

Advanced Concepts in Pain Control

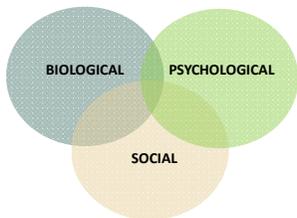
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Objectives

- Discuss key components of a comprehensive pain assessment
- Describe pharmacologic strategies used to manage pain, including risks, benefits, and essential principles to provide safe and effective use
- List nonpharmacologic techniques that can be integrated into the plan of care

Pain

- Pain is an unpleasant sensory and emotional experience, associated with actual or potential tissue damage
Merskey, 1979



Pain assessment is more than a number!

Those at Risk for Inadequate Assessment

Infants and children	Elderly - > 65 years of age	Cognitively impaired	Nonverbal individuals
People with mental health disorders	Minorities	Female gender	Good performance status
Non-English speaking	Long-term survivors	Socio-economically disadvantaged	Uninsured
Those with current or past substance use disorders			

Assessing Pain & Pain Relief

- Onset
- Location
- Duration
- Quality
- Intensity
 - Use rating scale
- Type of pain or pain syndrome
- Aggravating/alleviating factors

Assessment *cont'd*

- Effects of pain on the person, level of function and quality of life
- Current medications and schedules
- Previous treatment and outcomes
- Pain language and manner of expression
- Patient concerns or worries
- Patient goals for pain care
- Document assessment findings

Nociceptive versus Neuropathic Pain

Nociceptive Pain

- Physiologic pain
 - Sometimes called inflammatory pain
- Normal processing of noxious stimuli by intact nociceptors and nerves
 - Visceral pain
 - Somatic pain

Neuropathic Pain

- Pathophysiologic pain
- Results from damage to the central or peripheral nervous system

Framework for Assessment: Hierarchy of Pain Measures

1. Self report: Single most reliable
2. Behaviors, e.g., cry, grimace, moaning, guarding, change in activity
 - Surrogate report of behaviors
3. Physiologic measures, e.g., ↑ HR, BP
4. Presence of a pathologic condition or procedure that usually causes pain; assume pain present (“APP”)

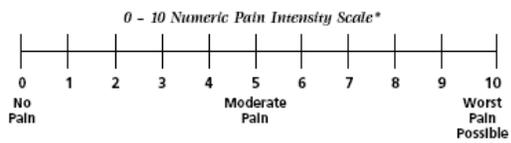
Assume Pain is Present

1. Unresponsive patients with underlying pathology thought to be painful (e.g., surgery, intubation, cancer).
2. Patients undergoing painful activities or procedures (e.g., turning, PT, wound care, ambulation) who are premedicated with the goal of preventing pain.
 - Document pathology or activity.

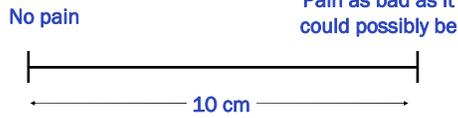
The Nature of Pain

Personal, subjective, unverifiable

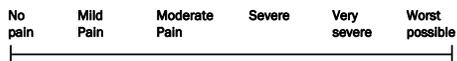
Numeric Pain Rating Scale (NRS)



Visual Analogue Scale (VAS)

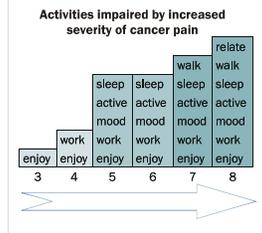


Simple Verbal Descriptor Scales



Pain Intensity and Functional Interference

- As pain intensity increases, so does the degree of functional interference
- The figure on the right shows the relationship in persons with cancer pain
- Studies of patients with AIDS and chronic noncancer pain show similar interferences with function with increasing pain.



Cleeland C and Wang S (1999) Oncology NCCN Proceedings

Challenges in Assessment

- Any patient who cannot report pain using customary self-report methods
 - Premies, infants, toddlers
 - Cognitively impaired
 - Anesthetized, sedated
 - Unconscious, intubated
 - Semi-comatose, comatose

Challenges in Assessment

- Apply the Hierarchy of Pain Assessment Measures:
 - **First Step:** Assess ability to provide self-report.
 - **Second Step:** Use behavioral pain assessment tools if appropriate.
 - **Third Step:** Assume pain is present.

