Pain Management Tables and Guidelines

Dana Farber Cancer Institute/ Brigham & Women's Hospital

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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)

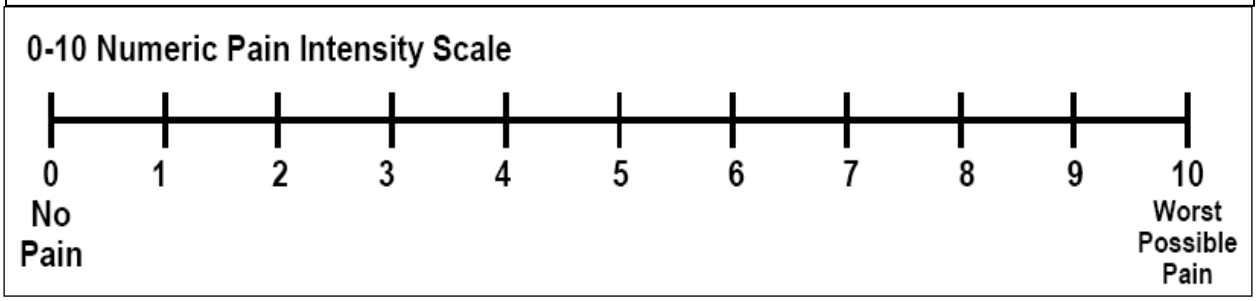
Region/ **R**adiates – Where is your pain primarily located? Does it travel anywhere?

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?

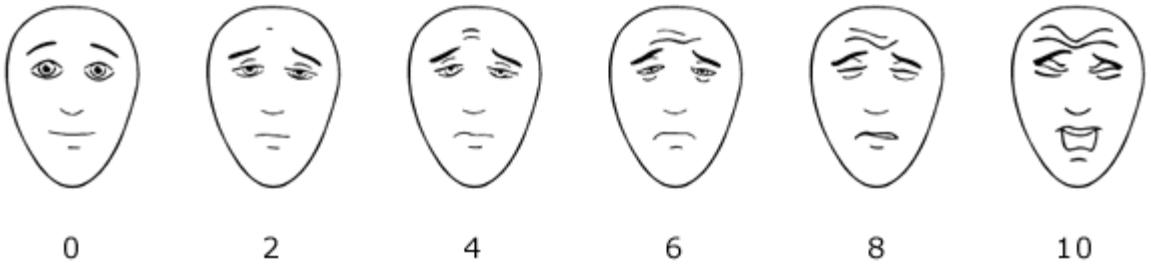
U- How is this pain affecting YOU and your life?

Verbal Numerical Scale
"If *0* is 'No Pain' and *10* is the 'Worst Pain Imaginable' what is your pain right now?"
Verbal Descriptor Scale
None ***Mild*** ***Moderate*** ***Severe***



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

The Faces Pain Scale - Revised, 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.

Important Definitions

Addiction/Substance Use Disorder is a primary, chronic, neurobiologic disease, with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Opioid Use Disorder is 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.

Physical Dependence is a 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.

Withdrawal refers to 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% abruptly. These symptoms include but are not limited to anxiety, agitation, muscle aches, sweating, diarrhea, nausea and vomiting.

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

Opioid tolerance and **physical dependence** are expected with long-term opioid treatment and should not be confused with addiction, which manifests as drug abuse behavior. The presence of opioid tolerance and physical dependence does not equate with addiction.

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 of the route of delivery.

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 is the redirection of a prescription drug from its lawful purpose to illicit use.

Harmful Drug Use is the self-administration of medications to alter one's state of consciousness. This is a maladaptive pattern of use of a medication leading to significant impairment or distress, and potentially leading to opioid or substance use disorders. Previously referred to as abuse, which has fallen out of favor since it uses stigmatizing, non-person-first language.

Urine Drug Screens 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 15 for common opioid metabolites.

Massachusetts Prescription Awareness Tool (MassPAT) is the online prescription monitoring program in Massachusetts (https://massachusetts.pmpaware.net/login). All clinicians who write controlled substances must register with MassPAT. Checking MassPAT before issuing any prescription for a drug in schedule II or III or before issuing a prescription for a benzodiazepine is mandatory.

Validated Risk Assessment Tools are useful 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

Guidelines for the Management of Pain[1] (Including Non-Opioid Therapy)

1. Pain management should begin with a differential diagnosis for pain etiology, and the pain should be categorized by its archetype (somatic vs. inflammatory vs. visceral vs neuropathic). The best aspect of the assessment to help determine this is the qualitative description of the pain.

2. Goal of treatment should be to maximize the patient's function, pain control and ability to enjoy life.

3. For pain with multiple etiologies a multimodal approach using non-opioid and opioid medications will be most effective.

4. Individualize each patient's regimen based on patient-specific factors including but not limited to age, organ function, other co-morbidities and a thorough risk assessment using a validated tool.

5. The oral route is the preferred route of analgesic administration. It is the most convenient, and cost-effective method.

6. Medications for persistent, chronic pain should be administered on a scheduled basis.

7. Intramuscular administration of medications should be avoided. This route is painful, inconvenient, and is prone to erratic absorption rates.

8. Placebos should not be used in the treatment of pain.

9. Follow a logical, stepwise process for the treatment of pain. Resources available include the World Health Organization Ladder for the treatment of Cancer Pain, Principles of Analgesic Use by the American Pain Society and the Centers for Disease Control Guidelines for Prescribing Opioids for Chronic Pain.

Generally:

- For Mild to Moderate Pain, use non-opioid analgesics and adjuvants when possible to control pain.

- Unless contraindicated, NSAIDs and acetaminophen should be used. Adjuvant agents are those agents that enhance analgesic efficacy, treat concurrent symptoms that exacerbate pain, and/or provide independent analgesic activity for specific types of pain.

- 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.

- For Severe Pain or Pain requiring around the clock pain control with short-acting opioids consider adding extended-release (ER) / long-acting opioids such as sustained release oxyCODONE, morphine, oxyMORphone, transdermal fentanyl, continuous opioid infusion or methadone. Long Acting opioids can be safely used with non-opioid therapy and short-acting as needed (PRN) opioid therapy.

Non-Opioids in the Treatment of Pain

1. Non-opioid therapies including pharmacologic and non-pharmacologic therapies can benefit many patients

2. Non-opioid therapies should be used whenever possible in consideration of patient-specific factors including but not limited to age, organ function, other co-morbidities and goals of care.

3. Non-pharmacologic interventions like exercise, cognitive behavioral therapy, and interdisciplinary rehabilitation can be helpful.

4. Treating underlying syndromes like depression and anxiety which can exacerbate pain can be effective methods of restoring patient function and quality of life.

5. Consider interventional therapies, like nerve blocks or corticosteroid injections, in patients who fail standard non-invasive therapies.

Opioid Dosing Guidelines

1. Opioids do not have a maximum pharmacologic dose; however, dosing may be limited by side effects, including hyperalgesia, and individual patient response.

2. The appropriate dose is the one needed to control (not eliminate) the patient's pain with the fewest side effects.

3. Dosing of combination products containing acetaminophen, aspirin, or ibuprofen is limited by the maximum dose of the non-opioid ingredients. Ordering individual components allows for more convenient opioid titration

4. Constipation is a preventable, yet common side effect of opioid administration. It should be anticipated, treated prophylactically, and monitored carefully. (see page #18)

5. Consider **opioid rotation** (changing from one opioid to another), when side effects become intolerable, when a drug is not available by a new route, when pain is not controlled despite optimal opioid dose escalation, or when cost is an issue.

6. Meperidine should be avoided in the treatment of pain. It has an active metabolite with a significantly longer half-life that can accumulate and cause CNS toxicity.

7. 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.

8. When prescribing opiates initially 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.

9. Patients using ER / long-acting opioids may require a short-acting opioid for breakthrough pain. **Each dose of the breakthrough opioid should equal 10-20% of the total daily requirement of ER opioid** (e.g. ER morphine 60 mg po q12h with immediate release morphine 15 mg po q3h PRN pain).

10. If more than 3-4 doses of breakthrough medication are used daily for persistent pain, increase the dose of the ER opioid by an amount equal to 50-100% of the total amount of breakthrough medication used in 24 hours

    a. E.G: A patient takes ER morphine 60 mg po q12h plus 6 doses of immediate release morphine 15 mg in 24 hours with noted end of dose failure. Increase the daily ER morphine dose by 45 to 90 mg according to the patient's status and pain intensity → New regimen MS Contin 60 mg Q8H and morphine 15-30mg q4h PRN pain

11. Incident pain (breakthrough pain that is related to specific activity, such as eating, defecation, socializing or walking) may not require an increase of baseline opioid.

12. When calculating the initial dose of a different opioid in opioid rotation, the dose of the new opioid should generally be reduced by 25-50% (exceptions to this rule are explained in the Fentanyl and Methadone sections). This is to account for incomplete cross-tolerance, due to differences in the structure of individual opioids and their intrinsic activity at the various mu opioid receptors.

13. **Naloxone reverses sedation, respiratory depression, and ANALGESIA**. In patients on chronic opioid therapy, reserve for use in life-threatening respiratory depression unresponsive to dose reduction and appropriate respiratory support. Administer cautiously to avoid withdrawal symptoms and severe pain. See page #19 for instructions on use.

14. For the management of pain, all opioids are equally effective, however, for the management of dyspnea the use of methadone may not be as effective as other opioids

15. **Caution:** benzodiazepines and antihistamines cause additive sedating effects but **NOT** analgesia.

16. Patients with chronic or persistent pain should be given a written pain management plan.

17. Patients may be encouraged to keep a pain diary including daily pain scores, use of prn medications, side effects and efficacy.

18. Communication about pain management should occur when a patient is transferred from one setting to another.

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.

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 a 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 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.

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.

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 page #10 for conversion	
FentaNYL (See page #12 for transdermal conversions)	n/a	0.1 (100 mcg)
OxyMORphone	10	1

How to use the Opioid Equianalgesic Doses Table

This data in this table represents approximate equianalgesic doses of the most commonly used opioids for the control of pain. In this table it can be inferred that for an opioid-naïve patient that a 10 mg oral dose of oxyMORphone 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. Common conversions are presented below.

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
75	25	19	3.75	50	250
90	30	22.5	4.5	60	300
120	40	30	6	80	400
150	50	37.5	7.5	100	500
180	60	45	9	120	600
210	70	52.5	10.5	140	700
240	80	60	12	160	800
270	90	67.5	13.5	180	900
300	100	75	15	200	1000

Other Equianalgesic tables

There are other equianalgesic tables published and used at other institutions. These tables reference recent papers suggesting an alternative conversion ratio of IV hydromorphone to other oral opioids. DFCI/BWH is not adopting newer conversion tables, as there is no consensus regarding a bidirectional conversion between IV hydromorphone and other oral opioids. The table chosen in the DFCI/BWH Pink Book was chosen to avoid overestimation of the dose of IV hydromorphone when converting from oral opioids. Please see the following for further information:

1. https://www.capc.org/documents/20/
2. https://www.ncbi.nlm.nih.gov/pubmed/28711751

METHADONE

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

- Methadone is classified as a diphenylheptane opioid, structurally unique from other opioids.
- Unlike other opioids, methadone has a dual mechanism of action as a mu-opioid receptor agonist and an NMDA receptor antagonist.
- Methadone use can prolong the QTc interval.
    - Chlorobutanol is present as a preservative in IV Methadone and independently increases the QTc interval.
- Methadone has a unique pharmacokinetic profile.
    - 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.
    - Higher doses of other opioids require a much more conservative conversion. Please refer to the chart on page #11 for recommended conversions at corresponding doses of other opioids.

Selected Drug Interactions (not comprehensive)	
Increase methadone levels	CYP 3A4 inhibitors, ciprofloxacin, isoniazid, diazepam, clonazepam, cimetidine, verapamil, diltiazem, nefazodone
Decrease methadone levels	CYP 3A4 inducers, carbamazepine, nevirapine, nelfinavir, phenytoin, phenobarbital, rifampin
Prolong QT interval	5-HT3 antagonists, haloperidol, quetiapine, olanzapine, chlorpromazine, amitriptyline, desipramine, imipramine, nortriptyline
Increase circulating methadone levels AND prolong QT interval	-azole antifungals, erythromycin, clarithromycin, azithromycin, fluvoxamine, paroxetine, fluoxetine, sertraline

The American Pain Society has issued general guidelines on the safe use of methadone for chronic pain and addiction, adapted below:

1. An ECG should be obtained prior to the initiation of methadone (if consistent with goals of care).
2. Follow up ECGs should be obtained with dose increases, with follow up ECG obtained 2-4 weeks after.
3. Methadone should not be started in any patient at doses of higher than 30-40 mg/daily.
4. Initial dose increases of methadone should not be more than 10 mg per day every 5-7 days.
5. Methadone should be used with care in patients concurrently taking medications that pharmacokinetically or pharmacodynamically interact with methadone as above.

Other important points

- When prescribing methadone for pain, “for pain” must appear clearly on the face of the prescription.
- Low dose methadone may be considered as a co-analgesic adjuvant for patients on other long acting opioids. **Strongly consider** consulting Non-Operative Pain Consult or Palliative Care in these patients for guidance.
- Methadone maintenance for opioid use disorder is limited to specialized clinics and cannot be prescribed or filled at a pharmacy for this indication.
- Experience converting patients **FROM methadone TO another opioid** is limited and may be difficult. Estimated equianalgesic conversion ranges from 3-5mg oral morphine equivalents for 1mg of oral methadone. **Strongly consider** consulting the Non-Operative Pain Consult or Palliative Care services in these cases.

Equianalgesic Conversion TO Methadone Dose-dependent potency changes well-established in the literature.		
Oral Morphine Equivalent	**Mg of oral Methadone = Mg of oral Morphine** (ratio)	
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 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		

Determine the starting dose of oral methadone as follows:

- Covert 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. **Further dose reduction is not needed.**
    - This is the every 8-hour dose of oral methadone in mg.
- **Prior to starting methadone contact appropriate outpatient provider to coordinate ongoing prescribing and monitoring,** if expected to continue methadone after discharge from hospital
- **Do NOT start oral methadone at higher than 40 mg daily (20 mg daily IV)** without consultation from appropriate Palliative Care or Non-Operative Pain service.
- *Strongly consider rotating to methadone **only after** consulting the appropriate Non-Operative Pain or Palliative Care team.*

BUPRENORPHINE

Buprenorphine is a mixed opioid agonist antagonist and partial μ-agonist that is indicated for both pain management and Medication Assisted Treatment (MAT) of Opioid Use Disorder.

- Doses used for pain are much lower than doses used for MAT, and at low doses buprenorphine acts similarly to a full μ-agonist.
- At doses used for MAT, buprenorphine will bind to opioid receptors more tightly than other opioids, increasing opioid requirements if administering full agonists for pain.
- If high dose buprenorphine is given to an opioid tolerant patient it will precipitate opioid withdrawal
- Patients on MAT and experiencing or expected to experience pain (procedures, new painful diagnoses) require consult to an appropriate Pain, Palliative Care, or Addiction Psychiatry service.

Please also refer to BWH Perioperative Management of Buprenorphine guidelines.

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
HYDROmorphone	IV	5-20	15-30	3-4
	Oral	15-30	90-120	4-6
HYDROcodone	Oral	30	90	3-4
OxyMORphone	IV	5-10	30-60	3-6
	Oral	30-60	60	4-6
OxyCODONE	Oral	15-30	30-60	4-6
FentaNYL (See Page #12)	IV	under 1	5-7	0.75-2+
Methadone (See Page #10)	IV	10-20	60-120	4-6
	Oral	30-60	90-120	4-12

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 CYP 3A4- use caution when administering concomitantly with CYP 3A4 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.

Available TIRF Medications and Doses (Not interchangeable or equivalent)			
Actiq® Transmucosal lozenge (OTL)	Fentora® Effervescent buccal tab (EBT)	Subsys® Sublingual Spray	Lazanda® Nasal Spray
200 mcg	100 mcg	100 mcg	100 mcg
400 mcg	200 mcg	200 mcg	400 mcg
600 mcg	400 mcg	400 mcg	
800 mcg	600mcg	600 mcg	
1200 mcg	800 mcg	800 mcg	
1600 mcg		1200 mcg	
		1600 mcg	

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 manufacture instructions and patient response. See website www.TIRFREMSaccess.com or call TIRF REMS Access program at 1-866-822-1483.

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 15 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 on Child Pugh Scoring page 30)
- 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 #7)			**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.

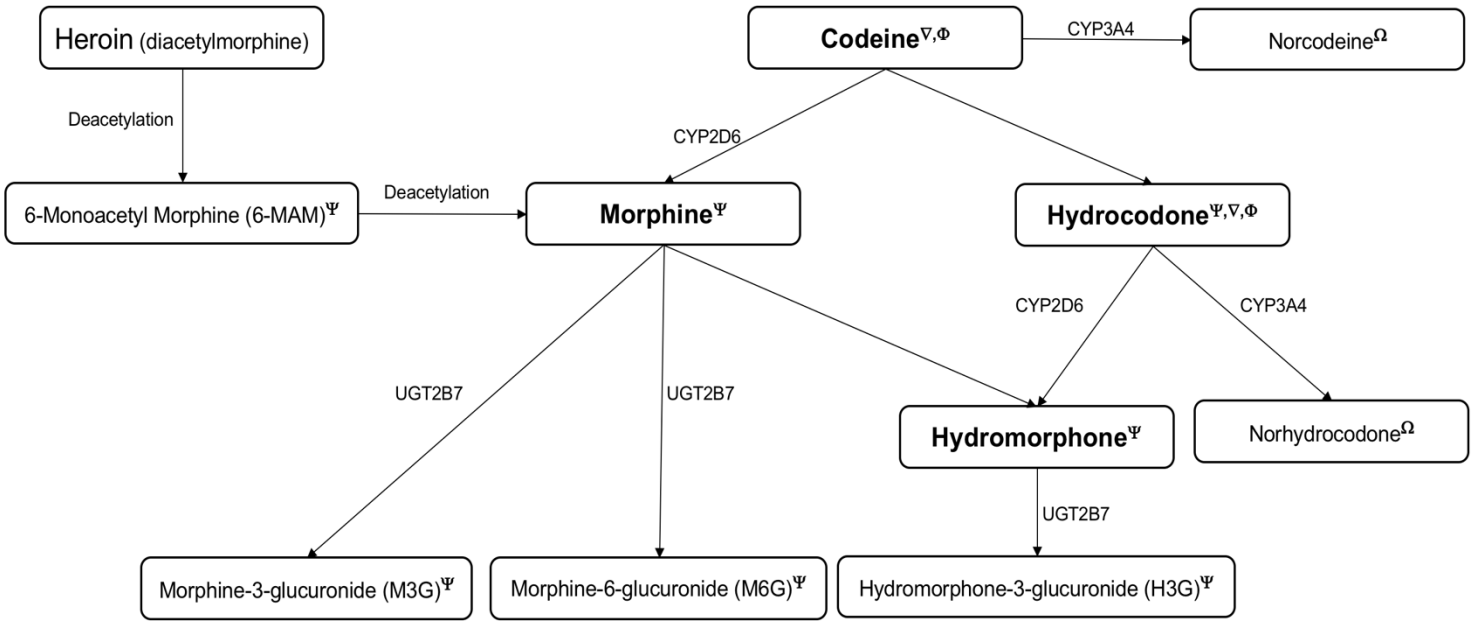
Opioid Dosing in Renal Impairment

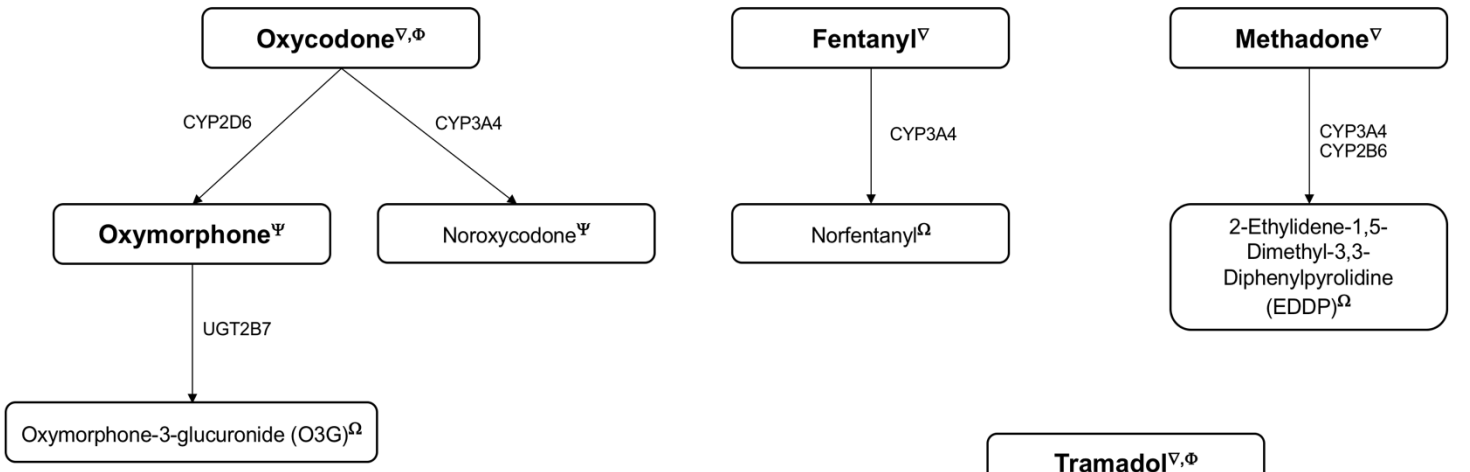
Agent	Renal Impairment		Dialysis	Renal Excretion Percentage	Comments
	GFR 10 – 50 mL/min*	GFR < 10 mL/min*			
Codeine	Do not use				**Do Not Use**
Morphine	Reduce dose by 25 – 50% if used	Avoid use; reduce dose by 50 – 75% if necessary	Use cautiously Dialyzable	~ 90% Not recommended in ESRD due to accumulation 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 7)				**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

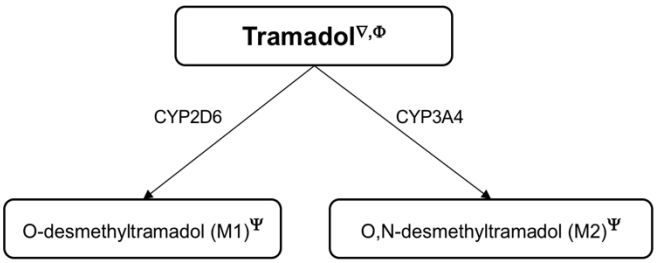
***** Glomerular filtration rate (GFR) recommendation interpretation should be coupled with evaluating the degree and duration of renal dysfunction, such as AKI, CKD, vs. acute on chronic CKD.

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 pages #10 and #12 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

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 PCA orders in an **opioid-naïve patient**. Patients who are already on opioids need additional dosing considerations such as higher bolus doses, addition of a continuous infusion and non-standard concentrations. Please contact the appropriate Pain Service for consultation on these patients.

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 (eg., age >65, morbid obesity, sleep apnea, RASS ≤ -3)

	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)

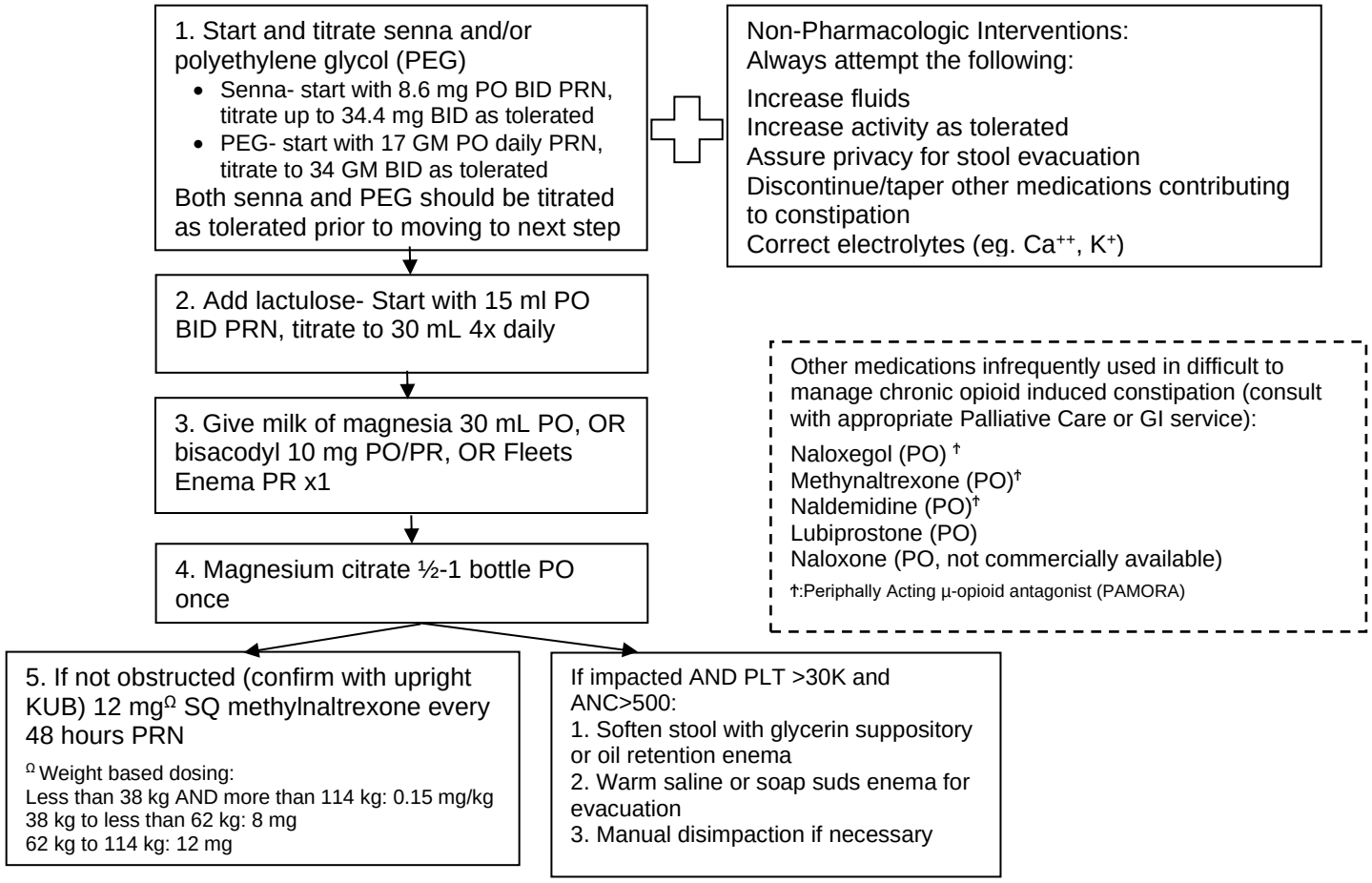
Ondansetron dosing for Post-Operative Nausea/Vomiting: 4 mg IV immediately prior to or following anesthesia induction</td></tr>
<tr><td>Pruritis</td><td>Pruritis in the absence of evidence of rash/allergic reaction is a central mu-related phenomenon (not histamine-related) and best treated with nalbuphine 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 #19.</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

