Practical Pain Management
Tips for Busy Practitioners

Gregory L. Holmquist, PharmD, CPE

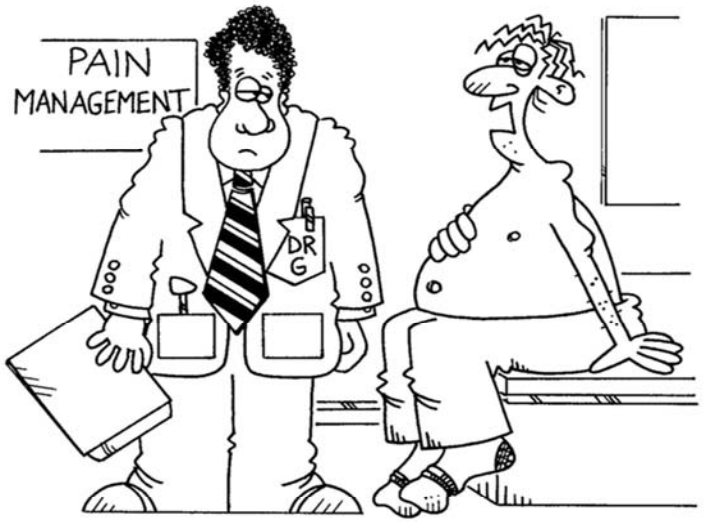
Certified Pain Educator
Board Certified Oncology Pharmacist
Pain Management / Palliative Care Pharmacist Specialist
Hospice Consultant
Chronic non-cancer Pain Team
LTC Elderly Pain Consultant
Private pain management consultant

Speaker Disclosure

- Speaker indicates that he has received honoraria from Depomed.

Objectives

- Assess the current state of pain management in your facility.
- Provide overview of the Best Practices for Hospital Pain Management.
- Coach staff on how to have difficult conversations about pain management with patients.
- Develop a strategy for systems-level management of pain medication.



Best Practices

- Keep you out of trouble
- Keep your patients out of trouble
- Treat our patients with respect
- Discourage abusers
- Meet federal and state guidelines
- Utilize technology

Laws, Regulations, Guidelines

- FDA Transmucosal Immediate-Release Fentanyl (TIRF) REMS (2012)
- FDA REMS Blueprint: Extended Release (ER) Opioid Analgesics & FDA Labeling Changes for ER Opioids (2014)
- CDC Guidelines for Prescribing Opioids for Chronic Pain (2016)
- State Specific Guidelines and Laws
  - Oregon Opioid Prescribing Guidelines (2017)

http://www.oregon.gov/obnm/rules/opioidprescribingguidelines.pdf

  - House Bill 2114 – Endorsed the Oregon Opioid Prescribing Guidelines

Pain is Complicated

- There are no “pain meters”
  - Pain is subjective to both the patient and the provider
- Pain can’t always be visualized even by our most sophisticated diagnostic imaging tests
- Pain is influenced by psychiatric co-morbidities and environmental stressors
- It is difficult to distinguish...
  - inappropriate drug-seeking (addiction) from...
  - appropriate pain relief-seeking

Benefit is Difficult to Measure

- What is the best way to measure pain, function, and quality of life?
- How much improvement in pain, function and quality of life is enough?
  - Is a decrease in pain from an 9 to a 7 on a 10 point scale enough?
  - Is limited ambulation enough?

Acute Pain Can Impact Patients' Lives

- Negative impacts of inadequate acute pain management include
  - Increased hospital stay or more frequent readmissions
  - Reduced quality of life
  - Impaired physical function
  - Decreased functional recovery
  - Increased complications
  - Impaired sleep

McCarberg BH, et al. *Am J Ther.* 2008;15(4):312-320.
Pavlin DJ, et al. *J Clin Anesth.* 2004;16(3):200-206.
Sinatra R. *Pain Med.* 2010;11(12):1859-1871.
Morrison RS, et al. *J Am Geriatr Soc.* 2009;57(1):1-10.

Inadequate Acute Pain Management Can Have Consequences

Chronic pain may develop after surgery as a result of complex biochemical and pathophysiological mechanisms

Clinically meaningful, severe acute postoperative pain may be a risk factor for the development of chronic pain

Up to 50% of patients reportedly suffer from chronic pain following common operations

Effectively managing acute pain can reduce the risk for pain progression

Sinatra R. *Pain Med.* 2010;11(12):1859-1871.
Morrison RS, et al. *J Am Geriatr Soc.* 2009;57(1):1-10.
Voscopoulos C, Lema M. *Br J Anaesth.* 2010;105(Suppl 1): i69-i85.

Determining the Right Patient

Pain Relief Seeking

Disease progression

Poorly opioid responsive pain

Withdrawal mediated pain

Opioid analgesic tolerance

Opioid-induced hyperalgesia

Pain Relief and Drug Seeking
e.g. pain with co-morbid addiction, patient taking some for pain and diverting some for income

Drug Seeking

Addiction

Other psychiatric

Diagnosis

Criminal intent (diversion)

Responsible and Ethical Prescribing of Opioids

- Pick the right patient
  - Reliability
  - History
  - Intensity
  - Syndrome
  - Duration of treatment
  - Severity
  - Molecule risks
- Outcomes
  - Office measurements
  - Pain diaries
  - ADL functioning
  - Diversion prevention
  - Pain agreement adherence
  - Drug tests & pill counts

Common Universal Precautions

- Comprehensive pain assessment including opioid misuse risk assessment
- Formulation of pain diagnosis(es)
- Opioid therapies should be considered a test or trial; continued or discontinued based on assessment and reassessment of risks and benefits
- Ongoing evaluation of pain and function
- Clear documentation

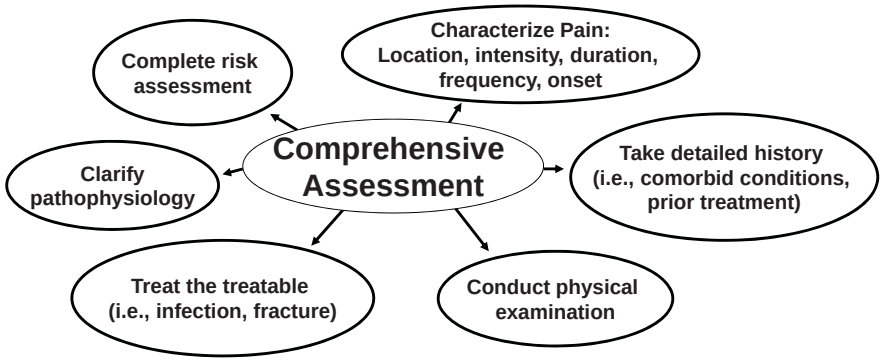
Federation of State Medical Boards Model Policy 2013. www.fsmb.org/grpol_policydocs.html
Gourlay DL, Heit HA, Almahrezi A. Pain Med. 2005;6(2):107-12.
Chou R, et al. J Pain. 2009;10(2):147-59.
Franklin GM. Neurology. 2014; 83:1277-1284

Common Universal Precautions

- Patient Prescriber Agreements (PPA) (Chronic pain)
- Informed Consent (goals and risks)
- Plan of Care
- Efficacy not well established but no evidence of a negative impact on patient outcomes
- Monitoring for adherence, misuse, and diversion (Chronic outpatient management)
  - Urine drug testing
  - Pill counts
  - Prescription Drug Monitoring Program (PDMP) data

FSMB Model Policy 2013. www.fsmb.org/grpol_policydocs.html
Gourlay DL, Heit HA, Almahrezi A. Pain Med. 2005;6(2):107-12.
Chou R, et al. J Pain. 2009;10(2):147-59.
Cheatle MD, Savage SR. J Pain Symptom Manage. 2012;44(1):105-16.
Fishman SM, Kreis PG. Clin J Pain. 2002;18(4 Suppl):S70-5.
Arnold RM, et al. Am J Med. 2006;119(4):292-6.
Starrels J, et al. Ann Intern Med. 2010;152(11):712-20.
Franklin GM. Neurology. 2014; 83:1277-1284

Comprehensive Pain Assessment



1. Turk D, Melzack R. *Handbook of Pain Assessment, 2nd Edition*. Guilford Press, 2001.
2. JCAHO. *Pain: Current Understanding, Assessment, and Treatment*. December 2001. Available at: http://www.npcnow.org/App_Themes/Public/pdf/Issues/pub_related_research/pub_quality_care/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf .

Function vs. Comfort

- Key to effective pain medication therapy is to achieve sustained improvement in pain and physical function.
  - Measure same elements to determine progress
  - No universally accepted tool, many options

Agency Medical Directors Group. Interagency Guideline on Opioid Dosing for Chronic Pain. 2010 Update. Available at: http://www.agencymeddirectors.wa.gov

Graded Chronic Pain Scale

(Chronic Pain Patients)

Pain intensity and interference
In the last month, on average, how would you rate your pain? Use a scale of from 0 to 10, where 0 is “no pain” and 10 is “pain as bad as could be”?
No pain — Pain as bad as could be
0 1 2 3 4 5 6 7 8 9 10
In the last month, how much has pain interfered with your daily activities? Use a scale from 0 to 10, where 0 is “no interference” and 10 is “unable to carry on any activities”?
No interference — Unable to carry on any activities
0 1 2 3 4 5 6 7 8 9 10

Scoring: For an individual patient, a reduction in pain intensity and Improvement in pain-related interference with activities of two points Is considered moderate but clinically significant improvement.

Somatic Pain

e.g. Osteoarthritis, muscle strains/sprains, post-operative incisional pain,

- Suggested medication therapy overview

APAP/ NSAID ***based on symptoms*** **(not always needed to include an opioid)**

Visceral Pain

e.g. bladder spams, colic pain, pancreatitis, kidney stones,

- Suggested medication therapy overview

Anticholinergic + NSAID
(may need opioid for acute phase)

Neuropathic Pain:

e.g. Peripheral neuropathies (PHN, DPN), radiculopathy, limb amputation, trigeminal neuralgia

- Suggested medication therapy overview

Adjuvant FIRST, then opioid for either:
add-on therapy or bridge therapy
****ONLY continue opioid if clear benefit****

