use opioids only as prescribed for your pain; don't change your dosage or stop taking them without talking to us; let us know if your pain gets worse
Medication interactions	Inform us of other prescribed medications
Storage	Lock up medications to protect children and pets; do not share with others
Driving laws	Be aware of state regulations regarding driving while on opioids
Naloxone	We will prescribe this for overdose emergencies; available at any pharmacy
Monitoring	You will attend scheduled visits; we will review the prescription fill history and may request urine drug tests

References:

American Pain Society (2016). Principles of analgesic use in the treatment of acute pain and chronic cancer pain, 7th edition. . Glenview, IL.

Bosilkovska, M., B. Walder, M. Besson, Y. Daali and J. Desmeules (2012). "Analgesics in patients with hepatic impairment." Drugs 72(12): 1645-1669.

Chou, R., R. A. Cruciani, D. A. Fiellin, P. Compton, J. T. Farrar, M. C. Haigney, C. Inturrisi, J. R. Knight, S. Otis-Green and S. M. Marcus (2014). "Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society." The Journal of Pain 15(4): 321-337.

Dean, M. (2004). "Opioids in renal failure and dialysis patients." Journal of pain and symptom management 28(5): 497-504.

Donner, B., M. Zenz, M. Tryba and M. Strumpf (1996). "Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain." Pain 64(3): 527-534.

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1

Dworkin, R. H., A. B. O'Connor, J. Audette, R. Baron, G. K. Gourlay, M. L. Haanpää, J. L. Kent, E. J. Krane, A. A. LeBel and R. M. Levy (2010). Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clinic Proceedings, Elsevier.

Fink RM, G. RA and M. RK (2014). Pain Assessment. Oxford textbook of palliative nursing, Oxford University Press.

Finnerup, N. B., N. Attal, S. Haroutounian, E. McNicol, R. Baron, R. H. Dworkin, I. Gilron, M. Haanpää, P. Hansson and T. S. Jensen (2015). "Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis." The Lancet Neurology 14(2): 162-173.

Foxwell, A. M. and T. J. Uritsky (2018). "Hydromorphone Conversion Dilemma: A Millennial Problem." J Pain Symptom Manage 56(3): e2-e3.

Gordon, D. B. and G. Love (2004). "Pharmacologic management of neuropathic pain." Pain Management Nursing 5: 19-33.

Grass, J. A. (2005). "Patient-controlled analgesia." Anesthesia & Analgesia 101(5S): S44-S61.

Huerta, C., J. Castellsague, C. Varas-Lorenzo and L. A. G. Rodríguez (2005). "Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population." American Journal of Kidney Diseases 45(3): 531-539.

King, S., K. Forbes, G. Hanks, C. Ferro and E. Chambers (2011). "A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project." Palliative medicine 25(5): 525-552.

Lehmann, K. A. (2005). "Recent developments in patient-controlled analgesia." Journal of pain and symptom management 29(5): 72-89.

McPherson, M. L. (2018). Demystifying opioid conversion calculations: a guide for effective dosing; Second edition. Bethesda, MD, ASHP.

McPherson, M. L., K. A. Walker, M. P. Davis, E. Bruera, A. Reddy, J. Paice, K. Malotte, D. K. Lockman, C. Wellman, S. Salpeter, N. M. Bemben, J. B. Ray, B. J. Lapointe and R. Chou (2019). "Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper." J Pain Symptom Manage 57(3): 635-645.e634.

Meier, T., G. Wasner, M. Faust, T. Kuntzer, F. Ochsner, M. Hueppe, J. Bogousslavsky and R. Baron (2003). "Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study." Pain 106(1-2): 151-158.

Motov, S., M. Yasavolian, A. Likourezos, I. Pushkar, R. Hossain, J. Drapkin, V. Cohen, N. Filk, A. Smith, F. Huang, B. Rockoff, P. Homel and C. Fromm (2017). "Comparison of Intravenous Ketorolac at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial." Ann Emerg Med 70(2): 177-184.

Paice, J. A. (2014). Pain at the end of life. Oxford textbook of palliative nursing, Oxford University Press.

Pereira, J., P. Lawlor, A. Vigano, M. Dorgan and E. Bruera (2001). "Equianalgesic dose ratios for opioids: a critical review and proposals for long-term dosing." Journal of pain and symptom management 22(2): 672-687.

Pickering, G. and V. Morel (2018). "Memantine for the treatment of general neuropathic pain: a narrative review." Fundam Clin Pharmacol 32(1): 4-13.

Reddy, A., Y. Heung and E. Bruera (2018). "Authors' Response." J Pain Symptom Manage 56(3): e3-e5.

Reddy, A., M. Vidal, S. Stephen, K. Baumgartner, S. Dost, A. Nguyen, Y. Heung, S. Kwan, A. Wong, I. Pangemanan, A. Azhar, S. Tayjasanant, E. Rodriguez, J. Waletich, K. H. Lim, J. Wu, D. Liu, J. Williams, S. Yennurajalingam and E. Bruera (2017). "The Conversion Ratio From Intravenous Hydromorphone to Oral Opioids in Cancer Patients." J Pain Symptom Manage 54(3): 280-288.

Reddy, A., S. Yennurajalingam, S. Reddy, J. Wu, D. Liu, R. Dev and E. Bruera (2016). "The opioid rotation ratio from transdermal fentanyl to “strong” opioids in patients with cancer pain." Journal of pain and symptom management 51(6): 1040-1045.

Romeo, C., Q. Li and L. Copeland (2015). "Severe pegfilgrastim-induced bone pain completely alleviated with loratadine: a case report." Journal of Oncology Pharmacy Practice 21(4): 301-304.

Smith, H. S. (2009). Opioid metabolism. Mayo Clinic Proceedings, Elsevier.

Soleimanpour, H., S. Safari, K. S. Nia, S. Sanaie and S. M. Alavian (2016). "Opioid drugs in patients with liver disease: a systematic review." Hepatitis monthly 16(4).

Tramer, M. (2001). "A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part I. Efficacy and harm of antiemetic interventions, and methodological issues." Acta Anaesthesiologica Scandinavica 45(1): 4-13.

Tramer, M. (2001). "A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part II. Recommendations for prevention and treatment, and research agenda." Acta anaesthesiologica scandinavica 45(1): 14-19.

Treillet, E., S. Laurent and Y. Hadjiat (2018). "Practical management of opioid rotation and equianalgesia." J Pain Res 11: 2587-2601.

Tremont-Lukats, I. W., C. Megeff and M.-M. Backonja (2000). "Anticonvulsants for neuropathic pain syndromes." Drugs 60(5): 1029-1052.

Webster, L., M. Andrews and G. Stoddard (2003). "Modafinil treatment of opioid-induced sedation." Pain Medicine 4(2): 135-140.

NOTES:

NOTES: