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: **PAINED**

Place - Where is the pain? Is it in more than one site?

Amount - What is the present and past intensity of the pain, at its worst and at its best?
How often does it occur? Is it constant or intermittent? When did it begin?

Intensifiers - What makes the pain worse?

Nullifiers - What makes the pain better? What pharmacological and non-pharmacological approaches (including complementary/alternative therapies) have been and are being used for the treatment of the pain? Were they and are they effective?

Effects - What side effects were/are experienced from past and present analgesics?
How does pain affect quality of life: physical, psychological and social function?

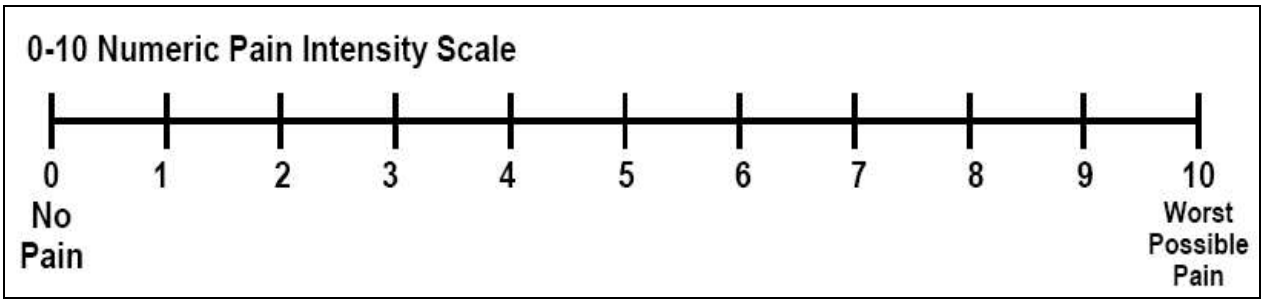
Description of pain - How does the pain feel?
sharp, stabbing, burning, shooting, dull, aching, throbbing, crampy

Verbal Numerical Scale

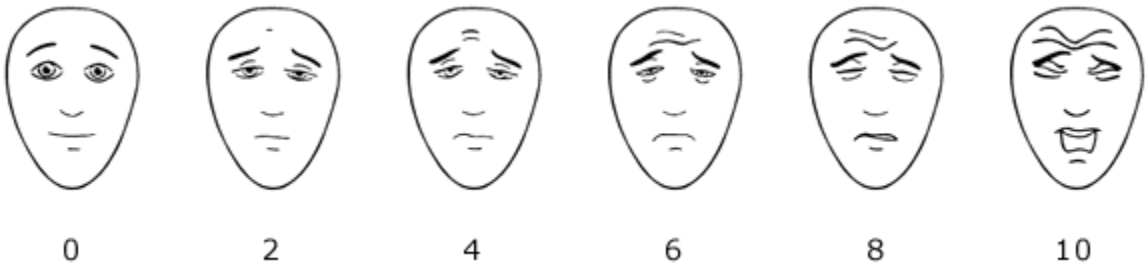
"If *0* is 'No Pain' and *10* is the 'Worst Pain Imaginable' what is your pain right now?"

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.

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

Important Definitions

Addiction 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.

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.

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 is the intentional or unintentional use of a prescribed medication in a manner that is contrary to directions, regardless of whether a harmful outcome occurs. Examples of misuse include not taking the medication according to the prescription, unsanctioned use of the prescription, altering of the route of delivery, and obtaining drugs from other sources (including other prescribers).

Abuse is the self-administration of medications to alter one's state of consciousness. This is an intentional, maladaptive pattern of use of a medication leading to significant impairment or distress, such as repeated failure to fulfill role obligations, recurrent use in situations in which it is physically hazardous, multiple legal problems, and recurrent social and interpersonal problems.

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.

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.

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

Urine Drug Screens can be used when prescribing medications for chronic pain to mitigate the risk of drug abuse and diversion. When reading the results of urine drug screens, it is important to understand the metabolism of the drugs being tested. For example the metabolite EDDP is expected when methadone is used, oxyMORphone will be seen with oxyCODONE use, HYDROmorphone will be seen with HYDROcodone use, and 6-monoacetylmorphine will only be seen in heroin use.

Massachusetts Prescription Awareness Tool (MassPAT) is the online prescription monitoring program in Massachusetts (https://massachusetts.pmpaware.net/login). All cininicians 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 new prescription for a benzodiazepine is mandatory.

Validated Risk Assessment Tools include but are not limited to SOAPP-R, ORT, DIRE, and COMM-17. These tools should be used alongside clinical judgement when prescribing opioids to a patient for chronic pain. Copies of these tools can be found at pinkbook.dfci.org.

Guidelines for the Management of Pain[1]

Including non-opioid therapy and dosing of opioid medications

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).

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 opioid and non-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 opiates consider adding extended-release (ER) / long-acting opioids such as sustained release oxyCODONE, morphine, oxyMORphone, transdermal fentanyl, continuous opioid infusion or the long-acting methadone. Continue non-opioid therapy and short-acting as needed opioid therapy.

Non-Opioid therapies

10. Non-opioid therapies including pharmacologic and non-pharmacologic therapies can benefit many patients, especially those with pain unrelated to cancer.

11. 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.

12. For treatment of neuropathic pain, medications such as pregabalin, gabapentin, tricyclic antidepressants and topical lidocaine may be useful.

13. For inflammatory pain, medications like NSAIDs and steroids can be used.

Guidelines for the Management of Pain (continued)

14. Topical agents like lidocaine, capsaicin and NSAIDs can be used to provide analgesia to discrete painful areas with limited systemic exposure.

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

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

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

Opioid Dosing Guidelines

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

19. The appropriate dose is the one needed to control the patient's pain with the fewest side effects.

20. 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

21. Constipation is a preventable yet common problem associated with opioid administration. It should be anticipated, treated prophylactically, and monitored carefully.

22. 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.

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

24. Codeine dosing is limited by constipation and nausea, and ≥10% of patients lack the enzyme necessary to convert codeine into active metabolites.

25. 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.

26. 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).

27. 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 (e.g., a patient takes ER morphine 60 mg po q12h plus 6 doses of immediate release morphine 15 mg in 24 hours. Increase the daily ER morphine dose by 45 to 90 mg according to the patient's status and pain intensity- New regimen MS Contin 100mg Q12H and morphine 30mg q3h PRN pain).

28. 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.

29. When calculating the initial dose of a different opioid in opioid rotation, the dose of the new opioid should be reduced by 25-50%. This is to account for incomplete cross-tolerance, due to differences in the structure of individual opioids and their action at the various mu opioid receptors. See page #8 for instruction.

Guidelines for the Management of Pain (continued)

30. **Naloxone reverses sedation, respiratory depression, and <u>ANALGESIA</u>**. 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 #15 for instructions on use.

31. 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

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

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

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

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

<u>Continuous Opioid Infusions</u>

36. 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.

37. "Titrate to comfort" is neither a clear nor acceptable order.

38. 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.

39. PRN boluses of opioids should be made available on an every 1 hour or every 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.

40. 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

41. 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.

42. Titrating the continuous infusion rate without the use of PRN boluses may provide inadequate or delayed symptom relief, and increase risk of undesirable side effects such as myoclonus.

43. Patients should be judiciously monitored for side effects such as myoclonus or delirium

44. Judicious use of opioids for pain or dyspnea in actively-dying patients has not been shown to hasten death.

45. 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 #11 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. An example of a conversion is presented below for review.

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, as only one rescue dose of 15 mg has been required for breakthrough pain each day. Oral administration has become contraindicated in this patient, and you wish to convert the pain management regimen to a continuous IV infusion of morphine.

STEP I. *Calculate the patient's total daily opioid requirement.*

Total daily dose (TDD) of oxyCODONE from ER oxyCODONE = 40 mg x 3 doses = 120 mg

Total daily dose of oxyCODONE from three, 5 mg oxyCODONE tablets = 15 mg

120 mg oxyCODONE + 15 mg oxyCODONE = 135 mg oxyCODONE/day

STEP II. *Convert the daily requirement of the old opioid to that of the new opioid.*

20 mg of oral oxyCODONE = 10 mg of IV morphine

$$\frac{\text{20 mg po oxyCODONE}}{\text{10 mg IV morphine}} = \frac{\text{135 mg po oxyCODONE}}{\textbf{X} \text{ mg IV morphine}}$$

X = 67.5 mg IV morphine/day

(i.e., 67.5 mg IV morphine/day is equianalgesic to 135 mg po oxyCODONE/day)

Reduce dose by 25% for incomplete cross tolerance: ~50 mg IV morphine/day

STEP III. 50 mg/day ÷ 24 hours/day ~ 2 mg of morphine/hour

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 requires a much more conservative conversion. Please refer to the chart on page #10 for recommended conversions at corresponding doses of other opioids.
- The cytochrome P450 system is highly involved in the metabolism of methadone, resulting in numerous clinically significant drug interaction, as well as interpatient genetic variability which can impact the effect as well as the toxicity of treatment

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 which 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.
- 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. Consider consulting the Anesthesia Pain or Palliative Care services in these cases.

Equianalgesic Conversion TO Methadone[14] Dose-dependent potency changes well-established in the literature.		
Oral Morphine Equivalent	Mg of oral Methadone **=** (ratio)	Mg of oral Morphine
under 100 mg/day	1	4
101-300 mg/day	1	8
301- 600 mg/day	1	10
601-800 mg/day	1	12
801-1000 mg/day	1	15
over 1000 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		

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.
- Reduce the calculated oral methadone dose by 30-50%.
- Divide the resulting reduced daily dose by 3.
- This is the every 8-hour dose of oral methadone in mg.
- *Only convert to methadone with a consultation to the appropriate Pain or Palliative Care team.*

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 #11)	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 to switch to another opioid, it is important to account for the fact that fentanyl will remain in the system for 6-18 hours after removal of the patch.

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)	Abstral® Sublingual Tab	Subsys® Sublingual Spray	Lazanda® Nasal Spray
200 mcg	100 mcg	100 mcg	100 mcg	100 mcg
400 mcg	200 mcg	200 mcg	200 mcg	300 mcg
600 mcg	400 mcg	300 mcg	400 mcg	400 mcg
800 mcg	600mcg	400 mcg	600 mcg	
1200 mcg	800 mcg	600 mcg	800 mcg	
1600 mcg		800 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.

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 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
Bolus dose	2 mg	0.3 mg	25 mcg

Opioid-Tolerant 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	
Bolus dose	5 mg	0.8 mg	60 mcg	

High Risk (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	10 minutes
Continuous dose	Continuous dose not allowed	Continuous dose not allowed	Continuous dose not allowed
Bolus dose	1 mg	0.2 mg	20 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 bid-qid or OLANZapine 2.5-5 mg PO daily-bid)</td></tr>
<tr><td>Constipation</td><td>Begin bowel regimen when opioid therapy is initiated.

Include a stimulant laxative as routine prophylaxis (senna 1-4 tabs po bedtime-bid)

Note: The addition of docusate for the management of constipation provides no additional benefit over senna alone, and as such has been removed from this algorithm.

Consider adding polyethylene glycol 17 grams PO daily or lactulose 30 grams PO daily when necessary.

In patients who are NPO consider metoclopramide 10 mg IV q 6 hours.

Subcutaneous methylnaltrexone may be added for patients with advanced illness on opioids who have failed multiple laxative therapy per Partners Healthcare Guidelines:
Less than 38 kg: 0.15 mg/kg Subcut every other day
38 kg to less than 62 kg: 8 mg Subcut every other day
62 kg to 114 kg: 12 mg Subcut every other day
More than 114 kg: 0.15 mg/kg Subcut every other day

Approved drugs for Opioid-Induced Constipation in Chronic Non-Cancer Pain

Naloxegol is a peripherally-acting mu-opioid receptor antagonist approved for opioid-induced constipation in patients with chronic non-malignant pain. The FDA also recently approved a formulation of oral methylnaltrexone for opioid-induced constipation in non-malignant pain.

Lubiprostone (Amitiza) and linaclotide (Linzess) are also FDA-approved for opioid-induced constipation in chronic non-malignant pain.</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 Side Effects*

Adverse Effect	***Management Considerations***
Nausea/ Vomiting	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) Ondansetron dosing for Post-Operative Nausea/Vomiting: 1 mg IV every 6 hours
Pruritis	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.
Respiratory Depression	Hold opioid; provide supportive measures; consider dilute naloxone. See page #15.
Myoclonic Jerking	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 qid; baclofen 5-10 mg po tid
Sedation	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).

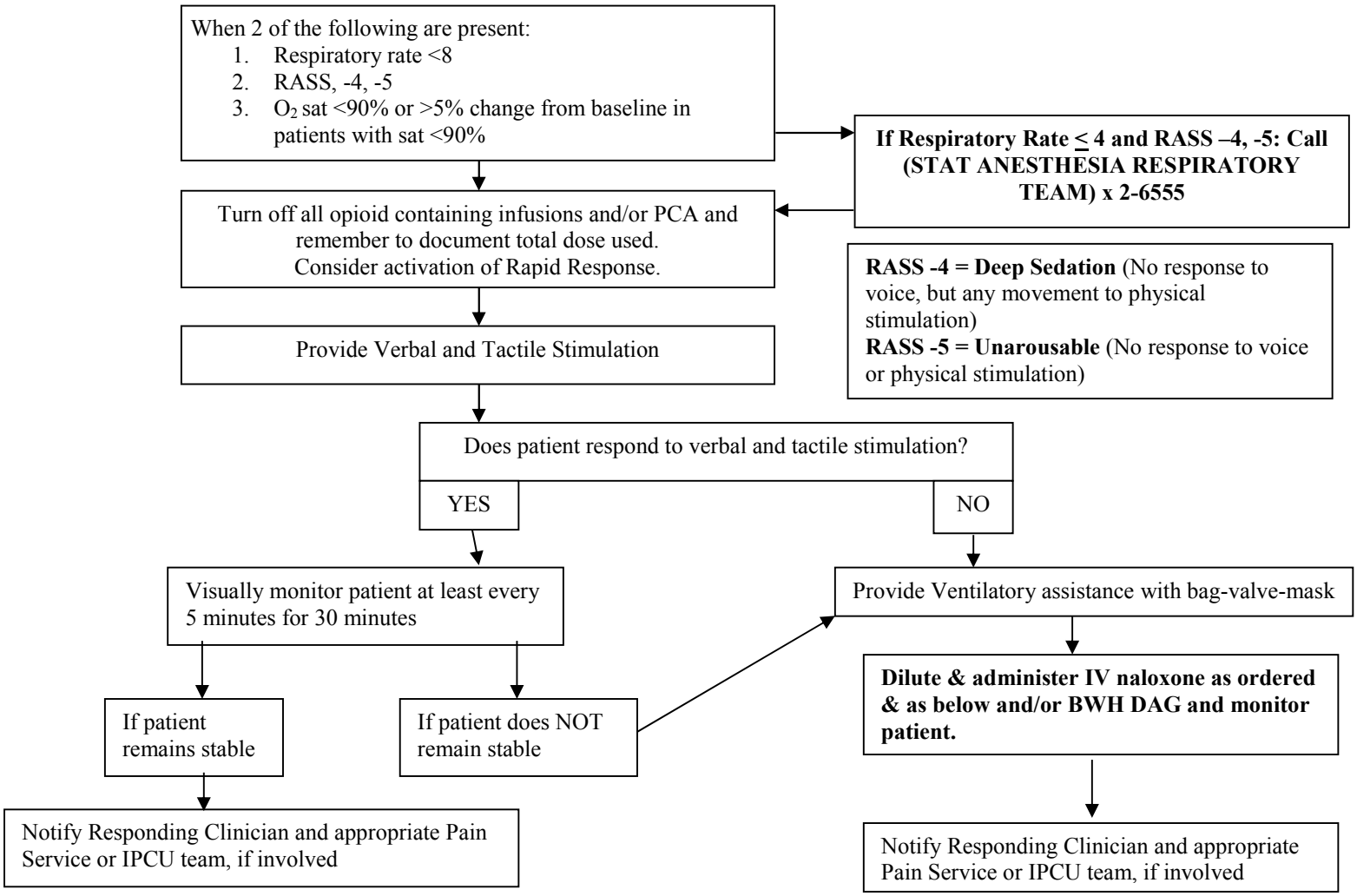
* The above assumes that opioid therapy is a necessity. Non-opioid therapy options or alternative routes of administration should be considered. A thorough evaluation for other causes of the effect should always be done.

Weaning Opioids

Patients may require the discontinuation of an opioid when the cause of pain is effectively eliminated. In such circumstances, physical withdrawal is prevented by providing the patient with an adequate percentage of the prior daily dose.

- To achieve this, provide an opioid dose equianalgesic to at least half the prior daily dose for each of the first two days.
- Then, reduce the daily dose by 25% every two days thereafter until the total dose (in oral morphine equivalents) is **30 mg/day.**
- The drug may be discontinued after two days on the 30 mg/day dose.
- If the patient experiences increased pain, the dose of the opioid may be increased.
- Some patients may require a slower taper, especially if taper-related side effects such as hypertension, nausea, insomnia, diarrhea or anxiety are observed.
- If more rapid weaning is required, please consult the Chronic 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.

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.

Available Single Active Agent Opioid Formulations		
Drug	**Available Strengths and Dosage Forms**	**Comments**
Morphine	Tab: 15, 30 mg SR Tab Ψ: 15, 30, 60, 100, 200 mg SR/Naltrexone (Embeda)Ψ: 20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2, 100/4 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	Morphine Extended-Release Capsules, biphasic release (Formerly Avinza®) (30, 45, 60, 75, 90, and 120 mg) and Kadian® (10, 20, 30, 50, 60, 80, 100 and 200 mg) marketed as 24 hour capsules that 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 Tab (Exalgo®) Ψ: 8, 12, 16, 32 mg Liquid: 1 mg/mL Suppository: 3 mg Injectable solution: 1 mg/mL, 2 mg/mL, 4 mg/mL, 10 mg/mL	
OxyCODONE	HCl Tab: 5, 10, 15, 20, 30 mg HCl SR* 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.

* Sustained release
Ψ Abuse Deterrent

Available Single Active Agent Opioid Formulations		
FentaNYL	Transdermal Patch (Duragesic®): 12, 25, 50, 75, 100 mcg/hr Injectable solution: 50 mcg/mL See Fentanyl Page for available TIRF meds	TIRF REMS please see page #11 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 See Methadone (page #9) **Please consult Anesthesia Pain or Palliative Care for questions.**
TraMADol**	Tab: 50 mg ER Tab: 100, 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 ER Tab Ψ: 50, 100, 150, 200, 250	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.

* Sustained release

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, abuse 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); no significant documented drug-drug interactions 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 bid ↑by 300 mg/day q 3 days	600-2400 mg/day	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 ↑by25-50 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	200mg bid Max dose 1600mg	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®)		100 mg po bid	200 mg po bid-qid	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)	
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 mg po tid	15-80 mg/day (tid)	When stopping muscle relaxants after chronic use, it may be necessary to taper over 1-2 weeks. Orphenadrine- IV product available 30 mg/mL
Metaxalone (Skelaxin®)		800 mg po tid	800 mg tid - qid	
Orphenadrine (Norflex®)		100 mg po bid 60mg IV/IM q12h	200 mg/day	
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 19

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 0.1-0.3 mg/kg/hr	Up to 0.9 mg/kg/hr	Restricted at BWH to pain services and ED attending physicians- please refer to Drug Administration Guideline (DAG)
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		Requires Acute Pain Service Consult
Dextromethorphan	Neuropathic pain	30-90 mg/day	30-380 mg/day studied	NMDA antagonist. Low affinity. Efficacy equivocal. GI and neuro effects, (diarrhea, nausea, dizziness)
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
Anxiolytics – Benzodiazepine Note: All benzodiazepines cause additive sedation and respiratory depression with opioids.				
LORazepam (Ativan®)	Anxiety, insomnia	0.5-2 mg po daily-tid	Use lowest effective dose	t½ = 10-20 h, no active metabolite
ClonazePAM (KlonoPIN®)		0.25–0.5 mg po bid		t½ = 19-50 h no active metabolites
Diazepam (Valium®)	Anxiety, insomnia, skeletal muscle spasm	5 mg po daily-bid		t½ = 20-80 h t½ (active metabolite) = 50-100 h
Oxazepam (Serax®)		10-15 mg po daily-tid		t½ = 5-20 h, no active metabolite
Temazepam (Restoril®)	Insomnia	15-30 mg po bedtime		t½ = 10-40 h, no active metabolite
ALPRAZolam (Xanax®)	Anxiety, skeletal muscle spasm	0.25-0.5 mg po daily-tid		t½ = 12-15 h, no active metabolite Very short acting with rebound anxiety.
Midazolam (Versed®)	Sedation	Doses vary depending on individual patient needs.		t½ = 2-5 h, no active metabolite
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.