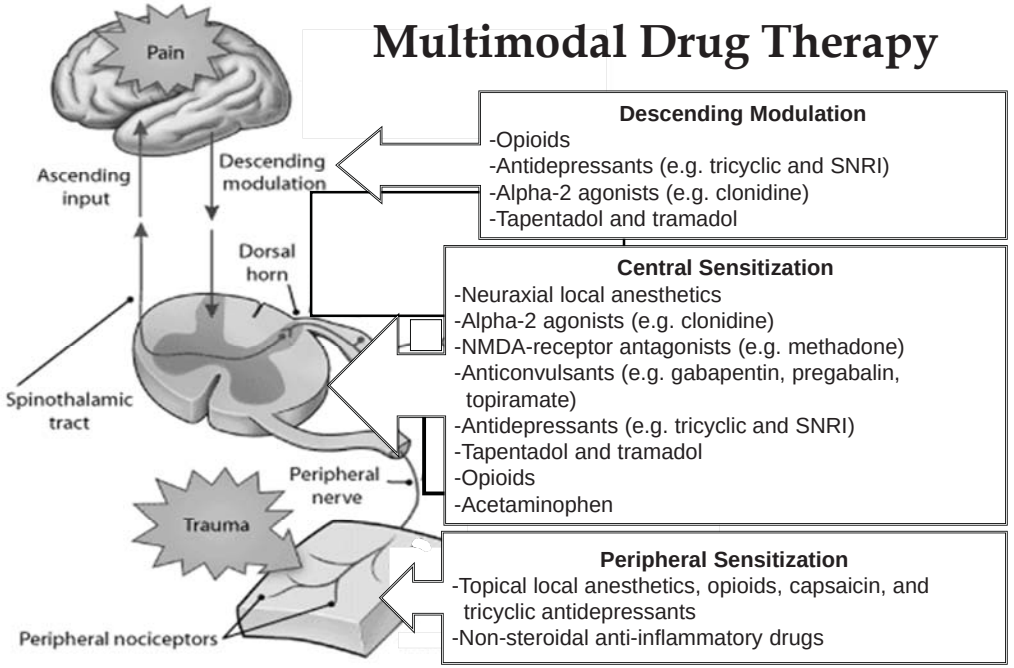
“Let the adjuvant be the engine and the opioid the caboose”

Multimodal Therapy

- Synchronous administration of two or more pharmacological agents or approaches, each with a distinct mechanism of action

American Society of Anesthesiologists Task Force on Acute Pain Management. Practice Guidelines for Acute Pain Management in the Perioperative Setting. Anesthesiology 2012;116:248-273.

Multimodal Drug Therapy



Adapted from Gottschalk A, Smith DS. *Am Fam Phys*. 2001;63:1979-1986.

Multimodal Therapy

- Rationale:
  - Targeting of different pathways
  - Synergism of multiple agents
  - Allow for dose reduction of individual agents, leading to less risk of adverse effects

Perioperative Techniques in Pain Management

Technique	Examples	Advantages	Disadvantages
Central Regional Analgesia	Intrathecal or epidural opioid*	• Improved pain relief	• Increased frequency of pruritus
	Epidural opioid* + local anesthetic**	• Improved pain scores	• Increased motor weakness
	Epidural opioid* + clonidine	• None noted	• None noted

* Examples of opioids include morphine, fentanyl, sufentanil
** Examples of local anesthetics include bupivacaine, ropivacaine

American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116:248-273.

Perioperative Techniques in Pain Management

Technique	Examples	Advantages	Disadvantages
Systemic opioids*	Staff administered intramuscular (IM) injections	• None noted	• Pain on injection • Tissue damage
	Staff administered intravenous injections	• Similar pain control to PCA	• Peak / trough opioid ADRs
	PCA without background infusion	• Improved pain scores vs. IM	• None noted
	PCA with background infusion	• Improved pain scores vs. IM	• Increased analgesic use vs. no background

* Examples of opioids include morphine, fentanyl, hydromorphone

PCA = Patient-controlled analgesia ADR = Adverse drug reaction

American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116:248-273.

Perioperative Techniques in Pain Management

Technique	Examples	Advantages	Disadvantages
Peripheral Regional Analgesia	Peripheral nerve blocks**	• Generally, improved pain relief and lower analgesic consumption compared to saline	• None noted
	Intraarticular blocks** or opioids*	• None noted compared to saline	• None noted
	Infiltration of incisions**	• Generally, improved pain relief and lower analgesic consumption compared to saline	• None noted

* Examples of opioids include morphine, fentanyl, sufentanil

** Examples of local anesthetics include bupivacaine, ropivacaine

American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116:248-273.

Perioperative Techniques in Pain Management

Technique	Examples	Advantages	Disadvantages
Non-opioid systemic analgesics	Acetaminophen (oral, rectal, injectable)	• Similar benefit to IV PCA opioid • Less ADRs	• None noted
	Injectable NSAIDS	• Improved pain scores • Reduced analgesic use	• NSAID risks / ADRs
	Oral NSAIDS (both non- and selective	• Improved pain scores	• NSAID risks / ADRs
	Gabapentenoids (both gabapentin and pregabalin)	When combined w/ opioids • Improved pain scores • Reduced analgesic use	• None noted

PCA = Patient-controlled analgesia ADR = Adverse drug reaction

NSAID = non-steroidal anti-inflammatory drug

American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116:248-273.

Multimodal Approaches: Evidence-Based Summary

- Acetaminophen – oral, single dose
  - Cochrane review*
    - 51 studies, 5762 patients, 3277 active, 2425 placebo.
      - 50% ↓ in pain with 50% APAP group, 20% placebo group for 4 hours
      - NNT based on dose:
        - APAP 500 mg: 3.5
        - APAP 650 mg: 4.6
        - APAP 1000 mg: 3.6
    - 50% of APAP and 70% of placebo needed additional analgesia
  - A systematic review** identified 21 studies comparing APAP alone or in combination with NSAIDS and reported increased efficacy with the combination of two agents than with either alone.

APAP = Acetaminophen NSAIDS = non-steroidal antiinflammatory drugs
NNT = Number needed to treat

*Toms L et al. Cochrane Database Syst Rev. Published Online: 8 OCT 2008

**Ong CK et al. Anesth Analg 2010;110(4):1170–1179

Multimodal Approaches: Evidence-Based Summary

- Acetaminophen – parenteral
  - Studied single dose, multiple dose over 24 hours compared to placebo
  - Orthopedic surgery, laminectomy, abdominal, gynecological, cardiac and thyroidectomy
    - Dosing: 1 gram IV, either single dose, or every 6 hours
  - Summary APAP patients:
    - Statistically significant shortened time to meaningful pain relief and in total relief compared to placebo.
    - Improved patient satisfaction with pain control, lower morphine consumption (up to 61%) and decreased incidence of vomiting.
    - No statistical significant difference in the rates of adverse events including liver function abnormalities compared to placebo.

APAP = Acetaminophen

Wininger SJ. Clin Ther. 2010;32:2348-2369.
Cakan T et al. J Neurosurg Anesthesiol. 2008;20:169-173
Mernis D. J Crit Care 2010;25:458-462
Macario A et al. Pain Pract 2011;11:290-296

Multimodal Approaches: Evidence-Based Summary

- Non-selective NSAIDS
  - Single dose oral ibuprofen* – Summary 72 RCTs, 9168 patients
    - ≥ 50% pain relief in approximately half of patients with moderate to severe postoperative pain, and adverse events were similar to placebo
  - Single dose oral aspirin** – Summary
    - ≥ 50% or greater reduction in pain in 39% of those with moderate to severe pain, compared with 15% of those in the placebo group.
    - The efficacy of aspirin was considered equivalent to that of acetaminophen.
    - Adverse events were statistically similar for those taking a lower aspirin dose, 600 mg to 650 mg, compared with placebo. However, patients who took 900 mg to 1000 mg experienced adverse events at more than twice the rate of patients receiving placebo (26% vs 12%). The most common events in the aspirin group were drowsiness, dizziness, nausea, vomiting, and gastric irritation.

RCT = Randomized controlled trials

*Derry C et al. Cochrane Database Syst Rev. Published Online Jan 2009
**Derry C et al. Cochrane Database Syst Rev. Published Online Jan 2012

Multimodal Approaches: Evidence-Based Summary

- Selective NSAIDS – Single dose Celecoxib
  - Cochrane review - 10 studies, 1785 patients
    - NNT for ≥ 50% decrease in pain over 4 to 6 hours:
      - Celecoxib 200 mg: 4.2
      - Celecoxib 400 mg: 3.4
    - Median time for rescue medication use:
      - Celecoxib 200 mg: 6.6 hours
      - Celecoxib 400 mg: 8.4 hours
      - Placebo: 2.3 hours
    - Proportion of patients requiring rescue medications:
      - Celecoxib 200 mg: 74%
      - Celecoxib 400 mg: 63%
      - Placebo: 91%
    - Adverse events mild to moderate in all groups with no difference in frequency

NNT = number needed to treat

Derry S et al. Cochrane Database Syst Rev. Published Online: 22 OCT 2013

Multimodal Approaches: Evidence-Based Summary

- Injectable NSAIDS
  - Ketorolac and ibuprofen studied in United States
  - Indicated for short-term moderate to severe acute pain that requires analgesia at the opioid level
    - Studies (variety of surgery types) with ketorolac[1,2] compared to placebo suggest patients received ketorolac:
      - Significant reduction in pain
      - Reduction in opioid consumption (~30%)
      - Facilitation of quicker recovery and rehabilitation
    - Studies with ibuprofen in orthopedic and abdominal surgery[3]
      - At 800 mg dose, reduced morphine use by 22% in first 24 hours
      - Significant reductions in pain at rest and with movement
      - No significant increases compared with placebo in adverse drug reactions

1. Cassinelli EH et al. Spine. 2008;33:1313-1317
2. Wong HY et al. Anesthesiology. 1993;78:6-14
3. Southworth S et al. Clin Ther. 2009;31:1922-1935

