

CANCER PAIN MANAGEMENT

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3 Teaching Goals

- Distinguishing pain mechanism guides your pain treatment options
 - Visceral Pain
 - Neuropathic Pain
 - Myofascial/Soft Tissue Pain
 - Bone Pain
- Utilizing long acting vs short acting opioids
- Choosing rational opioid doses

The Pain Problem: Cancer Pain Epidemiology

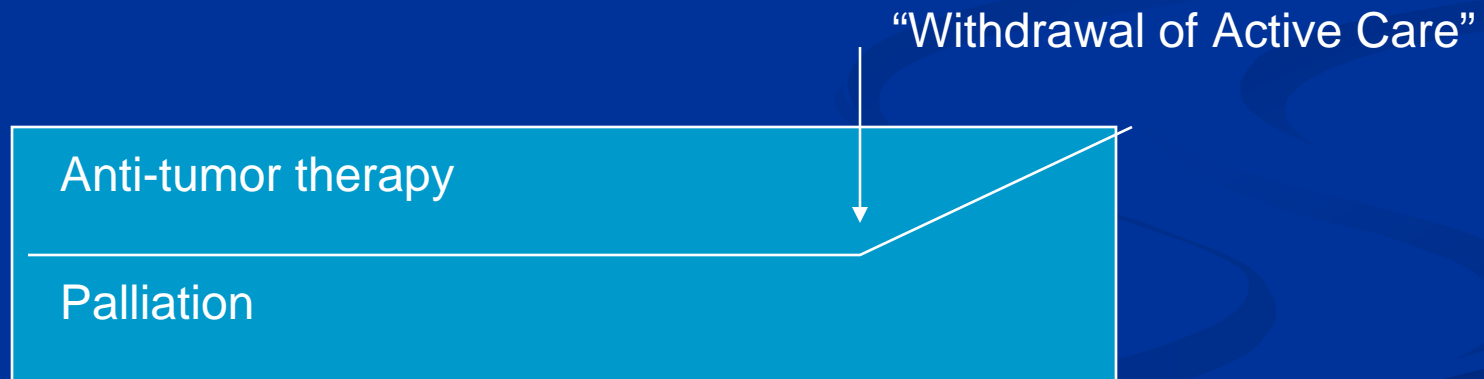
- Cancer Pain affects 15% of patients with localized disease , 30-40% in active treatment, and 60-90% of those with advanced disease
- Adverse effects on function, sleep, mood, immune factors, QOL
- Complex pathophysiologies
 - simultaneous nociceptive and neuropathic pain
 - co-exists with existential concerns, suffering
- Opioids are the pharmacologic mainstay but often suboptimal alone

Von Roenn 1993; Cleeland, 1994; LaRue 1995

Ideal Balance of Care: Palliation at all Phases of Illness



Contemporary Model for "Cure vs Care" Balance



Proposed Optimal Model for "Cure vs Care" Balance

Cancer Pain throughout the course of illness: Acute Treatment-Related

- Diagnostic procedural pain
- Post-operative pain
- Interventional pain
 - pleurodesis/catheters/embolizations
- Chemotherapy toxicity
 - mucositis/peripheral neuropathy/GCSF pain
- Radiotherapy toxicity
 - mucositis/enteritis/dermatitis
 - proctitis
 - myelopathy
 - avascular necrosis

Cancer Pain throughout the course of illness: Tumor related

- Visceral pain syndromes
 - hepatic distention
 - retroperitoneal disease
 - peritoneal carcinomatosis
 - bowel / ureteral obstruction
- Bone pain
 - Primary bone tumors
 - Bone metastases
- Neuropathic Pain
 - plexopathies/ paraneoplastic
- Soft tissue pain
 - cutaneous metastases
 - Sarcomas
 - Head and Neck Cancers

Cancer Pain throughout the course of illness: Chronic, Post-Therapy Cancer Pain Syndromes

- Post-Chemotherapy
 - Peripheral Neuropathy
- Post-surgical
 - mastectomy, neck dissection, thoracotomy, phantom limb, stump, pelvic floor
- Post-radiation
 - Plexopathies
 - Myelopathies
 - Enteritis/Proctitis
 - Acute
 - Chronic
 - Osteoradionecrosis

