Medication Management in An "Opioid Epidemic" and Patient Empowerment

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About Me

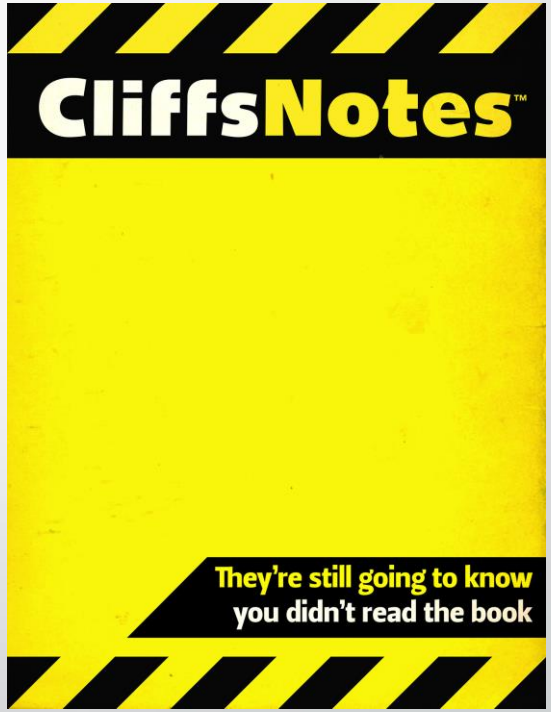
- Chronic Pain Medication Therapy Management Pharmacist,
  Park Nicollet, St Louis Park, Minnesota
- Consultant Pharmacist, Pain Partners LLC
- Patient Advocate and Educator, Scleroderma Foundation and American Pain Foundation
- BS Molecular and Cellular Biology, University of Arizona
- Doctorate of Pharmacy, Oregon State University
- Created the pharmacist-led pain management service at Tucson Medical Center
- Developed a program for post-op pain management plan development prior to surgery, St Luke's Regional Medical Center, Boise, ID
- Participated in a medical mission with Friends of The Children of Haiti

Disclosures

- Nothing to disclose
- No involvement with industry/organizations that may potentially influence this educational presentation.
- I will be discussing "off-label" uses of medications

Learning objectives

- Describe advantages and disadvantages of various medications and medication classes
- Learn "outside-of-the-box" options for pain management
- Determine appropriate medications for special populations and conditions
- Discuss how the "opioid epidemic" impacts our patients, and the importance of individual care
- Develop techniques to empower your patients to become active participants in their healthcare team



Government recommendations?

- Jeff Sessions
  - "I am operating on the assumption that this country prescribes too many opioids."
  - "People need to take some aspirin sometimes."
  - "Sometimes you just need to take two Bufferin or something and go to bed."
- Bob Twillman-Academy of Integrative Pain Medicine Executive Dir
  - "That remark reflects a failure to recognize the severity of pain of some patients."
  - "It's an unconscionable remark...[and] further illustrates how out of touch parts of the administration are with opioids and pain management."

Role of the Pharmacist

- Differences between medications in the same class
- Right drug for THAT patient
- Evaluate drug-drug and drug-disease interactions
- Monitor usage of controlled substances
- Assist with barriers of care
- Limited prescribing
- Naloxone when appropriate?

Medication Therapy Management (MTM)

- Comprehensive Medication Review
  - Different providers
  - OTC
  - Herbals
- Evaluate adherence
- Assess Barriers and find solutions
- Who pays for this service?
  - Medicare benefit for many patients
  - Commercially insured patients
  - Cash pay?
- Goals: Determine the lowest effective dose of the most appropriate medications to TREAT the pain, collaborate with providers to create an individual plan, encourage patient development and use of non-pharmacologic tools for pain management

Patient Comments

- Patient complaints
  - "My provider doesn't listen to me"
  - "Nobody has ever addressed the reason for my pain"
  - "All doctors think I am drug-seeking"
  - "You don't trust me"
  - "I never thought this would be my life"
  - "I feel like I have no control"
- Patient demands
  - "You MUST treat my pain"
  - "The opioid epidemic is forcing me to buy off the street."
- Patient success
  - "I never knew I could feel this good taking so little medication"
  - "I now feel like I have more options and control"

Patient as an Active Participant
Car analogy[1]

- Imagine a car with four totally flat tires
- 1 tire=Medications
- Other 3 tires?
- Living a full life with pain = patient taking an active role
- Patient responsibilities
  - Learn various tools
  - Determine when to use what tool
  - Maintain car
- "Successful" treatment of a person with chronic pain
  - Learn how to independently manage their condition
  - Maximize participation in everyday life activities
  - Minimize discomfort and side effects
- Pain takes a team effort, with the patient taking an active role, to live a full life despite pain

Pain

- *"… an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."*
- Other causes for pain:
  - Sleep Deprivation
  - Poor Coping Skills
  - Stress
  - Social Concerns
    - Financial problems
    - Relationship difficulties
  - Psychological Conditions
    - Anxiety
    - Depression
  - Untreated persistent pain

Classification of Major Complications of Persistent Pain

Deconditioning

a. "Overuse" of ancillary musculoskeletal tissue with degeneration
b. Decreased mobility
c. Obesity
d. Muscle atrophy
e. Contractures
f. Neuropathies

Hormonal

a. Excess catecholamine production with hypertension and tachycardia
b. Glucocorticoid excess or deficiency
c. Hypotestosteronemia
d. Insulin - Lipid abnormalities
e. Immune suppression

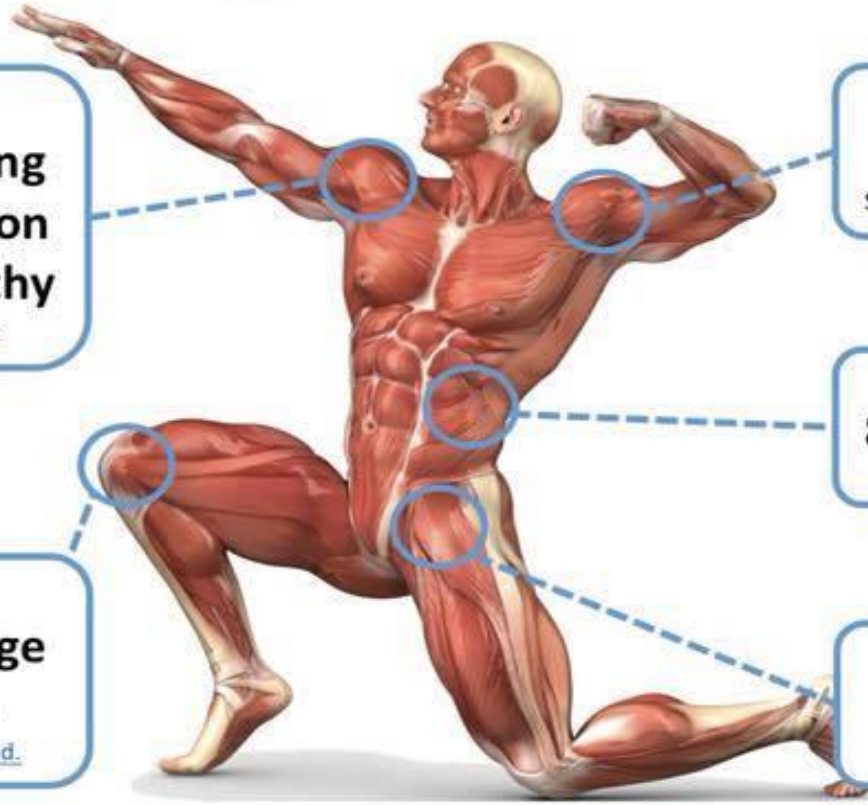
Neuropsychiatric

a. Nerve - Spinal cord degeneration
b. Cerebral atrophy
c. Depression/suicide
d. Insomnia
e. Attention deficit
f. Memory loss
g. Cognitive decline

Hormonal Complications

Signs and Symptoms of Glucocorticoid Abnormalities		
Glucocorticoid Excess		
Weight Gain	Menstrual Irregularity	Depression
Lethargy	Cognitive Dysfunction	Memory Loss
Osteoporosis	Paranoia/Psychosis	Back Ache
Fractures	Muscle Weakness	Hypertension
Bruising	Striae	Loss Scalp Hair
Ankle Edema	Renal Calculi	
Diabetes/Decreased Glucose Tolerance		
Glucocorticoid Deficiency		
Weakness	Fatigue/Tiredness	Salt Craving
Weight Loss	Constipation/Diarrhea	Tachycardia
Hyperpigmentation	Nausea/Vomiting/Anorexia	Anemia
Postural Dizziness	Vitiligo	Muscle/Joint Pains
Auricular Calcification	Hypokalemia	Hyponatremia
Hypotension (<110mm Hg Systolic)		

Scans on pain free people



51 people (age 40-70)
78% bursal thickening
65% ACJ degeneration
39% cuff tendinopathy
Girish et al (2011) Am J Roentgenol.

53 people (age 40-65)
72% SLAP lesions
Schwartzberg et al (2016) Ortho J Sports Med.

3110 people (age 20-80)
80% disc degeneration
Brinjiki et al (2015) Am J Neuroradiol.

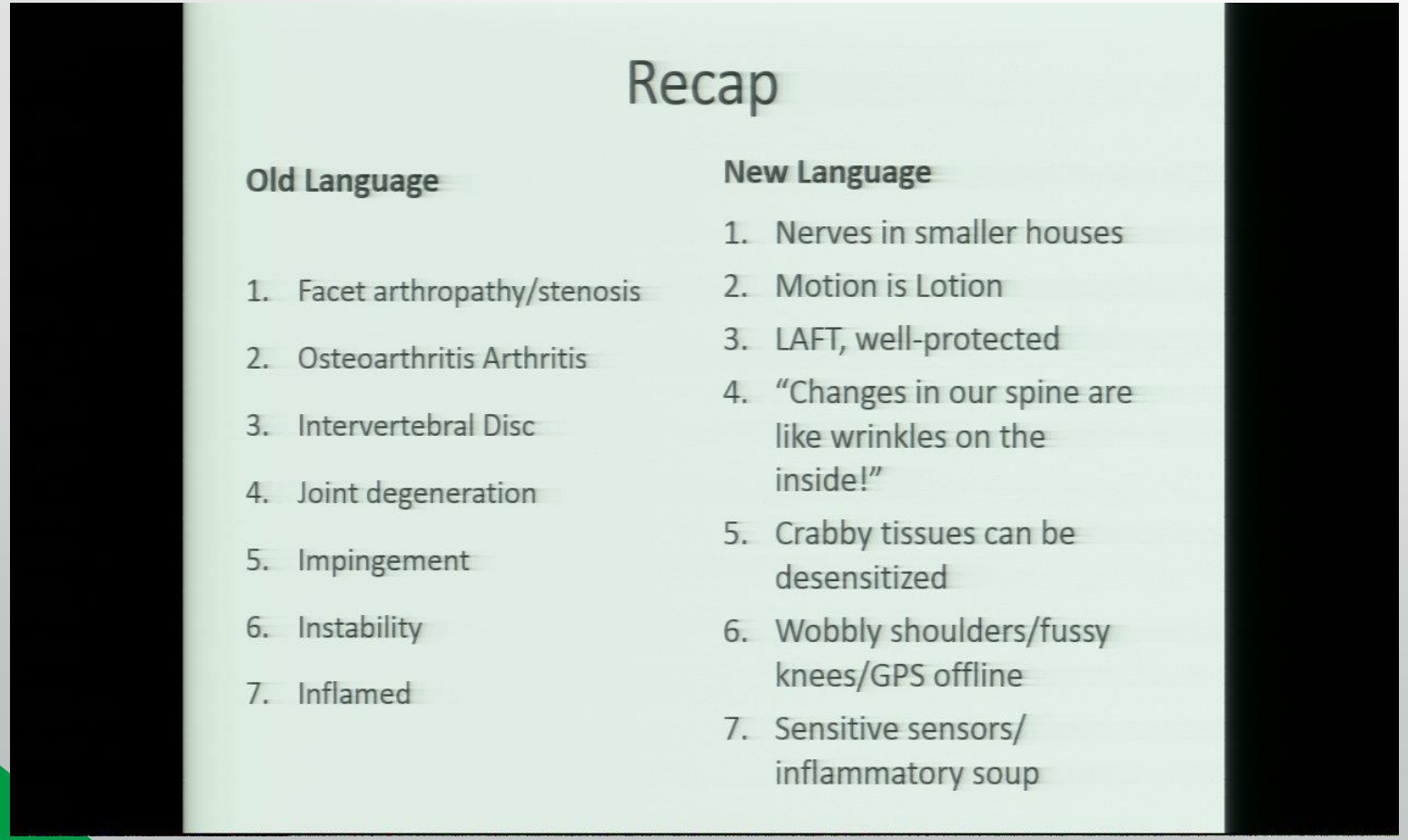
710 people (age 51-89)
68% cartilage damage
72% osteophytes
Guermazi et al (2012) Brit J Sports Med.

45 people (age 15-66)
69% labral lesions
Register et al (2012) Am J Sports Med.

The Sports Physio @adammeakins

Avoiding the Nocebo Effect

- Words that need more clarification: chronic, instability, bulging discs, degenerative, stenosis, inflammatory



Medications

- Analgesics
- Anti-inflammatory Medications
- Anticonvulsants
- Antidepressants
- Muscle Relaxants
- Sodium Channel Blocker
- Cannabinoids
- LDN
- Topicals
- Opioids

Question #1

- Which products have anti-inflammatory properties?
  - A. APAP 1000 mg TID
  - B. etodolac 400 mg BID
  - C. low dose naltrexone 4.5 mg QHS
  - D. B and C
  - E. All of the above

Acetaminophen

- Synergistic activity
- Max dose in 24 hours
  - 3-4g/d (limit 4 g to 2 weeks)
  - 2-3g/d elderly, liver dysfunction, history of alcohol abuse
- Watch OTC products, cough/cold, etc
  - Arthritis formulation – 650mg
- Anti-inflammatory action

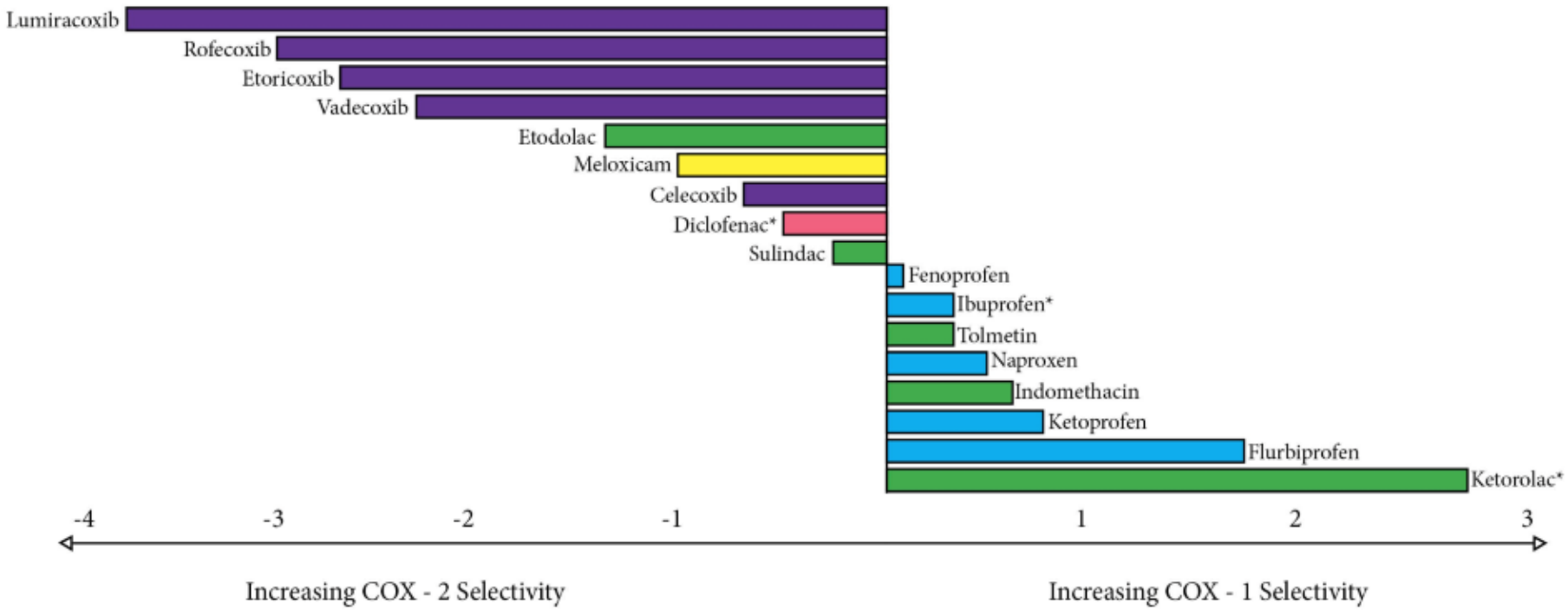
Anti-inflammatory Medications

- ASA (irreversible inactivation of COX enzyme)
  - ASA 400 mg+ Caffeine 32 mg/ tablet- 2 tabs/dose
  - ASA 250mg, APAP 250mg, Caffeine 65 mg- 2 tabs/dose
- COX 1 Inhibitors ± PPI- Increased risk of GI bleeds

  - Ketorolac- limit to 5 days for severe acute pain, max 40mg/day orally, usually only following IV therapy
  - Ibuprofen
  - Naproxen
  - Indomethacin
- COX 2 Inhibitors- Increased CV Risk

  - Etodolac 300-400mg BID
  - Celecoxib
  - Diclofenac
- Diclofenac 1% topical gel- limited systemic absorption (Cmax 53.8±32 (topical) vs 2270 ± 778 (oral 50mg TID))
- Topical (diclofenac, ketoprofen, and naproxen, salicylate products)
- Allergies
  - Diclofenac, nabumetone, meloxicam/piroxicam, aspirin-all SEPARATE classes
  - Etodolac, indomethacin, ketorolac, sulindac- SAME CLASS
  - Ibuprofen, ketoprofen, naproxen, and oxaprozin- SAME CLASS
- Additional concerns-renal dysfunction, + renally-cleared meds, elderly, signs of bleeding, abd pain, pregnancy, HTN, edema

Relative Selectivity of NSAIDs as Inhibitors of COX-1 and COX-2 by Chemical Class



- Propionic Acids
- Carbo - and Heterocyclic Acids
- Oxicams
- Phenylacetic Acids
- COX - 2 Seclective Coxibs

* Available as IV formulation in US

Fudin J. (July 2014). Chemical Classes of Non-Steroidal Anti-Inflammatories (NSAIDs) in US. (Accessed 10/6/2015, http://paindr.com/wp-content/uploads/2014/07/NSAIDS-Chemical-Classes_2014_Shahzad-Henderson-Fudin.pdf)

Herndon C, Hutchison R, Hildegarde B. et al Management of Chronic Nonmalignant pain with Nonsteroidal Anti-inflammatory Drugs Pharmacotherapy 2008; 28(6):788-805

Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. FASEB J. 2004; 18:790-804

Richard Wheeler Pharm D., BCPS
10-2015

Discontinue NSAIDs Prior to Surgery

Table 2. NSAID Discontinuation Recommendations Based on Half-Lives of NSAIDs in Normal Subjects