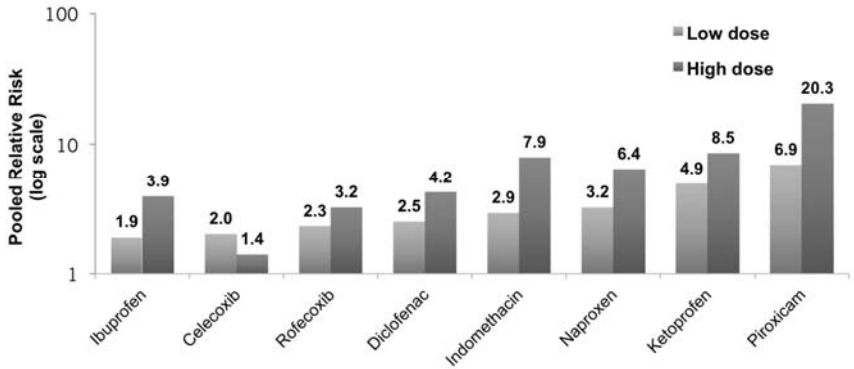
Safety decisions:

Acetaminophen: Watch your dosing

- Dosage limits:
  - Officially (FDA) - still at 4 grams per day
  - For at risk patients:
    - E.g. history alcohol use, Hepatitis, frail elderly
    - Dose reduction – 50% - 75%
  - Concerns:
    - Acetaminophen versus Tylenol – patient mix-ups
    - OTC products with "hidden" acetaminophen
    - Binge drinking / fasting
    - Combination acetaminophen-opioid products

GI Risk of Individual NSAIDs by Dose

- In a recent systematic review of observational studies, the risk of NSAID-induced GI events (perforations, ulcers, bleeds) was generally shown to be dose related



Reference: Castellsague J, et al. *Drug Saf.* 2012;35(12):1127-1146.

Graph adapted from Castellsague J, et al. 2012.

Risk Factors for Upper GI Adverse Event

- Age ≥ 75 RR = 3.7
- Cardiovascular disease RR = 2.7
- NSAID intolerance RR = 1.9
- Gastroduodenal ulcer RR = 3.1
- History of upper GI bleed RR = 3.4
- Aspirin use RR = 2.3
- Postive H pylori serology RR = 2.0
- Type of arthritis, duration of arthritis, alcohol use, tobacco use, anticoagulant use and sex of patient did not correlate as risk factor

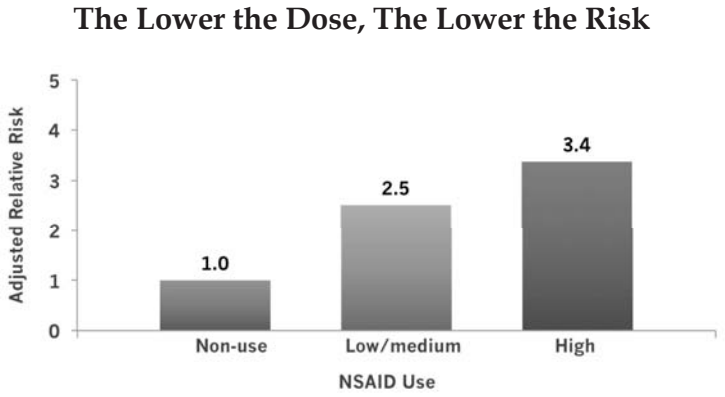
NSAIDs – Renal toxicities

- NSAIDs decrease perfusion of kidneys through vasoconstriction afferent arteriole
- Risk factors:
  - Pre-existing renal impairment
  - Heart failure
  - Cirrhosis
  - Volume depletion
  - Elderly
  - Concurrent diuretic therapy
  - Low sodium
  - Hypercalcemia

NSAID – Renal toxicities

- Minimizing the risk
  - Adequate hydration
  - Avoid in high-risk patients
  - Watch for drug-interactions (ACE inhibitors, multiple NSAIDs, diuretics)

The Risk of NSAID-Associated Acute Renal Failure (ARF) May be Dose-Related

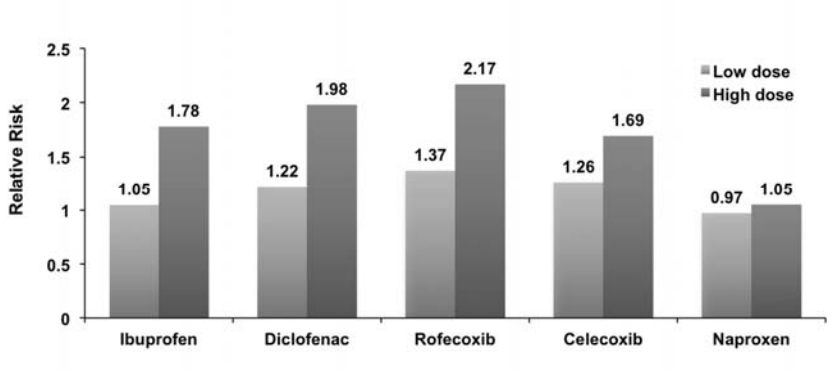


Reference: Huerta C, et al. *Am J Kidney Dis.* 2005;45(3):531-539.

Graph adapted from Huerta C, et al. 2005.