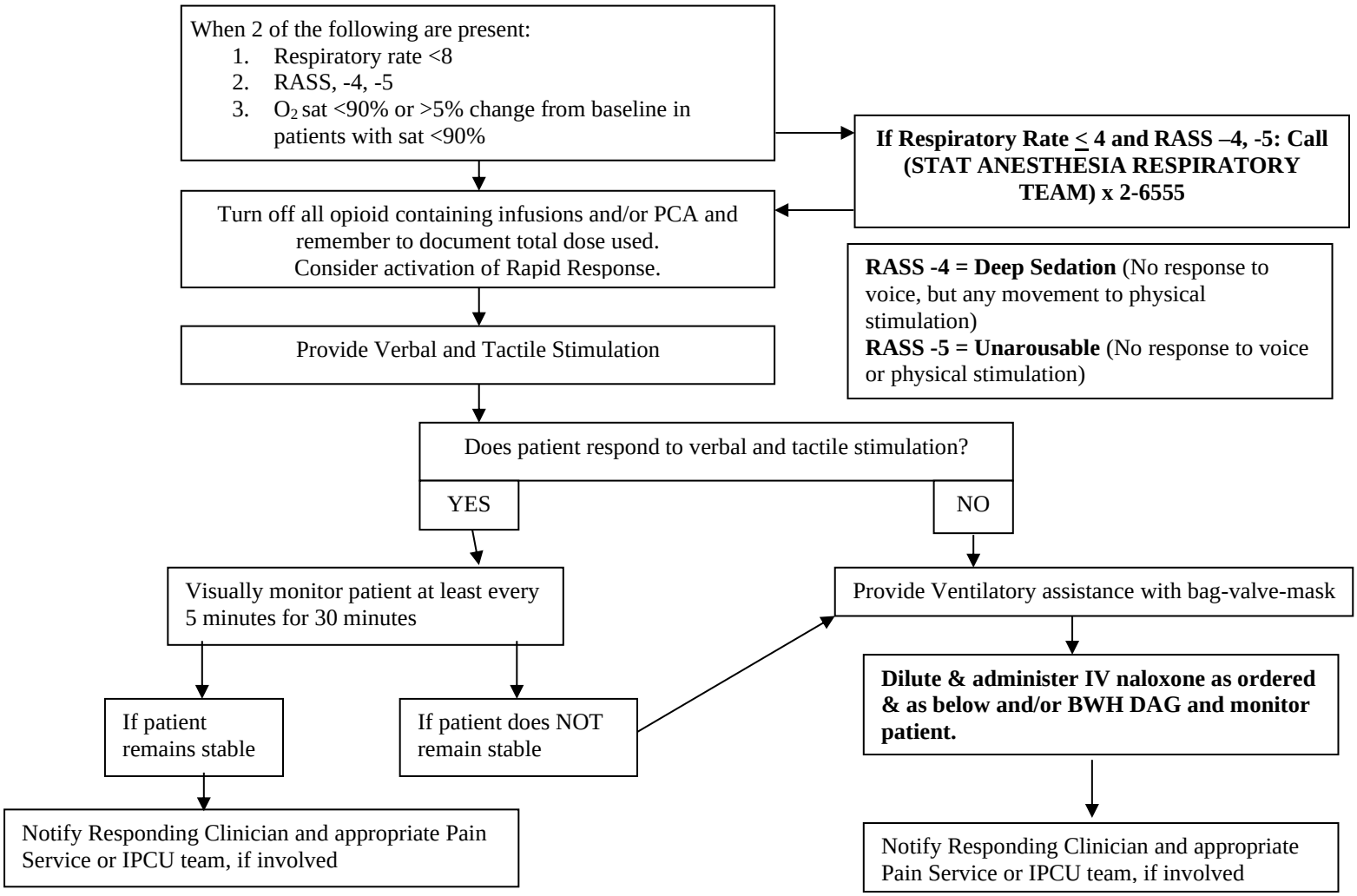
Long term use of opioids for chronic non-malignant pain (COT) has been associated with harm, or no clear evidence of benefit. Key points when considering tapering COT:

- 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 Medication-Assisted Therapy (MAT)
- 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 titrated, consider another etiology other than opioid-induced.
- If there is some, but not enough, improvement after 0.4 mg of naloxone has been titrated, 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 if a standing order is in place. Both BWH and DFCI Outpatient Pharmacy departments have standing orders in place to allow for patients to purchase naloxone rescue kits. Consider prescribing naloxone to patient on greater than 90 morphine equivalents daily.

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 (Kadian®): 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 ER Arymo and Morphabond available in ADF formulation
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	Two ER formulations formulated with a μ-receptor antagonist are FDA-approved for use, but are not currently marketed in the US. Troyca ER® (Oxycodone HCl/ Naltrexone) Targiniq® (Oxycodone HCl/ Naloxone) ***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.