Assessment Outline

- Believe patient's report and rate pain (n/10 and descriptors)
- Take a careful history
 - site, referral, aggravating/relieving factors, impact on function
 - temporal aspects: acute, subacute, chronic, intermittent, breakthrough or incident
- List and prioritize pains
- Evaluate response to prior therapies (analgesic and antitumor)
- Evaluate psychological status and take a substance use history
- Focused physical exam
- Review available tests/imaging; form provisional pain diagnoses
- Initiate rational treatment regimen based on available data pending further workup
- Provide continuity of care/ review response to therapy

Barriers to Accurate Assessment

- Patient-related
 - Reluctance to report
 - Reluctance to follow recommendations
 - Fears of tolerance and addiction
 - Concerns about side effects
 - Beliefs that pain is inevitable and untreatable, or necessary
 - Fears: pain = progression

Wallace, J Pain Sx Mgmt 1995; Ward, Pain, 1993;
Zenz, Lancet 1993

Barriers to Accurate Assessment

- Physician-related
 - Knowledge deficits: assessment / treatment
 - Not “getting” or devaluing pt report
 - Fear of regulatory oversight
 - Fear of doing harm
 - Fear of litigation (now both for acts of omission and commission)

Larue, Cancer; 1995; Cherny, Cancer 1995; Elliot, J Pain Sx Mgmt 1995;

Mechanisms of Pain

- Visceral Pain
- Neuropathic Pain
- Bone Pain
- Myofascial/Soft Tissue Pain

MECHANISM OF PAIN: Visceral Pain

- Direct tumor effects (stretch, obstruct, erode)
- Post-therapy effects (adhesion, post-op dysmotility, radiation enteritis/proctitis)
- Hyperactivity (carcinoid/HIV/terminal obstruction)
- Spasm of hollow viscus
- Ischemia

MECHANISM OF PAIN: Neuropathic Pain

- Direct tumor invasion of nerve
- Extrinsic nerve root compression by bone, tumor, or soft tissue
- Chemo-, radiation-, or surgical nerve injury
- Phantom visceral or limb pains
- Paraneoplastic inflammatory poly/mononeuropathies