Drug (Brand)	$t_{1/2}$, h	$5t_{1/2}$, h	Discontinuation, d
Salicylic Acids and Esthers			
Choline Magnesium Trisalicylate (Generic)	9-17	45-85	4
Diflunisal (Generic)	8-12	40-60	3
Phenylacetic Acids			
Diclofenac (Cambia, Cataflam, Flector, Pennsaid, Solaraze, Voltaren, Zipsor, Zorvolex, generic)	2.3	11.5	1
Carbocyclic and Heterocyclic Acids			
Etodolac (Lodine, generic)[a]	7.3 ±/ 4	36.5 +/ 20	3
Indomethacin (Indocin, generic)	4.5	22.5	1
Ketorolac (Sprix, generic)	= 5.3	26.5	2
Sulindac (Clinoril, generic)	16-18	80-90	4
Tolmetin (Tolectin, generic)	2-6	10-30	3
Propionic Acids			
Fenoprofen (Nalfon, generic)	2-3	10-15	1
Flurbiprofen (Ansaid, generic)	7.5	37.5	2
Ibuprofen (Advil, Motrin, generic)	1.8-2.0	9-10	1
Ketoprofen (Generic)	1.6-4	8-20	1
Naproxen (Aleve, Anaprox, Naprosyn, generic)	12-17	60-85	4
Meclofenamate (Generic)	3-4	15-20	1
Enoloic Acids			
Nabumetone (Generic)	26	130	6
Meloxicam (Mobic, generic)[a]	15-20	75-100	5
Piroxicam (Feldene, Therafeldamine, generic)	50	250	11
COX-2 Inhibitors			
Celecoxib (Celebrex)[a]	11	55	3

COX, cyclooxygenase, **NSAIDs**, non-steroidal anti-inflammatory drugs

[a] COX-2 selectivity: etodolac>meloxicam>celecoxib. If the clinician chooses to discontinue these medications due to presumed perioperative risk, the recommended times are listed. However, in the absence of significant bleeding risk, such as during CABG surgery or with thromboembolic disease, these medications could theoretically be continued safely to provide preemptive and perioperative analgesia.

Muscle Relaxants

Table 1. Difference Between Spasticity and Spasms

Description	Spasticity[4,10,13]	Spasms[3,5]
Definition	• Velocity-dependent increase in muscle tone caused by the increased excitability of the muscle stretch reflex	• Involuntary muscle contractions
Etiology	• Central • Disorder of upper motor neurons	• Peripheral • Muscle sprain or injury • Nerve compression (eg, spinal stenosis)
Symptoms	• Stiffness • Hypertonicity • Hyperreflexia	• Jerks • Twitches • Cramps
Causes	• Multiple sclerosis • Cerebral palsy • Spinal cord injury • Traumatic brain injury • Motor neuron disease • Post-stroke syndrome	• Musculoskeletal pain • Fibromyalgia • Sciatica • Mechanical low back pain • Herniated disk • Spinal stenosis • Myofascial pain
FDA-approved agents[a]	• Botulinum toxin[b] • Baclofen • Dantrolene[c] • Diazepam[d] • Riluzole[e] • Tizanidine	• Carisoprodol • Chlorzoxazone • Cyclobenzaprine • Metaxalone • Methocarbamol • Orphenadrine

[a] See Tables 3 and 4 for more in-depth review of agents.
[b] Indication depends on the product.
[c] Also approved for prophylaxis and treatment of malignant hyperthermia.
[d] Approved for treatment of both spasticity and muscle spasms.
[e] Mainly used in patients with amyotrophic lateral sclerosis.

Muscle Spasticity- Centrally-Acting

- Baclofen
  - SE: dry mouth, sedation, **W/D**
  - Cluster HA and nicotine, cocaine, alcohol dependence
- Tizanidine
  - Take with food for better tab absorption
  - Tablets DO NOT EQUAL Capsules
  - SE: dry mouth, hypotension, weakness, inc LFT, **W/D**
  - Taper slowly (2-4 mg/day)
  - CYP 1A2 substrate
    - Fluvoxamine and ciprofloxacin-⇧ Tizanidine
    - BC may⇧tizanidine
- Diazepam
  - Approved for both spasticity and muscle spasms
  - SE: sedation, potential for abuse/dependence, **W/D**
  - Active metabolites-desmethyldiazepam, temazepam, oxazepam
  - Caution with opioids-⇧ risk of resp depression

Muscle Spasticity-Peripherally-acting

- Dantrolene
  - like phenytoin
  - SE: muscle weakness, dyspnea, dysphasia, somnolence, diarrhea, hepatotoxicity (>800mg/d for 3-12 months)
- Botulinum toxin
  - Onset 14 days
  - Duration 3 months
  - Body develops new nerve terminals
  - Potential autoimmune response

Muscle Spasms- Centrally-Acting

- Recommended for short-term use
- Cyclobenzaprine-similar to TCA
  - No direct skeletal muscle activity
  - SE: sedation, dry mouth, urinary retention, fatigue, tachycardia, cardiac conduction disturbances
- Methocarbamol- like guaifenesin
  - Mechanism unknown
  - Less sedation than cyclobenzaprine, brown or green urine, less muscle coordination, grand mal sz
- Carisoprodol
  - alter interneuronal activity, reduce perception of pain
  - Metabolite-meprobamate (baribiturate-like activity)- psychoactive
  - Poor CYP 2C19 metabolizers – 4 fold inc carisoprodol and 50% meprobamate
  - SE: drowsiness, headache, vertigo, insomnia, an inc risk of resp depression, more dizziness, less anticholinergic
  - Holy Trinity of Death- opioids+ carisoprodol+ BZD (or barbiturates)

Muscle Spasms- Centrally-Acting

- Recommended for short-term use
- Orphenadrine- like a stronger diphenhydramine
  - Antimuscarinic Ach and NMDA receptors in CNS
  - SE: dry mouth, sedation, constipation, ocular hypertension, palpitations, sinus tachycardia
- Metaxolone
  - Mechanism unknown
  - SE: dizziness, headache, nervousness, epigastric discomfort, muscle cramping, less drowsiness or cognitive defects, inc risk of resp depression
  - Holy Trinity of Death Take 2- opioids+ metaxolone+ BZD (or barbiturates)
  - Avoid with renal or hepatic impairment
- Chlorzoxazone
  - Acts at the spinal cord and subcortical areas of the brain
  - SE: orange, red, or purple urine, dizziness, somnolence, possible overstimulation, hepatocellular toxicity (need LFTs)

Anticonvulsants

- Co-morbid anxiety
  - Gabapentin ****New drug of abuse**
    - First line therapy for Diabetic Peripheral Neuropathy, CRPS
    - Dec painful dysthesias, hyperalgesia, centralized pain and improve sleep
    - Possible to enhance morphine efficacy
    - Smaller dose adjustments possible (Titration based on tolerability)
    - Can dose BID with bigger dose at bedtime
    - SE: somnolence, dizziness, and infection (safer than TCAs-esp elderly)
    - Treatment dose 2400-3600 mg/d (Max 4800 mg),
      - Renal dysfunction: 1400mg/d (CrCl 30-59), 700mg/d (CrCl 15-29), 100-300 mg/d (CrCl < 15)
  - Pregabalin- more predictable PK
    - FDA approved -neuropathic pain associated with DPN, PHN, and **fibromyalgia**, and as adjunctive for partial seizures
    - Improves sleep
    - SE: dizziness, somnolence, **peripheral edema**, infection, and dry mouth
    - Treatment dose 300-600 mg/d
      - Renal dysfunction: Max 300mg/d (CrCl 30-60), 150mg/d (15-30), 75mg/d (< 15)
  - Efficacy with spasticity (1200-3600mg gabapentin/d or 150-600 mg pregabalin/d)