Ψ Abuse Deterrent

Available Single Active Agent Opioid Formulations		
FentaNYL	Transdermal Patch (Duragesic®): 12, 25, 37.5, 50, 62.5, 75, 87.5,100 mcg/hr Injectable solution: 50 mcg/mL See Fentanyl Page for available TIRF meds	TIRF REMS see page #12 A 25 mcg/hr transdermal patch is equianalgesic to ~ 50 mg of oral morphine per day.
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 #10 **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

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 formulations 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	Adjust dose for renal dysfunction: (CrCl < 60 mL/min); Significant increase in respiratory depressant effects of opioids Do not stop abruptly
Pregabalin* (Lyrica®)		150 mg po divided to bid or tid	300 mg in 2-3 divided doses	
OXcarbazepine (Trileptal®)		300 mg po daily, then ↑ to 300 mg bid, then ↑by 300 mg/day q5 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 q1-2 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 2wks	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 every 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 dose = 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 methylpred 20-40 mg po q8-12h	minimal effective dose	
	Alleviation of nausea, anorexia, or bone pain	dex 4-12 IV/po mg/day 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	A case report supports the use of loratadine in pegfilgrastim-related bone pain

#ICP = intracranial pressure **See "Systemic Equivalencies of Corticosteroids" page 26

Adjuvant Analgesic Agents (continued)

Drug	*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 policy)
Memantine (Namenda)	Neuropathic pain	10 mg/day; increase by 10 mg/day weekly	30-60 mg/day studied	NMDA antagonist
Octreotide (Sandostatin®)	Obstructed bowel spasm; chemo-induced diarrhea, VIPomas°	50-100 mcg Subcut bid-tid 20-30 mg IM intragluteally q 4 wks	Varies	-Monitor for changes in glucose control, cholelithiasis -Use caution in renal impairment
Pamidronate (Aredia®)	Metastatic bone pain; delay of bone metastasis progression, hypercalcemia	90 mg IV q4 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 Q4wks	120mg Subcut Q4wks	Administer with calcium ≥ 500 mg/d and vitamin D ≥ 400 units/d
Radio-pharmaceuticals				
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	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 q4weeks x 6 doses	55 kBq/kg q4weeks x 6 doses	Anemia, Leukopenia and neutropenia are commonly seen. Nadir is usually after 2-4 weeks.

°VIPomas = Vasoactive Intestinal Polypeptide secreting tumors

NON-ANALGESIC CNS ACTIVE AGENTS*

Drug	*Indications*	*Usual Starting Dose and Interval*	*Common Dosage Range*	Comments
Sedatives –Melatonin Receptor Agonist				
Ramelteon (Rozerem®)	Insomnia	8mg po daily at 2 hours before bedtime		
Sedating Anti-Depressants				
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	0.5mg 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 mg – 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 a 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 and depression	2.5-5 mg po daily/bid	5-20 mg in divided doses (8am and 2pm)	
(Concerta®)		18 mg or 36 mg podaily	Max dose = 72 mg	
(Metadate CD/ Ritalin LA®)		20 mg po daily	Max dose = 60 mg	
Modafinil (Provigil®)	Opioid induced sedation	100-200mg po Qam	200-400 mg	
Armodafinil (Nuvigil®)		150-250mg po Qam	150 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.

NON-ANALGESIC CNS ACTIVE AGENTS (Continued)*

Drug	*Indications*	*Usual Starting Dose and Interval*	*Common Dosage Range*	Comments
Anxiolytics – Benzodiazepine Note: All benzodiazepines cause additive sedation and respiratory depression with opioids.				
LORazepam α (Ativan®)	Anxiety, insomnia	0.5-2 mg po daily-tid	Use lowest effective dose	t½ = 10-20 h
ClonazePAM α (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 α (Serax®)		10-15 mg po daily-tid		t½ = 5-20 h
Temazepam α (Restoril®)	Insomnia	15-30 mg po bedtime		t½ = 10-40 h
ALPRAZolam α (Xanax®)	Anxiety, skeletal muscle spasm	0.25-0.5 mg po daily-tid		t½ = 12-15 h, Very short acting with rebound anxiety.
Midazolam α (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.
Zolpidem (Ambien CR®)		12.5 mg po bedtime		
Zolpidem *(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*
Short-Acting			
Cortisone	25 mg	0.8	2
Hydrocortisone	20 mg	1	2
Intermediate-Acting			
Prednisone	5 mg	4	1
Prednisolone	5 mg	4	1
Triamcinolone	4 mg	5	0
Methylprednisolone	4 mg	5	0
Long-Acting			
Dexamethasone	0.75 mg	25-30	0
Betamethasone	0.6-0.75 mg	25	0

Non-Opioid Analgesics: Available Dosing 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 ER Tab: 650 Elixir: 160 mg/5 mL Supp: 120, 325, 650 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 Chew Tab: 81 EC Tab: 325, 650 Supp: 300, 600	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 Cap: 18, 35 SR Tab: 100 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	↓ nephrotoxicity; related to salicylates, and may inhibit platelet function and prolong bleeding time
Etodolac (Lodine®)	1000 mg	6-8 hrs 24 Hrs for ER	Cap: 200, 300, 500 ER Tab: 400, 500, 600	↓ 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 Cap: 200, 300, 400	↑ incidence of headache, somnolence, dizziness; may cause genitourinary tract side effects
Flurbiprofen (Ansaid®)	300 mg	6-12 hrs	Tab: 50, 100	↑ dizziness; use with caution in hepatic dysfunction.
Ibuprofen (Advil® Motrin®)	2400 mg	4-8 hrs	Tab: 100, 200, 400, 600, 800 Chew Tab: 50,100 Liquid: 100 mg/5 mL, 50 mg/1.25 mL Drops: 40 mg/mL Injectable (Neoprofen®): 10mg/mL	Repeated studies have shown doses of 1500 mg/day or less to 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 SR Cap: 75 Susp: 25 mg/5 mL Supp: 50 Injectable: 1mg /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 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
Ketorolac (Toradol®)	max 120 mg IV max 40 mg po	6 hrs	Tab: 10 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 SR Cap: 200	↓ dose in hepatic dysfunction; SR Cap allows for DAILY dosing; Topical preps in development or compounded
Nabumetone (Relafen®)	1500 mg	12-24 hrs	Tab: 500, 750	↓ 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 Cap: 220 SR Tab: 375, 500, 750 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% (Tab: 220, 275, 550)
Meclofenamate (Meclomen®)	300 mg	4-6 hrs	Cap: 50, 100	High incidence of diarrhea, ↑ GI side effects; do not use for > 1 continuous week
Mefenamic Acid (Ponstel®)	1000 mg	6 hrs	Cap: 250	↑ GI side effects
Meloxicam (Mobic®)	7.5 mg	24 hrs	Tabs: 7.5, 15 Susp: 7.5 mg/ 5 mL	↓ GI bleeding ** and side effects
Oxaprozin (Daypro®)	1200 mg	12-24 hrs	Tab: 600	DAILY - BID dosing; use caution in severe hepatic impairment
Piroxicam (Feldene®)	20 mg	12-24 hrs	Cap: 10, 20	High risk of serious GI adverse events vs. other NSAIDs; ↑ hepatotoxicity; DAILY - BID dosing
Sulindac (Clinoril®)	300 mg	12 hrs	Tab: 150, 200	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 Cap: 400	↑ incidence of auditory toxicity and GI adverse events