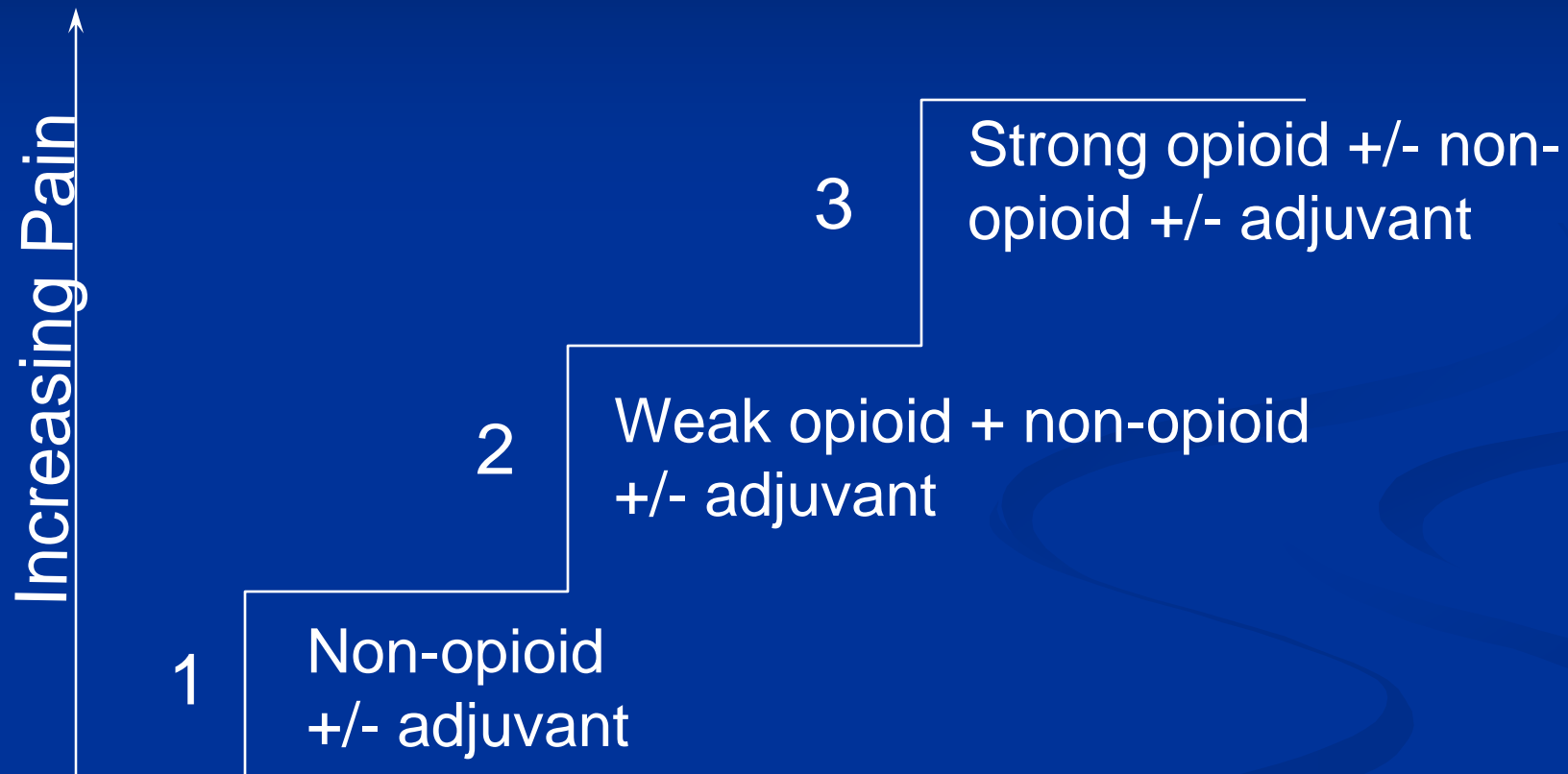
MECHANISM OF PAIN: Bone Pain

- Primary/metastatic tumor
- GCSF-pain
- Osteoporotic fracture
- Pathologic fracture
- Marrow replacement
- Avascular necrosis
- Osteoradionecrosis

MECHANISM OF PAIN: Myofascial Pain

- Soft tissue cancer growth
- Non-specific chemo/radiation side-effect
- Benign postural effects of compensating for sites of malignant pain (splinting)

TREATMENT OF PAIN: WHO ANALGESIC LADDER FOR CANCER PAIN



Jacox et al, 1994 (AHCPR Guidelines)

Mechanisms of Pain guides treatment

- ◆ Visceral Pain = opioids
- ◆ Neuropathic Pain = neuropathic pain meds +/- opioids
- ◆ Bone Pain = anti-inflammatory +/- opioids
- ◆ Myofascial/Soft Tissue Pain = opioids +/- other adjuvant pain meds

Common non-opioid analgesics

- Salicylates
 - Antiplatelet
 - Gastric irritant
- NSAIDS
 - Antiplatelet (except Celebrex)
 - Gastric irritant
 - Nephrotoxicity
- Acetaminophen
 - Hepatotoxicity (3000 - 6000 mg/day)
 - Compounded with weak opioids

Opioids

- Codeine (Tylenol with Codeine)
- Hydrocodone (Vicodin, Lortab)
- Meperidine (Demerol)
- Oxycodone (Percocet)
- Morphine (MSIR)
- Hydromorphone (Dilaudid)
- Methadone
- Fentanyl (Actiq, Fentora, patches)

Immediate-release Preparations

- Codeine
 - Tylenol #2,3,4 (15/300, 30/300, 60/300), elixers
- Hydrocodone
 - Vicodin, Lortab, Norco, Vicoprofen, elixers
- Oxycodone
 - Oxycodone, Percocet, Percodan, elixers
- Hydromorphone
 - Dilaudid (2, 4mg), elixers, suppositories
- Morphine
 - MSIR (15mg, 30mg), elixers, suppositories
- Methadone (5, 10mg)
- Fentanyl
 - Actiq oralette (200, 400, 600, 800, 1200, 1600mcg)
 - Fentora buccal tablets (100, 200, 400, 600, 800mcg)

Sustained-release Preparations

- Oxycodone
 - Oxycontin, Oxycodone SR
 - 10, 20, 40, 80 mg doses
- Morphine
 - MS Contin, Oramorph, Kadian, Avinza
 - 15 - 200 mg doses
- Fentanyl
 - Transdermal fentanyl patch, Duragesic patch
 - 12, 25, 50, 75, 100 mcg doses
- (Dilaudid)
 - Palladone
 - 12, 16, 24, 32 mg doses