CV Risk of Individual NSAIDs by Dose

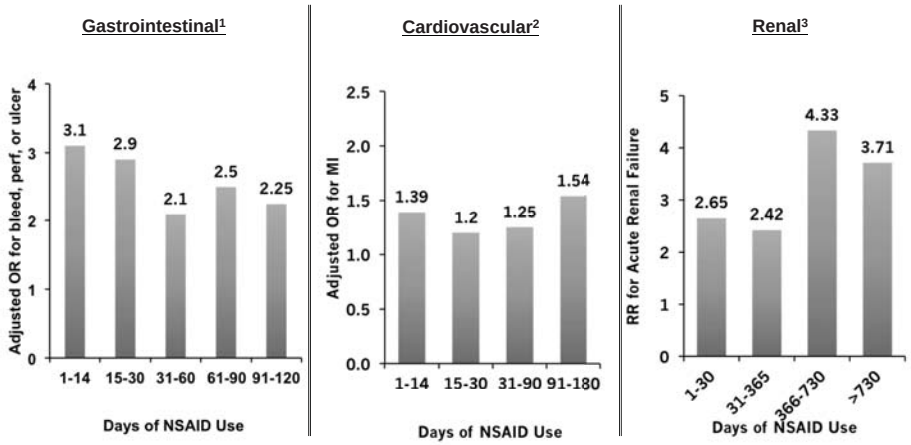
- In a recent systematic review of observational studies, the risk of NSAID-induced CV events (acute MI and strokes) was generally shown to be dose-related



Reference: McGettigan P, et al. *PLoS Med.* 2011;8(9):1-18.

Graph adapted from McGettigan P, et al. 2011.

Even Short Term Use Carries Risk



References: 1. Helin-Salmivaara A, et al. *Scand J Gastroenterol.* 2007;42(8):923-932. **2.** Helin-Salmivaara A, et al. *Eur Heart J.* 2006;27(14):1657-1663. **3.** Huerta C, et al. *Am J Kidney Dis.* 2005;45(3):531-539.

Graphs adapted from Helin-Salmivaara A, et al, 2007, Helin-Salmivaara A, et al, 2006, and Huerta C, et al. 2005.

Topical NSAIDS:
What is their role?

	FDA indications	Serum levels
Diclofenac epolamine patch1.8% (Flector®)	Acute pain due to contusions	Single application: C_{max} 0.7 – 6 ng/ml Continuous therapy one patch BID: C_{max} 1.3 – 8.8 ng/ml
Diclofenac sodium (Voltaren® gel)	Chronic pain due to OA	Continuous @ 4 gm gel QID C_{max} 15 ± 7.3 ng/ml Continuous @12 gm gel QID C_{max} 53.8 ± 32 ng/ml
Diclofenac topical (Pennsaid®)	OA of the knee	Single dose: (80 drops) C_{max} 8.1 ± 5.9 ng/ml Multiple dose: (80 drops QID x 7 days) C_{max} 19.4 ± 9.3 ng/ml
Diclofenac oral	Acute and chronic pain	ORAL dosing @ 150 mg / day C_{max} 2270 ± 778 ng/ml

Efficacy of Antidepressants (NNT)
(Number needed to treat to obtain one patient with > 50% pain relief)

	Painful polyneuropathy	Post-herpetic neuralgia	Central Pain	Neuropathic pain (general)
TCA antidepressants	2.1 (A, I) 2.5 (D, N)	2.6 (A, N)	4.0	3.1
SSRI antidepressants	6.8	No RCTs	No RCTs	6.8
Venlafaxine	4.6	2.7	No RCTs	5.5
Duloxetine	4	4	No RCTs	No RCTs

TCA = tricyclic antidepressants (A = amitriptyline, I = imipramine, D = desipramine, N = nortriptyline)

EFNS Task Force Euro J Neuro 2006;13:1153-1169
Finnerup NB et al Pain 2005;118:289-305
Cochrane database reviews 2007;4:CD005454

Efficacy of Anticonvulsants (NNT)
(Number needed to treat to obtain one patient with > 50% pain relief)

	Painful poly-neuropathy	Post-herpetic neuralgia	Central Pain	Trigeminal neuralgia	HIV sensory neuropathy	Neuropathic pain (general)
Carbamazepine	2.3	no RCTs	3.4 (NS)	1.8 (efficacy ↓ over time)	No RCTs	2.0
Valproic acid	2.5	2.1 (one study)	NS	No RCTs	No RCTs	2.8
Topiramate	7.4 (3 studies NS)	No RCTs	No RCTs	No RCTs	No RCTs	7.4
Gabapentin	3.8	3.2	Effective, unknown NNT	No RCTs	No RCTs	5.1
Lamotrigine	4.0	No RCTs	NS	2.1	5.4	4.9
Pregabalin	4.2	4.9	Effective, unknown NNT	No RCTs	No RCTs	Effective, unknown NNT

EFNS Task Force Euro J Neuro 2006;13:1153-1169
Finnerup NB et al Pain 2005;118:289-305
Cochrane database reviews 2005;3:CD001133

NS = results did not demonstrate statistical significance

Should we be fearful of managing pain with opioids?