** 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	↓ 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	↓ 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

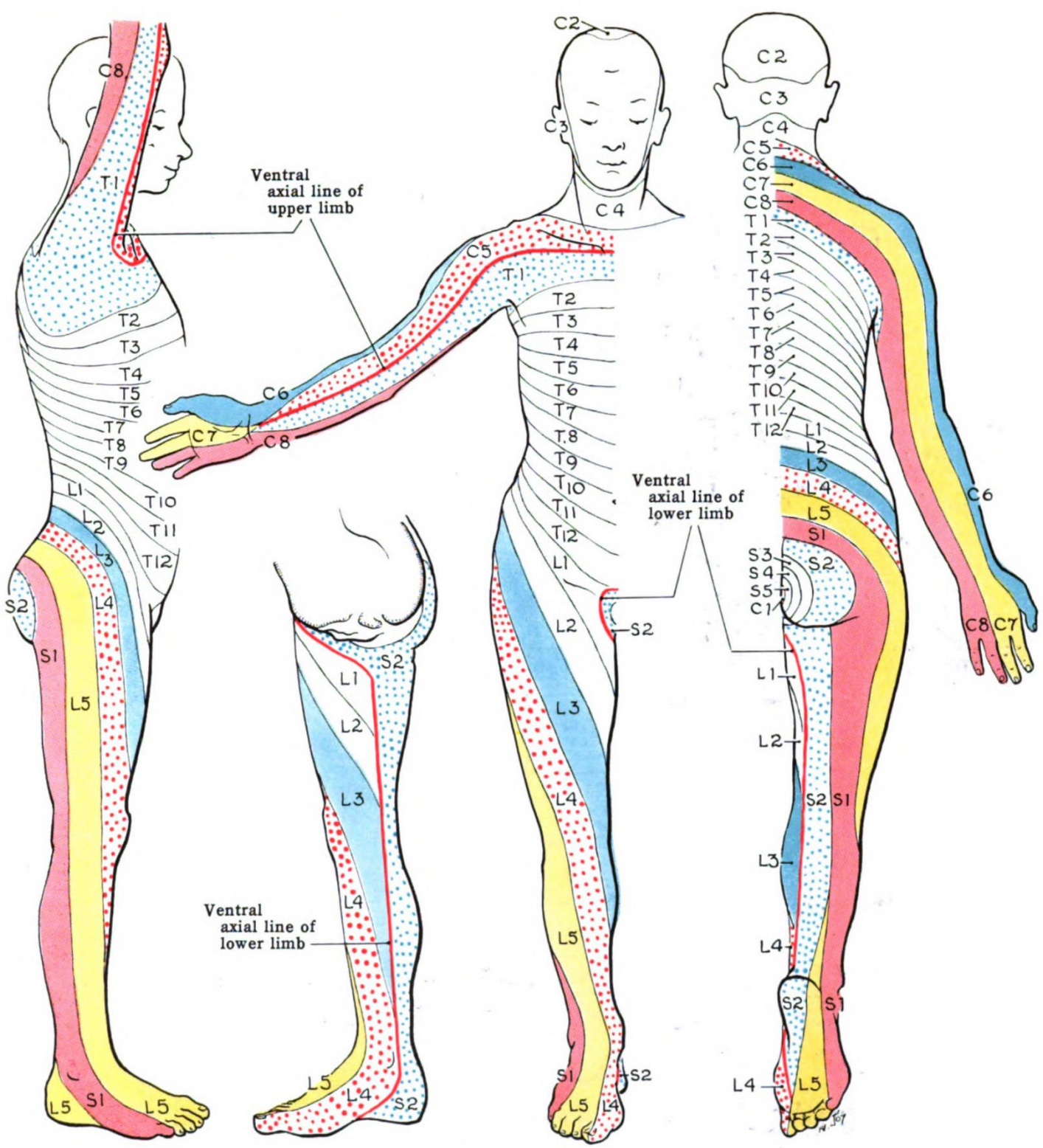
Limitations: Only for Chronic Kidney Disease, more accurately predicts GFR than MDRD in patients with preserved function. Online calculators available. Automatically calculated in Epic at Mass General Brigham, with assumption of non-Black race. If patient is Black, you will need to multiply by 1.159.

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



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