Neonatal Pain, Agitation & Sedation Scale (N-PASS for NICU)

Criteria	Sedation		Sedation/Pain	Pain / Agitation	
	-2	-1	0/0	1	2
Crying Irritability	No cry with painful stimuli	Moans or cries minimally with painful stimuli	No sedation/ No pain signs	Irritable or crying at intervals Consolable	High-pitched or silent-continuous cry Inconsolable
Behavior State	No arousal to any stimuli No spontaneous movement	Arouses minimally to stimuli Little spontaneous movement	No sedation/ No pain signs	Restless, squirming Awakens frequently	Arching, kicking Constantly awake or Arouses minimally / no movement (not sedated)
Facial Expression	Mouth is lax No expression	Minimal expression with stimuli	No sedation/ No pain signs	Any pain expression intermittent	Any pain expression continual
Extremities Tone	No grasp reflex Flaccid tone	Weak grasp reflex ↓ muscle tone	No sedation/ No pain signs	Intermittent clenched toes, fists or finger splay Body is not tense	Continual clenched toes, fists, or finger splay Body is tense
Vital Signs HR, RR, BP, SaO₂	No variability with stimuli Hypoventilation or apnea	< 10% variability from baseline with stimuli	No sedation/ No pain signs	↑↑ 10-20% from baseline SaO ₂ 75-85% with stimulation - quick recovery ↑	↑↑ 20% from baseline SaO ₂ ≤ 75% with stimulation - slow recovery ↑ Out of sync with vent

Neonatal Infant Pain Scale (NIPS for Healthy Neonates)

PARAMETER	0 POINTS	1 POINT	2 POINTS
Facial Expression	Relaxed	Grimace	_____
Cry	No cry	Whimper	Vigorous crying
Breathing Patterns	Relaxed	Change in breathing	_____
Arms	Relaxed	Flexed/stretched	_____
Legs	Relaxed	Flexed/stretched	_____
State of Arousal	Sleeping/calm Awake/calm	Fussy/uncomfortable	_____

FLACC for Preverbal to 5 years

CATEGORIES	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or talking to, distractible	Difficult to console or comfort

Cognitively Impaired Adults

- Insure eyeglasses are on and hearing aids are functioning.
- Ask about pain in the present.
- Repeat question more than once and allow time to respond.
- Try to obtain self-report.

Checklist of Nonverbal
Pain Indicators (CNPI)

- Behavioral pain score range: 0 – 6
- Facial grimacing or wincing 0-1
 - Vocal complaints (words) 0-1
 - Nonverbal vocalizations (sounds) 0-1
 - Bracing or guarding 0-1
 - Restlessness: Constant or intermittent 0-1
 - Rubbing: Massaging affected area 0-1

Pain Assessment in Advanced Dementia
(PAINAD) Scale

- Behavioral score range: 0 – 10
- Breathing: Normal → Noisy, labored 0 - 2
 - Neg vocalization: None → Crying 0 - 2
 - Facial expression: Smile → Grimace 0 - 2
 - Body language: Relaxed → Pushing 0 - 2
 - Consolability: No need → Unable to 0 - 2

Critical-Care Pain Observation Tool
(CPOT)

Score Range: 0 (no pain) – 8 (worst pain)

- Facial: Relaxed → Grimace 0 – 2
- Body movements: None → Restless 0 – 2
- Muscle tension: Relaxed → Very tense 0 – 2
- Ventilator: Tolerating → Fighting 0 – 2 or
- Vocalization: Normal → Crying out 0 – 2

Physical Exam

- Look for a cause of pain, if possible
 - ▣ Observe the site for inflammation or infection
 - ▣ Note and rebound or referred pain
 - ▣ Palpate for trigger points
 - ▣ Observe effects of weight bearing
 - ▣ Note skin color, warmth, irritation, integrity
- Look for de-conditioning with persistent pain
- Watch the person move
 - ▣ notice gait changes or other abnormalities
- Look for subtle changes in behavior or function

Underlying Principles

- Behavioral score ≠ pain intensity rating
- If a patient cannot express intensity of pain, the exact intensity is unknown
- Perform an analgesic trial to determine the presence of pain, or assume and treat appropriately
- Begin with recommended starting doses and increase based on response, or maintain at starting dose if no response

Pharmacologic Management

- Non-opioids
 - ▣ Acetaminophen
 - ▣ NSAIDs
- Opioids
- Adjuvants
- Disease modifying therapies
 - ▣ Arthritis
 - ▣ Cancer
 - ▣ Headache

Pharmacologic Management

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Acetaminophen (APAP)

- Analgesic, antipyretic, not an anti-inflammatory
- Few if any side effects at therapeutic doses
- Hepatotoxic at high dose
 - ▣ Use caution with opioid combination drugs
 - ▣ Those with alcoholic misuse at special risk

NSAIDs

- Analgesic
- Antipyretic
- Anti-inflammatory

- Non-selective NSAIDs decrease platelet aggregation; selective COX-2 inhibitors should not because there is no COX-2 in platelets
- Affect uterine contractility

NSAIDs

- No NSAID is superior to the others as an analgesic/anti-inflammatory
- If one fails, try another
- Different potencies and durations of action
- Consider half-life, dosage regimen, toxicity, cost
- Aspirin, ibuprofen, naproxen and ketoprofen are available without a prescription

Adverse Effects of NSAIDs

- GI tract – upper and lower gut: risk of GI bleed reduced 50% with a COX-2 inhibitor for first 6 months, but not if taking low dose aspirin
- Kidney – risk with both classes: fluid retention, increase in BP, renal failure
- “Hypersensitivity” reactions: aspirin-sensitive asthma with non-selective NSAIDs
- Platelets – only COX-1 inhibitors
- CNS Effects – changes may be subtle

Pharmacologic Therapy

- Non-opioids
- Opioids
- Adjuvants

Opioids

- Buprenorphine
- Codeine
- Fentanyl
- Hydrocodone
- Hydromorphone
- Methadone
- Morphine
- Oxycodone
- Oxymorphone
- Tapentadol
- Tramadol

Classes of Opioids

- Full agonists: morphine
- Partial agonists: buprenorphine (Buprenex®)
- Mixed agonist-antagonists: nalbuphine (Nubain®), butorphanol (Stadol®)
- Antagonists: naloxone (Narcan®), naltrexone
- Tramadol (Ultram®)– a “binary” analgesic
 - Inhibits the reuptake of NE and 5-HT
 - Is an opioid agonist

Morphine

- Morphine is the gold standard, the drug against which other opioid agonists are compared ... but it is not the right drug for everyone
- Variety of formulations:
 - Immediate release tablets – 15, 30 mg
 - High concentration liquid – 20 mg/mL
 - Extended release – 15, 30, 60, 100, 200 mg
 - Suppository
 - Parenteral

Morphine

- Morphine has active metabolites: M-6-G can accumulate with impaired renal function
- Side effect profiles may be different
- Equianalgesic dosing:
 - 10 mg parenteral (IV, SQ, IM) ~ 30 mg oral

Codeine

- Codeine
 - ~10% of codeine is metabolized to morphine by CYP 2D6
 - 7-10% of Caucasians poor metabolizers, 1-7% and 25% of Ethiopians ultra rapid metabolizers
 - practical dose ceiling of 65-100 mg, above that, side effects become limiting

Hydrocodone

- A variety of combination products are available, most with APAP, three with ibuprofen
 - Lortab, Norco, Vicodin – with APAP
 - Vicoprofen – 7.5/200 mg ibuprofen
 - Hycodan – with homatropine (liquid – for cough)
- Hydrocodone is now Schedule II of the Controlled Substances Act
- Extended release formulation
 - Hysingla – 20, 30, 40, 60, 80, 100, 120 mg once daily
 - Zohydro – 10, 15, 20, 30, 40, 50 mg q 12 hours

Hydromorphone

- Pharmacological effects essentially identical to those of morphine
- More potent
- No active metabolites?
- Available in short-acting formulations
 - 2, 4, and 8 mg doses of hydromorphone
 - Liquid 1 mg/mL
 - Suppository 3 mg
- Available in parenteral formulations
- Hydromorphone is available in ER form (Exalgo®) for once daily dosing: 8, 12, 16, 32 mg

Oxymorphone

- Pharmacological effects essentially identical to those of morphine
- More potent
- No active metabolites?
- Available in short-acting formulations
 - 5 and 10 mg doses
- Oxymorphone is available in an extended release form (Opana ER®) for twice daily dosing: 5, 10, 20 and 40 mg tablets
- Food and alcohol affect the absorption of oxymorphone from the extended release formulation

Oxycodone

- Oxycodone
 - Short-acting tablets – alone, with APAP or ibuprofen
 - Liquid – high concentration 20 mg/mL
 - ER formulation – OxyContin 10, 20, 30, 40, 50, 60, 80 mg

Fentanyl

- Fentanyl is very lipid soluble, very potent, μg rather than mg doses
- Available for IV, transmucosal and transdermal
 - ▣ Transmucosal immediate release fentanyl – TIRF REMS – risk evaluation mitigation strategy
- Transdermal patch delivery system
 - ▣ Conversion: divide 24 h morphine dose by 2 to get the approximate patch dose

Methadone

- Benefits
 - ▣ Cheap
 - ▣ Useful in neuropathic pain?
 - ▣ Prevents opioid hyperalgesia? (NMDA receptor antagonist)
- Challenges
 - ▣ Long and unpredictable half-life
 - ▣ Prolongation of the QT interval
 - ▣ Drug-drug interactions (especially 3A4)
 - ▣ Equianalgesic dosing uncertain
- Methadone-related deaths increasing

Buprenorphine

- Suboxone
 - ▣ Buprenorphine/naloxone
 - ▣ Oral tablets, SL strips, SL tabs
- Subutex
 - ▣ Buprenorphine SL tabs
- Buprenorphine – partial agonist
 - ▣ Blocks pure agonist
 - ▣ Patient on buprenorphine who comes in after MVA needing pain control – high doses of pure agonist may be needed

Tramadol (Ultram®)

- Dual mechanism - μ -opioid agonist, blocks reuptake of NE and 5-HT
- Active metabolite
- Analgesic ceiling
- Nausea, confusion, dizziness
- Can lower seizure threshold
- Short-acting formulation – 50 mg alone or 37.5mg +325 mg APAP
 - Maximum of 400 mg
- Ultram ER® – once daily dosing
 - 100, 200, 300 mg doses
 - Increase the dose by 100 mg every 3-4 days to a total of 300 mg if needed and tolerated

Tapentadol

- Opioid antagonist and NE selective reuptake inhibitor (weak 5-HT inhibitor)
- Immediate release – Nucynta – 50, 75, 100 mg
- Extended release – Nucynta ER – 50, 100, 150, 200, 250 mg

Meperidine (Demerol®)

- Only a 2-3 hour duration of action
- 300 mg PO = 10 mg IV morphine
- Metabolite, normeperidine, has a longer duration of action, is excreted by the kidney, is a CNS stimulant: tremors, twitches, seizures
- Restrict meperidine to short procedures
- No evidence that efficacy enhanced by Vistaril® or Phenergan®
- It does not have less effect on the sphincter of Oddi

Opioid Dosing

- Effective dosing requires knowledge of time to peak effect
 - Immediate release oral agents – 60 minutes
 - IV – 15 minutes (except fentanyl)
 - SQ – 30 minutes
- Effective pain control with opioids requires titration of the dose
 - Increase by % of current dose
 - mild pain: 25-50% increase
 - moderate to severe: 50-100% increase

Opioid Side Effects

- Constipation
- Sedation
- Psychomotor and cognitive impairment
- Nausea and vomiting
- Pruritus
- Respiratory depression
- Delirium
- Hormonal changes
- At high dose, myoclonus and hallucinations

Therapeutic Advances in Pain

- Non-opioids
- Opioids
- Adjuvants
 - Antiepilepsy drugs
 - Antidepressants
 - Corticosteroids
 - Local anesthetics
 - NMDA receptor antagonists
 - Cannabinoids

Antiepileptic Drugs

- First generation
 - ▣ Older drugs such as carbamazepine (Tegretol®) and phenytoin (Dilantin®)
- Second generation
 - ▣ Gabapentin and now pregabalin most used
 - ▣ Greater tolerability, fewer drug-drug interactions, new mechanisms of action

Gabapentin (Neurontin®) and pregabalin (Lyrica®)

- Blocks $\alpha_2\delta$ subunit of voltage-dependent calcium channel; reduce influx of Ca^{++} , less glutamate released from nerve endings
- Not metabolized, few drug interactions, monitor kidney function
- Possible role in managing postop pain?
- Significant antianxiety effects

Antidepressants

- Tricyclics – differ in side effect profiles
- SNRIs: Non-tricyclic dual reuptake inhibitors
duloxetine and venlafaxine (dual reuptake inhibitors)
- SSRIs
 - ▣ Not proven effective against NP
 - ▣ Effective antidepressants
- Others (sometimes called atypical drugs)
 - ▣ Include bupropion, mirtazapine, nefezodone
 - ▣ Limited evidence of efficacy
- Caution when using with tramadol!