Gabapentin to Pregabalin

- Gabapentin ≤900 mg/day → pregabalin 150mg/day
- Gabapentin 901 mg/day to 1500 mg/day → pregabalin 225 mg/day
- Gabapentin 1501 mg/day 2100 mg/day → pregabalin 300 mg/day
- Gabapentin 2101 mg/day 2700 mg/day → pregabalin 450 mg/day
- Gabapentin >2700 mg/day → pregabalin 600 mg/day

Anticonvulsants

- Obese or sz history
  - topiramate (Topamax)- approved for migraines, DPN mixed reviews
- Co-morbid bipolar or sz history
  - Carbamazepine (Tegretol)
    - most appropriate for lancrinating neuropathic pain, inc trigeminal neuralgia
    - SE: sedation, nausea, vomiting, hepatic enzyme induction, transient leukopenia and thrombocytopenia, aplastic anemia (CBC, LFTs, BUN, sCr baseline and 2,4,6 weeks and Q6mo)
  - Oxcarbazepine (Trileptal)-analog of carbamazepine- no blood dyscrasias or hepatic insult
  - Phenytoin-less effective than carbamazepine for trigeminal neuralgia
    - Slow and variable absorption and many drug interactions
    - Narrow therapeutic window, cardiac conduction abnormalities, hirsutism, GI and hematologic effects, gingival hyperplasia
  - Lamotrigine (Lamictal)
    - central pain syndromes (trigeminal neuralgia)
    - Long-term -Stevens-Johnson syndrome, toxic epidermal necrolysis, and visual blurring.
  - Valproic acid (Depakote)- migraine HE, potential birth defects

Antidepressants

- SNRI
  - Duloxetine –more NE, 5HT
    - Start 20mg daily if sensitive to medications
    - Max dose 60mg/day for pain (120mg for GAD and MDD)
    - SE: nausea, increased anxiety, dry mouth, insomnia, sedation, fatigue, sexual SE
  - Milnacipan - 3:1 NE:5HT
    - Start 12.5 mg QD x 1d, then 12.5mg BID x 2d, 25mg BID x 4d, then 50mg BID
    - Max 200mg/d
    - Baseline sCr
  - Venlafaxine (Effexor) – higher doses needed for NE effect, inc BP more with IR
  - Desvenlafaxine (Pristiq) – less drug interactions of metabolism concerns
- TCAs –more sedating, possible hangover effect, weight gain, not recommended for elderly (more NE and histamine, less 5HT), QTc prolongation?, cardiac conduction disturbances
  - Nortriptyline – less anticholinergic and antihistamine
  - Amitriptyline- most 5HT, mod anticholinergic
  - Imipramine – middle of the pack for receptor activity
  - Desipramine - best for pain- most NE
- Atypicals
  - Bupropion – less sexual SE, wt loss, stimulating, inc risk of seizures skinny and/or elderly, avoid w/ sz or bulimia
  - Mirtazapine-⇑⇑Antihistamine, ⇑Anticholinergic, less sexual SE, wt gain
  - Trazodone- sedation, "messy drug" more 5HT, minimal anticholinergic

Serotonin Syndrome

- Serotonin syndrome symptoms within several hours new drug or increasing a dose of a drug
- Signs and symptoms include:
  - Agitation or restlessness
  - Confusion
  - Rapid heart rate and high blood pressure
  - Dilated pupils
  - Loss of muscle coordination or twitching muscles
  - Muscle rigidity
  - Heavy sweating
  - Diarrhea
  - Headache
  - Shivering
  - Goose bumps
- Severe serotonin syndrome can be life-threatening.
  - High fever
  - Seizures
  - Irregular heartbeat
  - Unconsciousness

Lidocaine

- Lidocaine 5% patch- Rx (often not covered)
- Lidocaine 4% patch- OTC
- Lidocaine cream
- FDA approved- post-herpetic neuralgia
- Off-label- Neuropathic pain

NMDA antagonists

- Ketamine- topical, oral
  - hypnotic, analgesic, amnesia
  - SE: hallucinations, confusion, delirium
  - Concerns for diversion, harm to patient
- Dextromethorphan
  - reduce opioid dose in surgery
  - diabetic neuropathy

Medical Cannabis/THC

- Dr Gonzaga

Topicals

- Biofreeze- 6 times daily, avoid mucous membranes
  - Consists of Menthol 10%, Amica Montana, Calendula, chamomile, dimethyl sulfone (MSM), echinacea, ethanol, ilex paraguariensis, isopropyl myristate, Juniper Berry, white tea.
  - Classified as topical analgesics- a 'counter irritant' mechanism
  - Menthol may stimulate cold receptors in the skin that may help regulate pain
- Capsaicin- cream and patch
- Essential Oils
  - Oral possible-avoid high doses
  - Copaiba- cannabinoid receptor

Elephant In The Room- OPIOIDs

- Mu, Delta, Kappa
- Pure Mu agonists
  - Have active metabolites- Morphine, codeine, hydrocodone, oxycodone
  - No active metabolites- oxymorphone, hydromorphone
- Partial Mu agonists
  - Buprenorphine (patch, oral)
  - Butorphanol –partial agonist at kappa (IV or nasal)
- Mixed agonist/antagonist
  - Nalbuphine (IV, IM, SQ)
  - Pentazocine (oral, IV, IM)- higher risk of psychosis
- Central (Mu+NE/5HT)
  - Tramadol (+ 5HT)
  - Tapentadol- NO 5HT
    - Ideal for risk of serotonin syndrome and neuropathic pain
    - NO CYP drug interactions
    - Allergies to pure mu agonists
- Mu opioid+ NDMA antagonist activity

Mu opioid + NDMA antagonist

- Methadone
  - 5HT, NE, NMDA antagonist, Mu-opioid agonist
  - Good for neuropathic pain
  - QTc prolongation-consider baseline EKG, 30 days, and annually
    - More if >100mg/day, seizures, or QTc 450-500ms (D/C at >500ms?)
  - T1/2 7-49 hours
  - Cyp 3A4, 2B6, 2C19
  - Monitor K+
  - Danger highest on conversion not linear (higher morphine dose=less methadone needed)
    - days 1-3 and 7-10
  - Wait 5-7 days between dosage changes
  - 2.5mg Q12H for opiate naïve
- Levorphanol
  - 5HT, NE, NMDA antagonist, Mu-opioid agonist, delta agonism, kappa1 and kappa3 receptor agonism
  - Great for hyperalgesia, centralized pain, neuropathic pain
  - Increased pressure in bile duct, urinary retention, mood changes (irritable, angry)