Choosing Routes of Administration

- Absorption
 - GI Function
 - Degree of Cachexia
- Behavioral Aspects
 - Pt. Beliefs
 - Ability to adhere to Oral Regimen
 - Preferences / Conditioned Behavior
- Sheer opioid requirements

Immediate-release preparations

- For acute pain expected to resolve quickly
- For dose-finding in preparation for sustained-release regimen
- For “rescue” or “breakthrough” dosing as part of a SR/IR regimen
- For longer term management of patients at risk for toxic accumulation of opioid metabolites (eg, with hepatic or renal insufficiency / failure)

Reasons for Choosing Sustained Release Opioids

- Cancer Pain majority of time during waking hours
- Cancer Pain that disrupts night-time sleep
- Cancer Pain that requires q 4 hourly short-acting analgesics (constant catch-up)
- Cancer Pain that requires potentially organotoxic doses of compounded coanalgesics
- “Peak and Valley” side effects with short-acting drugs alone

Potential Benefits of Choosing Sustained Release Opioids

- Improved regimen adherence
- Lower mean pain ratings
- Sparing opioid mgs requirements/24hr periods
- Improved sleep
- Reduced pain-related disability
- Reduced CNS side effect burden with more consistent serum/CNS opioid levels
- Avoiding unnecessary / potentially toxic compounded co-analgesics

Managing Poor Opioid Responsiveness

- Reassess pain physiology (bone? neuropathic? Distress?)
 - Add targeted adjuvants to spare or enhance
- Reassess route of delivery (?absorption?)
- Reassess adherence/understanding
- Reassess goals/expectations/ratings (0/10?)
- Manage opioid side effects
- Rotate opioids
- Spinal opioids

Adjuvant Analgesics...

- enhance analgesic efficacy of opioids
- treat concurrent symptoms that exacerbate pain
- provide independent mechanisms of analgesia (thus may “spare” opioids)
- Types
 - Antidepressants
 - Anticonvulsants
 - Calcium Channel Blockers
 - Benzodiazepines
 - anti-arrhythmic/anesthetic
 - Anti-inflammatories
 - Corticosteroids
 - Bisphosphonates
 - NMDA antagonists

Neuropathic Pain Medications

- Anticonvulsants

- Neurontin, Lyrica, Topamax, Dilantin, Tegretol, Depakote

- Antidepressants

- Tricyclics, venlafaxine, duloxetine

- NMDA antagonists

- dextromethorphan, ketamine, methadone, memantine

- Anti-arrhythmic/anesthetic

- Mexiletine

Bone Pain Treatments

- NSAIDS
 - Ibuprofen, Celebrex, Naproxen, Torodol
 - Antiplatelet (except Celebrex), Gastric irritant, Nephrotoxicity
- Corticosteroids
- Bisphosphonates
- Radiation Therapy
- Strontium-89 and Samarium-153

Approach to cancer pain management

- ◆ Rational pain therapy is based on generating and testing clinical hypotheses about pain pathophysiology
- ◆ Cancer pain often represents multiple simultaneous mechanisms at play
- ◆ Multi-modal therapy is often necessary
- ◆ Lack of clinical response generally reflects problems with clinician's formulation of pathophysiology of pain

QUESTIONS??



Adjuvant Analgesics...

■ Antidepressants

- Most positive studies report on older cyclic compounds (IMI, AMI, DOX)
 - Tricyclic doses lower than “antidepressant” doses frequently produce analgesic augmentation
 - Start low (NTP 10; DMI 25; AMI 10) and go slow
- Cymbalta
 - norepinephrine / serotonin reuptake inhibitor
 - FDA approvals for Major Depressive Disorder (8/04) and Diabetic Peripheral Neuropathy (9/04)
 - Reduces non-neuropathic painful physical symptoms in depressive disorders

Adjuvant Analgesics...

■ Anticonvulsants

- Phenytoin *Dilantin*
 - 100-300 mgs/day
- Carbamazepine *Tegretol*
 - 100-200 mgs BID/TID
- Valproic Acid *Depakote*
 - 125-250 mgs BID/TID
- Clonazepam *Klonopin*
 - 0.5-1.0 mgs TID

Adjuvant Analgesics...