What is the Role of Opioids in Acute Pain

- The state of the art is multimodal therapy with:
  - Non-steroidal anti-inflammatories (NSAIDs)
  - Acetaminophen (APAP)
  - Local anesthetics
    - Wound site infiltration or perfusion
    - Peripheral nerve infusions via catheters
    - Epidural
    - Intravenous PCA
    - Pre-peritoneal catheters
  - Opioids
    - intravenous (IV)
    - intraspinal (IS)
    - oral route

ASA Task Force on Acute Pain Management. Anesthesiology 2012; 116:248

Beware and Be Aware:
Prescribing Opioids for Acute Pain

- Oregon Guidelines:
  - Lowest effective dose of short-acting, immediate-release
  - No greater quantity than needed for expected duration of pain
    - Three days or less will often be sufficient
    - More than 7 days will be rarely needed
- There can be a rapid shift to long-term opioid use after the initial prescription of an immediate-release opioid:
  - Opioid dependence can begin within days
  - One year later:
    - 1 day's supply ➔ 1 year later 6 % taking opioid
    - $\geq$ 8 day's supply ➔ 1 year later 13.5% taking opioids
    - $\geq$ 31 day's supply ➔ 1 year later 29.9% taking opioids

Beware and be aware:
Prescribing Opioids for Acute Pain

- > 2/3rds of surgery patients end up with leftover opioids and do not get rid of them
  - 75% of patients do not store unused medication in locked cabinets
- Taking opioids before surgery can raise pain later
- Seven-fold spike seen in opioid-linked fatal car crashes
- Half of opioid prescriptions are prescribed to people with mental illnesses

Beware and be aware:
Prescribing Opioids for Acute Pain

- Deadly combinations:
  - Opioids + alcohol = enhanced respiratory depression, especially in geriatric population
  - Opioids + benzodiazepines = death due to lowered threshold for over-dosage, and drug-drug metabolism inhibition by the benzodiazepine of the opioid
- Street value – medications transferred into hands of opioid naïve or teens
- Ease of manipulation for nasal and injection abuse

Four Risks of Prescribing Opioids for Chronic Pain

- Deterioration of functioning / increasing pain
- Misuse, abuse, diversion
- Over-dosage
- Significant side effects

Hyperalgesia

- Thought to involved NMDA receptor activation → sensitization of pronociceptive pathways
- Characterized by patients who once responded to an opioid and in spite of being on a stable doses for a period of time now have increased pain sensitivity

1. Chang G, Chen L and Mao J. Opioid tolerance and hyperalgesia. Med Clin N Am 2007;91:199-211.
2. Angst MS and Clark JD. Opioid-induced hyperalgesia. A qualitative systematic review. Anesthesiology 2006;104:570-587.

Opioid-induced Hyperalgesia (OIH)

- Two forms of OIH can be distinguished
  - All can result in either: Increased sensitivity to pain; aggravation of pre-existing pain; or, expression of novel pain symptoms.
  - OIH_1: Very high and escalating doses of opioids
    - Usually implicated with high doses of morphine or hydromorphone
    - Severe allodynia, myoclonus noted
    - Thought to be due to metabolites inhibiting glycineric inhibition at spinal cord level inducing a strychnine-like excitatory intoxication.
  - OIH_1: Opioid maintenance therapy
    - Involves up-regulation of pain facilitating neuronal pathways at multiple levels of the central and peripheral nervous system
    - Stimulation of excitatory amino acid neurotransmitter system.

Angst MS and Clark JD. Opioid-induced hyperalgesia. A qualitative systematic review. Anesthesiology 2006;104:570-587.
Davis MP, Shaiova LA, Angst. When opioids cause pain. J Clin Oncol 2007;25:4497-4498.

Prevention Strategies Opioid-Induced Hyperalgesia

- Use of adjuvant therapies for "opioid sparing" effect
  - ✓ Anticonvulsants
  - ✓ Antidepressants
- Opioid rotation
  - ✓ To take advantage of "incomplete cross tolerance"
  - ✓ To avoid toxic metabolites
- Combination of opioid and low-dose mu receptor antagonist (e.g. buprenorphine and naltrexone)
- Blockade of the NMDA receptor (e.g., ketamine)

Silverman SM. *Pain Physician.* 2009;12(3):679-684.

Misuse, abuse and diversion

- Misuse
  - Using opioid for purposes other than intended
    - Depression, sleep, anxiety, constipation pain, euphoria, “party time”
- Abuse
  - Manipulating the opioid delivery system, or using the opioid at a higher than prescribed dose to attempt to obtain a faster onset, or greater euphoria
  - FDA definition: “Intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect”
- Diversion
  - Selling/giving/buying a portion of a prescription to/from another person
  - Stealing medication from a friend/relative/stranger

Methods of abuse

- Crush/grind/grate
- Mastication
- Intravenous injection
- Nasal insufflation
- Inhalation by vaporization
- Ethanol co-ingestion
- Multiple oral dose administration
- Heating/microwaving
- Freezing
- Solvent extraction

Current ER Opioids with ADT

(in order of date of FDA approval)

Opioid Product	Description of technology
Embeda®	Addition of sequestered naltrexone – designed to release antagonist if crushed, and then intravenously
OxyContin®	Resistec polymer matrix – designed to be plastic-like, hard to break, becomes gel in water, thus
Opana®	INTAC polyethylene oxide matrix – designed to render tablet highly resistant to crushing; when difficulty drawing into a syringe.
Nucynta®	Polyethylene oxide matrix – designed to render tablet highly resistant to crushing or extraction
Exalgo®	OROS technology - osmotically active bilayer core enclosed in a semipermeable tablet shell active drug extraction
Targiniq®	Addition of naloxone – designed to block the euphoric effect if its crushed and then snorted, or intravenously.
Hysingla®	Resistec polymer matrix – designed to be plastic-like, hard to break, becomes gel in water, thus
Zohydro®	BeadTek formulation – designed to make it hard to crush and snort.
Xtampza®	DETERx microsphere technology – manipulation resistant, has no FDA warnings regarding
Troxyca®	Addition of sequestered naltrexone – designed to release antagonist if crushed, and then intravenously

Mythology of ADT Technology

- Prevents abuse/misuse/diversion
- All ADT technology is the same
- All ADT technology is fail-safe
- ADT technology has been proven to decrease addiction, abuse, over-dosages, misuse, diversion, etc.
- ADT technology alone will ensure that my patients will not misuse, abuse or divert their opioids
- ADT technology ensures the best pharmacokinetics of the opioid delivery system.