Buprenorphine

- Butrans patch does NOT require special addiction licensing
- Partial mu-opioid agonist, kappa antagonist
- PO morphine: burprenorphine is 100:1 or 115:1
  - 20mcg/hr patch roughly equal to morphine PO 36-55mg/day
  - BUT start at 5mcg/hr and titrate (unless pt not opiate naïve, then 10mcg/hr)
- Butrans Patch 7 day matrix patch
  - Available in 5mcg/hr, 10mcg/hr, and 20mcg/hr
- Buprenorphine+ Nalaxone- Suboxone (X waiver)
- **Increased respiratory depression with other CNS depressants
- Adding opiates to buprenorphine patient-acceptable
- Adding buprenorphine to opiates- CAUTION
- Tolerance doesn't generally develop
- CYP3A4 and CYP 2D6 metabolism to norbuprenorphine
  - Caution with amiodarone, ketoconazole, erythromycin, and ritonavir
- QTc prolongation (congenital, other QTc prolongation drugs, or >20mcg/hr patch)
- **CONCERN for surgery- continue buprenorphine through surgery
  - Increased risk of OD after 2-3 days after patch removal

Opioid Conversions

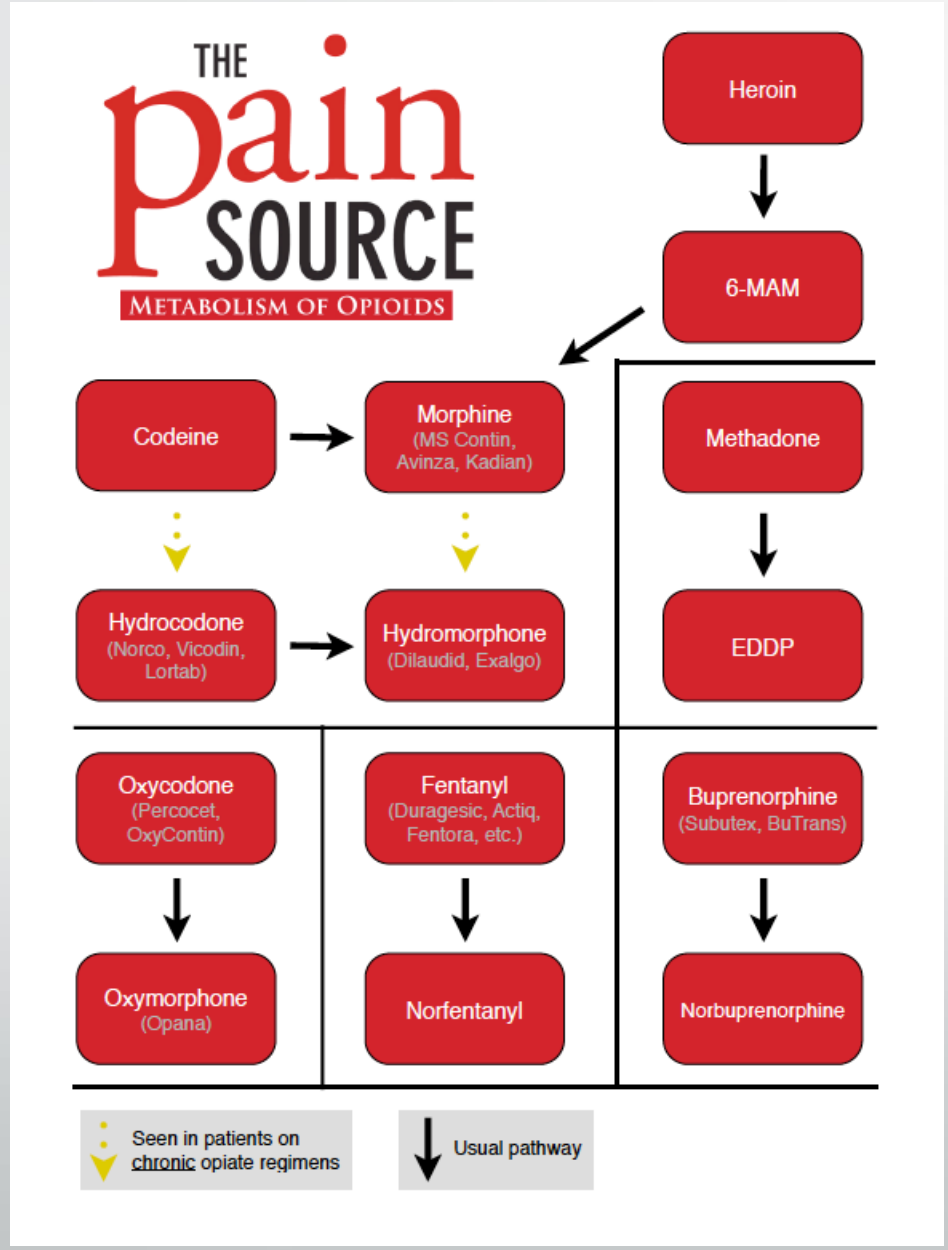
- Most comprehensive calculator https://opioidcalculator.practicalpainmanagement.com/
- Morphine 15 mg = oxycodone 10mg = hydromorphone 4 mg
- Tramadol-variable conversion recommendations (partial agonist)
  - Mu binding affinity 6,000 times less than that of morphine
- Tapentadol 100mg= morphine 40mg =oxycodone 20mg (practical)
  - Mu binding affinity
- Methadone- Conversion not linear (higher morphine dose=less methadone needed)
- Levorphanol- 1/12th to 1/15th dose of oral morphine
- Cross-tolerance and equi-analgesic doses
- Drug-Drug Interactions

Fentanyl Patch Conversions

Initiating Fentanyl Patch (mcg/hr)	Morphine PO (mg/day)	Oxycodone PO (mg/day)
25	60-134	30-67
50	135-224	68-112
75	225-314	113-157
100	315-404	158-202
125	405-494	203-247
150	495-584	248-292
175	585-674	293-337
200	675-764	338-382
225	765-854	383-427
250	855-944	428-472
275	945-1034	473-517
300	1035-1124	518-562

Fentanyl (mcg/hr) to PO opioids	Morphine PO (mg/day)	Morphine IM/IV	Oxycodone PO	Hydromorphone PO	Hydromorphone IM/IV
25	60	10	30	7.5	1.5
50	120	23	60	15	3.5
75	180	38	90	22.5	5.7
100	240	53	120	30	8

Conversions are for education purposes only and clinicians should use sound clinical judgment on an individual basis.