■ Newer Anticonvulsants

■ Lamotrigine

Lamictal

■ Gabapentin

Neurontin

■ Tiagabine

Gabapril

■ Oxcarbazepine

Trileptal

■ Levetiracetam

Keppra

■ Zonisamide

Zonegran

■ Topiramate

Topamax

Adjuvant Analgesics...

■ Anticonvulsants

■ Neurontin

- MOA: GABAergic; Ca⁺ channel blockade?
- **Most studied / most used modern anticonvulsant for neuropathic pain**
- No hepatic metabolism; excreted unchanged in urine; no drug interactions
- Mild, “typical” anticonvulsant SE profile: sedation/dizziness
- Action in GAD / panic/ +/- BAD
- 300-4500 mgs/day in 3 divided doses

Adjuvant Analgesics...

- Anticonvulsants
 - Pregabalin (Lyrica)

Calcium Channel Blockers

- Nimodipine 120mgs/day reduced opiate requirements in 65% of patients in a DBPC trial of 54 patients with escalating cancer pain
- Ca-channel blockade may “re-sensitize” tolerant receptors to opioid effects, “supersensitize” to acute opiate effects
- Ca-channel blockade may be similar (later step) to NMDA antagonism

Santillan et al. Pain 1998 (76):17-26

Benzodiazepines

■ MECHANISMS

- “Skeletal muscle relaxants,” reduce pain related to spasm, splinting, clonus
- No direct analgesic effect
- Diminish emotional reactivity to pain but not sensory-discriminative aspects

AHCPR Consensus: not rated as analgesic

Benzodiazepines: clinical uses in cancer

- Anxiety
- Skeletal muscle spasm
- Anticipatory nausea (amnestogen?)
- Procedural sedation
- Antidote to opiate-induced myoclonus (clonazepam)
- Akathisia due to necessary agents (metoclopramide, cisapride, ondansetron, compazine)

Mexiletine

- Oral anti-arrhythmic/anesthetic
- Can be useful in refractory neuropathy and phantom limb pain
- Can be used following successful lidocaine infusional test dose, or empirically
- Dosing 150-300 mgs PO TID

AHCPR Guidelines Ratings as analgesic: B

Corticosteroids: Uses in Cancer Pain

- Acute nerve/cord compression
- Visceral distention
- Increased intracranial pressure
- Soft-tissue infiltration by disease
- Bone pain
- Nausea

AHCPR Guidelines Rating as analgesic: B

Bisphosphonates

- Inhibit osteoclast activity and reduce pain/analgesic requirements as much as 50%
- Proven efficacy in bone pain of breast ca, myeloma, prostate
- Broader empiric use
- Pamidronate: 90-120 mgs IVPB over 3-6 hrs
- Zoledronate: 4 mgs IVPB over 15 minutes
- Alendronate: 5, 35, 40, 70 mg tablets daily

AHCPR Guidelines Rating as analgesic: C

Calcitonin

- Synthetic or bovine polypeptide
- Inhibits osteoclasts
- Can improve bone and phantom limb pain
- Now available in nasal spray; no anaphylaxis and easy administration

AHCPR Guidelines Rating an analgesic: C

Other CNS-active agents...

- Baclofen: GABA-agonist with demonstrated efficacy in neuropathy and spasticity
- Clonidine: Alpha-2 adrenergic agonist with efficacy in neuropathic and sympathetically maintained pain. May activate endogenous noradrenergic systems, reducing nociceptive inputs to CNS; may interrupt sympathetic systems.

Strontium-89 and Samarium-153

- Beta-particle emitting radionuclides
- Selectively taken up by osteoclasts
- May temporarily reduce pain 60-90% in pts with blastic mets
- Can cause marrow suppression, limit future chemo options

AHCPR Guidelines Rating as analgesic: A
Samarium 153 (Quadramet) unrated by AHCPR

The NMDA Receptor in Pain (N-Methyl-D-Aspartate)

- Excitatory amino acids (NMDA agonists) released by afferent neurons during acute injury
- “Central sensitization” and opioid tolerance may be mediated by NMDA receptors
- NMDA antagonists (*dextromethorphan, ketamine, methadone, memantine*) have analgesic properties for acute, chronic, neuropathic, and “opioid tachyphylaxis” pain