Antidepressants: TCA

- Most studied agent, amitriptyline, has most anticholinergic effects
- Alternate agents: nortriptyline, desipramine
- Usually sedating, administer at night
- Start low, titrate gradually every 2 or 3 days
- Prevent constipation

Antidepressants:SNRI

- Venlafaxine
- Mechanism: inhibits NE, 5HT, Dopamine reuptake
- Start low 37.5 – 75 po bid or tid; titrate gradually every 3 -4 days
- Take with food
- Reduce dose with hepatic/renal disorder

Antidepressants: SNRI

- Duloxetine (interaction with tamoxifen?)
- Mechanism: inhibits NE, 5HT, Dopamine reuptake
- 60 mg po daily – no benefit in increase to 60 mg bid
- Don't crush/cut/chew
- Reduce dose with renal disorder, may be contraindicated with hepatic impairment

Corticosteroids

- Dexamethasone has least mineralocorticoid effect
- All can product glucocorticoid effects
- Can be given orally, IV, SQ, epidurally
- May produce psychosis
- Long-term use can cause proximal muscle wasting
- Drug-drug interactions

Local Anesthetics

- Surgical or procedural site infiltration
- Single-shot blocks
- Continuous peripheral nerve blocks and wound infusions
- Epidural and intrathecal analgesia
- IV lidocaine infusion
- Topicals for procedural pain
- Topicals for neuropathic pain

Lidocaine (5%) Topical Patch

- Post herpetic neuralgia, neuropathies, low back and neck pain, migraines, variety of acute, postop, and persistent (chronic) pain conditions
- Analgesic, not anesthetic; minimal systemic absorption (3%) and side effects
- Cut and apply directly to intact painful site; up to 4 patches, up to 24 hours

Local Anesthetics

- Topical
 - EMLA® Cream – eutectic mixture local anesthetic (lidocaine and prilocaine)
 - LMX – lidocaine OTC
 - Lidoderm® patch
- Intravenous
- Epidural/intrathecal

Muscle Relaxants: But Are They?

- Benzodiazepines possibly effective
- Other so-called “centrally acting” muscle relaxants: very limited or inconsistent data relating to their efficacy
 - Methocarbamol (Robaxin®)
 - Chlorzoxazone (Panaflex®)
 - Metaxalone (Skelaxin®)
 - Cyclobenzaprine (Flexeril®)
 - Carisoprodol (Soma®)

Bisphosphonates

(Not analgesics, for osteoporosis)

- Alendronate (Fosamax®, Fosamax Plus D®), risedronate (Actonel®, Actonel with Calcium®), ibandronate (Boniva®), zoledronic acid (Reclast®) [latter once-yearly IV injection]
- Studies show a significant reduction in vertebral fractures, thus less pain.
- Oral bisphosphonates poorly absorbed; must take after overnight fast while in an upright position along with 8 ounces of water.
- Many potential adverse GI effects, osteonecrosis of jaw?

Other Agents

- Clonidine and tizanidine are α_2 -adrenergic agonists that may be used by pain specialists to treat challenging pain problems
- Baclofen is a GABA_B receptor agonist that is used to treat spasticity and neuropathic pain
- Capsaicin cream
- Menthol may work at TRK8 (heat/cold) receptor

Cannabinoids

- CB₁ and CB₂ receptors
- Marinol (dronabinol) – THC
- Cesamet (nabilone)
 - Approved for CINV
- Sativex (nabiximols)
 - THC and cannabidiol (CBD) – CBD may moderate euphoric effects of THC
 - Oral spray approved in Canada for MS spasticity, neuropathic pain and cancer pain
 - In US approved only for clinical trials
 - May inhibit metastatic growth

Cannabinoids: Indications

- Glaucoma: Other standard treatments more effective
- Nausea: Suppresses nausea more than vomiting; can cause hyperemesis
- AIDS-associated anorexia/wasting: Data inconclusive
- Chronic pain: Various models of pain
- Inflammation: Induce apoptosis, inhibit cell proliferation, suppress cytokine (RA, Crohn's)
- Multiple sclerosis: Nabiximol – neuropathic pain, sleep, spasticity
- Epilepsy: Small survey +, animal models +, safety ?

Volkow ND, et al. Adverse health effects of marijuana use. *NEJM* 370;23:2219-27, 2014.