THE pain SOURCE
METABOLISM OF OPIOIDS
Heroin
6-MAM
Codeine
Morphine
(MS Contin, Avinza, Kadian)
Methadone
Hydrocodone
(Norco, Vicodin, Lortab)
Hydromorphone
(Dilaudid, Exalgo)
EDDP
Oxycodone
(Percocet, OxyContin)
Fentanyl
(Duragesic, Actiq, Fentora, etc.)
Buprenorphine
(Subutex, BuTrans)
Oxymorphone
(Opana)
Norfentanyl
Norbuprenorphine
Seen in patients on chronic opiate regimens
Usual pathway

Urine Drug Screens

- "Bedside" test initially?
- Use very specific tests (mass spectrometry) if questionable
- Many metabolites
  - APAP/Codeine-morphine, hydrocodone, hydromorphone possible
  - Morphine and Hydrocodone- Hydromorphone possible
- Fentanyl and buprenorphine patches often negative
- CONTACT Lab for concerns

Urine Drug Screening: Practical Guide for Clinicians[1]

Federal Workplace Cutoff Values		
Substance	Initial drug test level (immunoassay) (ng/mL)	Confirmatory drug test level (GC-MS) (ng/mL)
Marijuana	50	15
Cocaine metabolites	300	150
Opiate metabolites	2000	2000
Phencyclidine	25	25
Amphetamines	1000	500
Methamphetamine	Incomplete data	500

Length of Time Drugs of Abuse Can Be Detected in Urine	
Drug	Time
Alcohol	7-12 h
Amphetamine	48 h
Methamphetamine	48 h
Barbiturate	
Short-acting	24 h
Long-acting	3 wk
Benzodiazepine	
Short-acting (e.g., lorazepam)	3 d
Long-acting (e.g., diazepam)	30 d
Cocaine metabolites	2-4 d
Marijuana	
Single use	3 d
Moderate use (4 times/wk)	5-7 d
Daily use	10-15 d
Long-term heavy smoker	>30 d
Opioids	
Codeine	48 h
Heroin (morphine)	48 h
Hydromorphone	2-4 d
Methadone	3 d
Morphine	48-72 h
Oxycodone	2-4 d
Propoxyphene	6-48 h
Phencyclidine	8 d

Summary of Agents Contributing to Positive Results by Immunoassay			
Substance tested via immunoassay	Potential agents causing false-positive result	Substance tested via immunoassay	Potential agents causing false-positive result
Alcohol	Short-chain alcohols (isopropyl alcohol)	**Cannabinoids**	Dronabinol
Amphetamines	Amantadine		Efavirenz
	Benzphetamine		Hemp-containing foods
	Bupropion		NSAIDs
	Chlorpromazine		PPIs
	Clobenzorex		Tolmetin
	l-Deprenyl	**Cocaine**	Coca leaf tea
	Desipramine		Topical anesthetics containing cocaine
	Dextroamphetamine	**Opioids, opiates, and heroin**	Dextromethorphan
	Ephedrine		Diphenhydramine
	Fenproporex		Heroin
	Isometheptene		Opiates
	Isoxsuprine		Poppy seeds
	Labetalol		Quinine
	MDMA		Quinolones
	Methamphetamine		Rifampin
	l-Methamphetamine (Vick's inhaler)		Verapamil and metabolites
	Methylphenidate	**Phencyclidine**	Dextromethorphan
	Phentermine		Diphenhydramine
	Phenylephrine		Doxylamine
	Phenylpropanolamine		Ibuprofen
	Promethazine		Imipramine
	Pseudoephedrine		Ketamine
	Ranitidine		Meperidine
	Ritodrine		Mesoridazine
	Selegiline		Thioridazine
	Thioridazine		Tramadol
	Trazodone		Venlafaxine, O-desmethylvenlafaxine
	Trimethobenzamide	**TCAs**	Carbamazepine
	Trmipramine		Cyclobenzaprine
			Cyproheptadine
Benzodiazepines	Oxaprozin		Diphenhydramine
	Sertraline		Hydroxyzine
			Quetiapine

1) Moeller KE, Lee KC, Kissack JC. Urine Drug Screening: Practical Guide for Clinicians. Mayo Clin Proc. 2008;83(1)66-76.

Information compiled by Keegan Harse, PharmD Candidate. June 2008.

Opioid Concerns

- Side Effects/Concerns
  - Dependence, sedation, respiratory depression, **constipation**, nausea, pruritus
  - Urinary retention, flushing, sphincter of Oddi pressure changes, hypotension
  - Hypogonadism, reduction of endogenous endorphins **
- Renal Dysfunction
  - Caution with Morphine (neurotoxic morphine-3-glucuronide), hydromorphone (moderate impairment)
  - AVOID meperidine (normeperidine)
- Hepatic Dysfunction
  - Caution with morphine, hydrocodone (APAP), buprenorphine
  - AVOID meperidine, oxymorphone (mod-severe), methadone (severe)
- CYP metabolism-increased drug interactions
  - Cyp3A4-fentanyl, buprenorphine
  - Cyp 2D6-codeine to morphine, hydrocodone to hydromorphone, tramadol, oxycodone to oxymorphone
- Allergy vs Pseudo allergy
- Addiction vs Pseudo addiction
- Hyperalgesia
- Street Value
- Wean- decrease by no more than 30% every 3 days

Patient Buy-In On Opioid Risks

- Opioid pain medications do not treat the pain
- They block the brains perception of pain
- Long-term use often leads to:
  - Depression
  - Weight gain
  - Changes in hormones (6 that are vital for life)
  - Decrease in sex drive
  - Fatigue
  - Decrease in function
  - Development of tolerance-meds become less effective
  - Decreased coping skills-psychologically NEED the opioids for your pain
  - Fear and isolation
  - Increased complications as you age
  - Drug-Drug interactions
    - Even if stable, add ABX CAN = OD
- "If meds aren't improving function, they may not be appropriate for you"

Opioid Patient Education

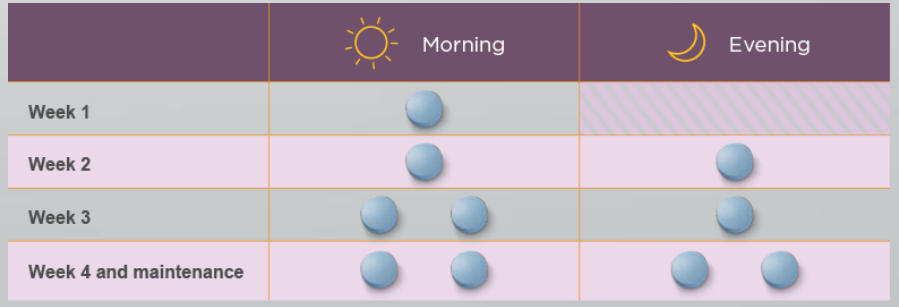
- Side effects (including death)
- BM every 2 days
  - consistent fiber recommended
  - powder with large glass of water
  - Polyethylene glycol 17g QD PRN if no BM the day before
  - Senna-docusate QD to BID
- What to do about missed doses
- Make a proactive plan for periods of increased pain
- Swallow whole and do not cut opioid patches
- Avoid hypnotics, anxiolytics, CNS depressants, illegal drugs, and alcohol
- Selling or giving opioids away is illegal