NON-ANALGESIC CNS ACTIVE AGENTS (Continued)*

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, agitiation	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-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 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 **not** on BWH formulary
Aspirin	3000 mg	4-6 hrs	Tab: 81, 325 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®, Cataflam®, Arthrotec®, Flector®)	150 mg	12 hrs	Tab:25, 50, 75 SR Tab: 100 (DAILY dosing) Patch: 1.3% Gel/Jelly: 1%(Voltaren®) 3%(Solaraze®)	↑ 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: 250, 500	↓ nephrotoxicity; related to salicylates, and may inhibit platelet function and prolong bleeding time
Etodolac (Lodine®)	1000 mg	6-8 hrs	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 (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: 200, 400, 600, 800 Chew Tab: 50,100 Liquid: 160 mg/5 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: 25, 50 SR Cap: 75 (bid) Susp: 5 mg/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	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	Cap: 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	Tab: 375, 500 EC Tab: 250, 375, 500 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	↓ 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 (Disalcid®)	3000 mg	8-12 hrs	Tab: 500, 750 Cap: 500	↓ 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	Idomethacin, 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.

Systemic Equivalencies of Corticosteroids

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

Regional Anesthesia

Neuraxial analgesia may be delivered via percutaneously placed or implanted epidural catheters, or implanted intrathecal pumps. Percutaneously placed epidurals are commonly used for post-operative pain management.

1. Epidurals- Epidural catheters generally deliver a mix of a local anesthetic (e.g., bupivacaine) and occasionally an opioid (e.g., HYDROmorphone).
    a. Example of settings: 6/2/20/48 {6 mL per hour/2 mL per activation/20 min lockout/48 mL 4-hour limit}
    b. Opioids delivered via an epidural have some systemic effect.
    c. Common solutions include:
        i. Bupivacaine 0.2% +/- Dilaudid 0.02mg/mL
        ii. Bupivacaine 0.125% +/- Dilaudid 0.02mg/mL
        iii. Bupivacaine 0.0625% +/- Dilaudid 0.02mg/mL
    d. Considerations for post op use:
        i. Lumbar level catheter: no ambulation; requires foley catheter
            a) Commonly used in LE orthopedic surgery
        ii. Low thoracic catheter: may ambulate if LE strength OK; in post surgical patient generally remain in until regular diet, do not require foley catheter
            a) Commonly used in GI/GYN/Urology procedures
        iii. High thoracic: May ambulate; Generally stay in until regular diet and any chest tubes are out, does not require foley catheter
            a) Commonly used in thoracic surgery

2. Peripheral Nerve Catheters {Bupivacaine 0.0625-0.25%; Ropivacaine 0.2% or Mepivacaine 0.5-0.75% at 6-10 mL/hr – usually no patient-controlled mode}
    a. Femoral nerve
        i. Total Knee Replacements
        ii. Cover anterior portion of knee only
        iii. Need a PCA as well to “cover” sciatic component (back of knee)
    b. Popliteal Fossa
        i. Foot and ankle surgery
    c. Brachial Plexus (Interscalene, Supra/Infra-Clavicular, Axillary)
        i. Shoulder and arm surgery