Overdosing with Opioids…

- Inadvertent patient errors
  - Chewing, breaking, crushing ER opioids
- Wrong dose/delivery system in opioid-naïve patients
- Wrong conversions in dosing

Potential reasons for Inadvertent Over-dosages with Extended-Release (ER) Opioids

- Patient error
  - Misread dose or dosing instructions
  - Chew, split, break or crush ER formulation for ease of swallowing
  - Food / alcohol interactions and/or dose dumping
- Patient not opioid tolerant
- Wrong conversions
- In appropriate use of Fentanyl products
- Methadone

Short-Acting Fentanyl Products

- Indication: management of breakthrough pain in adult cancer patients who are already receiving and are tolerant to opioid therapy
- Contraindications include:
  - Acute pain, post-op pain, dental pain, migraines
- May be dispensed only to patients enrolled in the transmucosal immediate release fentanyl (TIRF) REMS Access program @ www.TIRFREMSaccess.com
- Do NOT interchange products without first starting over at the LOWEST dose available of the new product
- Limit use of TIRF medications to 4 or fewer doses per day.

Checklist for Appropriate Use of Transdermal Fentanyl

✓ Patient should not be cachectic or edematous or sweaty.

***(remember fentanyl is lipophilic, doesn't pass easily through aqueous media)*

AND

✓ Patient should not be running fevers or putting a heat source (pads, water beds, etc) directly on or near the transdermal patch

**(remember heat dramatically speeds up transdermal delivery of drug)

AND

✓ Patient's pain should be relatively stable.

***(remember fentanyl has a lag time of 16-24 hrs to absorb)*

AND

✓ Patient has pain described as "moderate" or "severe" and is not opioid naive.

***(remember even the lowest size patch is "worth" ≥ 30 mg oral morphine per day)*

AND

✓ Patient cannot tolerate oral therapies

***(remember sustained-release oral morphine provides greater consistency in serum opioid levels)*

Side Effects from Opioids

- CNS toxicities
  - Dysphoria, euphoria, agitation, disorientation
  - Sedation
- Gastro-intestinal
  - Nausea / vomiting
  - Constipation (Opioid-Induced Constipation = OIC)
- Respiratory depression
- Hypersensitivity, itching
- Urinary retention
- Myoclonus

Summary Opioid Induced Constipation (OIC)

- PAMORAs represent a new class of medication specifically designed to antagonize the opioid at the bowel level with negligible penetration to the CNS
  - Typically will be effective in patients with failure to other laxatives
- Most common side effects in the studies included abdominal pain (usually mild to moderate), diarrhea, nausea, flatulence.
- Two currently FDA approved:
  - Methylnaltrexone (SQ & oral) - Relistor®
  - Naloxegol (oral) - Movantik®

Discharge Communications: “Nevers” while on Opioids

- Drink alcohol while on opioids
- Drive while on opioids
- Crush, chew, snort, smoke, pulverize, inject, etc. long-acting / extended-release (LA/ER) opioid products
- Use an external heat source on transdermal opioids
- Cut, tear, rip open transdermal opioid patches
- Share with a friend or relative any of your opioid products
- Take more medication than your physician has prescribed
- Take illicit and/or non-prescribed drugs while on opioid medications
- Brag to neighbors, friends, relatives about being on LA/ER/IR opioids

Discharge Communications: “Always” while on Opioids

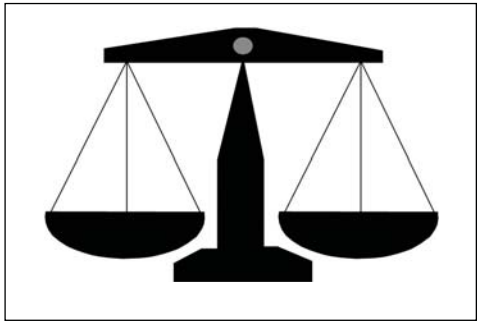
- Store medication in a safe (preferably locked) place
- Keep opioids away from children, teens
- Adhere to the instructions listed on the prescription
- Adhere to your medication agreement
- Properly dispose of unused medications
- Ask your pharmacist or physician FIRST if you are planning on taking any OTC medication or herbal/vitamin product while on LA/ER/IR opioids
- Call 911 if you experience shortness of breath orhave difficulty breathing while on LA/ER/IR opioids

Balancing Medication Use in Patients

√ Non-pharmacological strategies

√ Pain control

√ Comfort level



√ Improving overall function

√ Minimizing side effects

√ Medical / legal guidelines for opioid use

√ Ethical issues