Nondrug Interventions

Physical Modalities

- Ice, heat, massage, TENS
- Acupuncture
- Physical therapy, hydrotherapy, functional restoration

Nondrug Interventions

□ Cognitive-behavioral Approaches

- ▣ Simple: Relaxation breathing, music, art, focusing, prayer, being present, providing information
- ▣ Complex: Imagery, meditation, humor, hypnosis, healing touch, biofeedback, virtual reality

Nondrug Interventions

□ Complementary therapies

- ▣ Acupuncture
- ▣ Aromatherapy
- ▣ Energy therapy
- ▣ Herbal therapy

Principles of Pain Management

Goals of Treatment

- Prevention
- Relief of pain
- Improved function
- Safety
- Prevent diversion

Quality of Pain: Treatment

Type of pain	Pharmacologic interventions
Somatic (nociceptive)	Non opioids <ul style="list-style-type: none">• Acetaminophen• NSAIDs Opioids
Neuropathic	Opioids (may require higher doses) Adjuvant analgesics <ul style="list-style-type: none">• Antiepileptics• Antidepressants• Corticosteroids• Local anesthetics• NMDA antagonists
Visceral	Opioids Corticosteroids Adjuvant analgesics?

Routes of Administration

- Oral
- Mucosal
- Rectal/ stomal
- Transdermal
- Topical
- Parenteral (IV, SQ)
- Spinal (epidural, intrathecal)
- Nasal

Avoid IM as much as possible

Equianalgesia

- Doses approximately equal to one another in ability to relieve pain
- Equianalgesic charts are not exact; just guidelines for starting dose
- Helpful when switching from one opioid to another or one route of administration to another

Equianalgesic Dose Chart

Opioid	IM, IV, SC	PO
Morphine	10	30
Hydrocodone	--	30
Hydromorphone	1.5	7.5
Meperidine	75	300
Oxycodone	--	20
Oxymorphone	1	10
Fentanyl	100 mcg	

Long-acting Opioids

- Fentanyl: Transdermal patch q 72 h
- Morphine: Morphine ER, MSContin, Oramorph q 12 h; Kadian and Avinza q 24 h
- Oxycodone: OxyContin q 12 h
- Oxymorphone: Opana ER q 12 h
- Hydromorphone: Exalgo q 24 h
- Hydrocodone: Zohydro q 12 h; Hsingla q 24 h
- Methadone: q 8 h oral dosing; long half-life; multiple drug interactions

Patient-Controlled Analgesia

- Multiple routes of administration
- Patients must be able to:
 - ▣ Understand the relationships between pain, pressing a button and pain relief
 - ▣ Use PCA equipment
- Allows patient to individualized dose

Renal Dysfunction and Opioids: Preparations Not Recommended

- Meperidine
 - ▣ Accumulation of normeperidine may cause seizures
- Codeine
 - ▣ Reported to cause profound toxicity, can be delayed, after small doses
 - ▣ Recommend codeine be avoided in patients with a Glomerular Filtration Rate (GFR) <30 mL/min
- Morphine
 - ▣ Not recommended for chronic use in renal insufficiency (GFR <30 mL/min) due to the rapid accumulation of active, nondialyzable neurotoxic metabolites. Avoid long-acting preparations; monitor closely for toxicity

Renal Dysfunction and Opioids: Use Preparations with Caution

- Oxycodone
 - ▣ Metabolized in the liver with 19% excreted unchanged in the urine
 - ▣ Reports of accumulation of both the parent compound and metabolites in renal failure resulting in CNS toxicity and sedation
- Hydromorphone
 - ▣ Does not substantially accumulate in hemodialysis patients
 - ▣ Active metabolite, hydromorphone-3-glucuronide, quickly accumulates between dialysis treatments but appears to be removed during hemodialysis
 - ▣ With careful monitoring, can be used safely in dialysis patients. However, it should be used with caution in patients with a GFR < 30mL/min who have yet to start dialysis or who have withdrawn from dialysis.

Renal Dysfunction and Opioids: Preparations Likely Safe

- Fentanyl
 - ▣ No active metabolites?
 - ▣ Very little pharmacokinetic data in end stage renal disease
 - ▣ Fentanyl not dialyzable due to high protein binding and a high volume of distribution
- Methadone
 - ▣ Has no active metabolites and limited plasma accumulation in renal failure due to enhanced elimination in the feces
 - ▣ It does not appear to be removed by dialysis



Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it is the only thing that ever has.

Margaret Mead