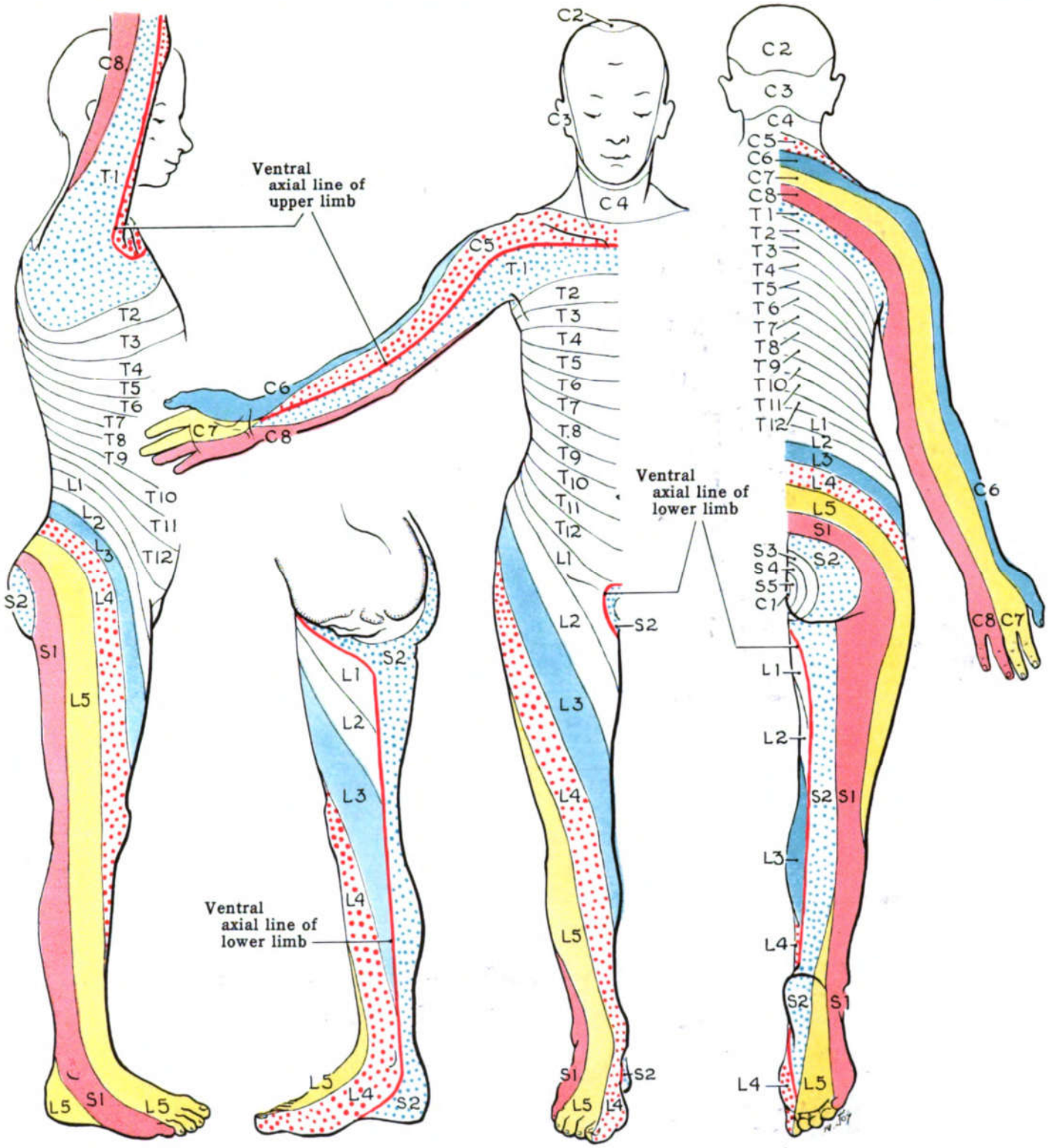
Potential Epidural Complications

(aside from potential opioid-related side effects of nausea, pruritus, and respiratory depression)

Problem	Signs & Symptoms	Intervention	Comment
Hematoma {Estimated risk: 1:150,000 nl coags 1:3,000 on anticoag}	Motor weakness (46%) Back Pain (38%)	Prevention by limiting anticoagulants (see below). If suspected, order MRI and consult Neurosurgery. Best outcome if decompression laminectomy within 8 hours of symptom onset.	May occur at insertion or removal. MRI best for diagnosis; spiral CT may be used for more rapid diagnosis if MRI not available.
Hypotension	20% ↓ SBP from baseline; ↓ urine output; dizziness, nausea, confusion.	See guideline on intranet.	
Numbness	Patient report; ↓ sensation by exam.	None needed if only covering the area of the incision. Reassure patient.	Excessive or increasing numbness should be evaluated by team managing the epidural.
Infection/Abscess	Fever; back pain; drainage, erythema or swelling at insertion site or along catheter track.	Report to team managing epidural. MRI to diagnose abscess, if confirmed requires removal of epidural.	May require prolonged antibiotic treatment or surgical intervention.
Weakness	Patient report; ↓ motor function by exam.	Report to team managing epidural. Assure patient safety.	Often managed with adjustment of dose.

Please see the complete BWH Guidelines for Regional Anesthesia and Anticoagulants with epidurals and guidelines for the evaluation of hypotension with epidurals on the BWH Intranet

Dermatome Chart



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