NMDA Antagonists: Possible Clinical Indications

- Treatment refractory neuropathic pain
- Opioid tachyphylaxis or toxicity
- Prevention of further excitotoxic nerve injury (eg, from neurotoxic chemotherapy)
- Terminal pain crisis

NMDA Antagonists: dosing

- Methadone: 2.5-5.0 mgs BID (in addition to high dose opioids)
- Dextromethorphan: 15-30 mgs TID (Delsym) ranging to 1 gm/day
- Ketamine: 0.1-0.15 mgs/kg/hr
- Memantine (Namenda): dose unknown/unproved*

* DPNP Trials show no benefit over placebo

Indications for Epidural / Intrathecal Opioids

- Often helpful when systemic enteral or parenteral therapy is ineffective or toxic
- Technical variables (catheter placement, tumor, anatomy) may result in primarily regional analgesia, requiring continued systemic therapy at lower doses

AHCPR Guidelines rating as analgesic: A

Interventional Analgesic Techniques for Cancer Pain

- Peripheral Nerve blocks
- Sympathetic Blockade
- Spinal Opioids / local anesthetics/ alpha-adrenergics/ antispasmodics
- Neurolytic (destructive) blocks: phenol, cryoablation

Neurosurgical Approaches to Cancer Pain

- Ablative
 - Commisurotomy, cordotomy, thalamotomy, rhizotomy
- Augmentative
 - Stimulators
- Complex risk/benefit and cost/benefit considerations
- Single-event treatments often optimal

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Opioid Equipotency:

<i>Drug</i>	<i>Dose IM/IV/SC</i>	<i>Dose PO</i>	<i>PO:IM/IV ratio</i>	<i>Half-life (hrs)</i>	<i>Duration of Action (hrs)</i>
<u>Morphine</u>	<u>10</u>	30	2-3:1	2-3.5	3-6
Codeine	130	200	1.5:1	2-3	2-4
Oxycodone	6	20	2:1	3-4	2-4
Hydro- morphine	1.5	7.5	5:1	2-3	2-4
Methadone	10	20	2:1	15-120	4-8
Levor- phanol	2	4	2:1	12-16	4-8
Fentanyl	100 ucg	*200 ucg OTF	1:1	1-2	1-3
Tramadol	100	120	1:1	?	4-6

Common Doses / Strengths Non-Compounded Opioid Agonists in US

<u>Drug</u>	<u>Injection</u>	<u>Oral Tablet</u>	<u>Oral Soln</u>	<u>Suppos.</u>	<u>Other</u>
Morphine	2,4,10,15 mg tubex	15 (IR, SR) 30 (IR, SR) 60, 100 SR	20mg/ml 20mg/5ml 10 mg/5 ml	10	24-hr PO SR: Kadian, Avinza
Codeine	60	30			
Oxycodone		5, 10 (IR) 10, 20, 40, 80 mg SR	20mg/ml 5mg/5ml		
Hydro-morphone	2, 4	2, 4, 8	5 mg/5ml	3	Palladone 1/05
Methadone	10	5, 10	5 mg/5ml		Q 6-8 for pain
Levor-phanol	2	2, 4, 8			
Fentanyl	100 ucg		Transderm: 25, 50, 75, 100 ucg.hr		OTF: 2-4-6-8- 12-1600 ucg/dose

Common Doses / Strengths Compounded Opioid Agonists in US

<i>Drug</i>	<i>Trade Name</i>	<i>Compounded with:</i>	<i>Opioid/co-analgesic</i>	<i>Suppos.</i>	<i>Other</i>
Oxycodone	Percocet, Tylox and others	Tylenol	2.5/325, 5/325, 7.5/500, 10/500		Elixirs
	Percodan	ASA	5/325		
Hydrocodone	Vicodin	Tylenol	5/500; 7.5/750, 10/660		Elixirs
	Lortab	Tylenol	2.5/500, 5/500, 7.5/500, 10/500		
	Norco	Tylenol	5/325, 7.5/325, 10/325		
	Vicoprofen	Ibuprofen	7.5/200		
Tramadol	Ultram	Tylenol	37.5/325		
Codeine	Tylenol #2,3, 4	Tylenol	15/300, 30/300, 60/300		Elixirs