Opioid antagonists

- Naloxone
  - > 50 MME/d
  - + BZD
- Naltrexone
  - Alcohol and opioid abuse
  - Improve mood
  - Decrease appetite

Low dose Naltrexone (LDN)

- LDN- reduce pain in inflammatory conditions
  - Fibromyalgia
  - Crohn's disease
  - multiple sclerosis
  - complex regional pain syndrome
- Anti-inflammatory properties on microglial cells
  - Toll-like receptor-4 (TLR4) antagonism found on microglia
  - Microglia produce inflammatory and excitatory factors = increase pain sensitivity, fatigue, cognitive disruption, sleep disorders, mood disorders, and general malaise
- Potentially enhances endogenous opioid production
- LDN has antagonist activity on
  - mu, delta and kappa (lesser degree)
- Co-administered with opioid analgesics, dose is too low to compete
  - Synergistic effect on pain relief - less opioids and less adverse effects
- Additional inflammatory processes (food, environmental)
- Contrave (bupropion 90 mg+ naltrexone 8mg)
- Studies indicate treatment for autoimmune conditions?



Medication considerations

- Sometimes, we just have to start over.
- Starting dosage too high
- Titrate slowly
- Change 1 med at a time
- Use side effects as potential benefits (sedation, hypertension)
- Use med peak times and space out medications

Question #2

- Patient, CS, tested positive for methamphetamine and you are prescribing oxycodone 10mg 4 times daily for failed back syndrome. There have been no other violations of her contract in the past 6 months at your clinic. Do you:
  - A. Cut her off of the oxycodone and discharge the patient
  - B. Wean her off the opioid pain medication
  - C. Have an open discussion with her
  - D. Call the lab for clarification
  - E. C and D

Improving Opioid Prescribing

- 77% ask for records release from prior pain provider
- 16% routinely order serum testosterone (free and total) level early on for long-term opioid use
- 67% call the lab to clarify urine drug screen results

Improving Opioid Prescribing

- 42% think a patient is a drug abuser if they request a certain med
  - Histamine or N/V from morphine
  - Poor metabolizers?
- Opioid dependence vs addiction (loss of control, continue despite harm)
  - 32% write "opioid dependent" for chronic opioid use
  - 40% expect addiction for patients their prescribe opioids regularly
- 50% document that they "detoxed" the patient, once opioids not needed
  - X waiver needed
  - Taper or Wean
- 69% will not speak to a family member without a release
  - HIPAA-We do not provide info, but we can listen
- 23% obtain UDS at each visit
  - Unexpected more effective
- 61% reduce opioid amount for sedation or constipation
  - Sedation-transient (modafinil or methylphenidate?)
  - Constipation- persistent (proactive daily bowel regimen)
  - **INDIVIDUALIZED CARE
- 46% discharge a patient after violating "contract"
  - HAVE A DISCUSSION WITH THEM
  - Absolute "NO-NOs"- diversion, continuing – imminent risk, active addiction

Tips For Obtaining Patient Buy-In

- I want to treat the cause of your pain
- Ask the patient their thoughts and preferences
- This is your car, and I am only a passenger her to help you navigate
- Pain meds can only fill up one tire. What would you like to try for the other three tires?
- I want to work with your develop a plan and functional goals to determine what is working and what may need more modifications
- Follow up with previous plan
- What difficulties are you experiencing with …?
- Do not hesitate to say that … isn't your area of expertise, but you can arrange them to see those that you trust
- No two pain patients are alike and shouldn't be treated the same
- Think outside of the box

Vitamin D

- Low vitamin D levels associated with increased:
  - Muscle pain
  - Joint pain
  - Fatigue
  - Headaches
  - Difficulty sleeping
- Determine current dose (Vit D, Fish Oil, Calcium, MVI, herbals)
- Monitor initially (bone disorder)
- Need Ca and Phos (avoid if high), sCr if not last 6 months
- Supplementation
  - make sure to add what they are taking if substitution
  - Leave MVI and Calcium alone if continuing
  - Keep track of total daily values from all sources
- Recheck 3 months after dosage change
- Every 1-2 years once stable or if pain worsens
- Goal 40-80 ng/ml blood levels (I prefer 50-60ng/ml)
- May discontinue?

Starting Vitamin D Dosing if no prior supplement		
Vit D level (ng/ml)	Cholecalciferol D3 (OTC) /daily	Ergocalciferol D2 (RX) /daily
0-10		50,000 units twice weekly x 2 months
10-20	5000-6000 units	50,000 units weekly x 2 months
20-30	3000-4000 units	50,000 units every 2 weeks x 3 months
30-40	2000 units	
40-50	1000 units	

Pharmacogenetic testing

- PK biomarkers -CYP2D6, CYP2C9, CYP3A4, CYP3A5, and CYP2B6
- PD biomarkers included are OPRM1 and COMT
- Poor vs rapid metabolizers
- Poor CYP2D6 metabolizer-like having a CYP2D6 Inhibitors
- APAP/Codeine + Paxil= no conversion to morphine= less effective

Table 2. Common Drugs Used in Pain and Their Metabolism Pathway

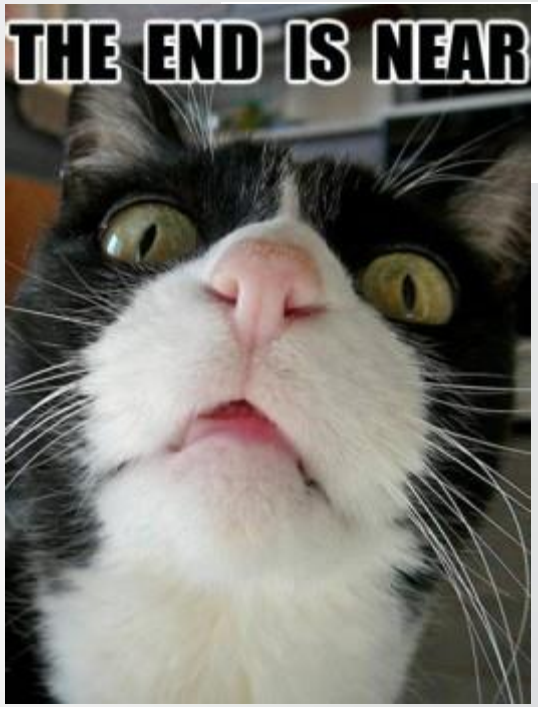
CYP2D6	CYP2C9	CYP3A4/5	CYP2B6
Amitriptyline	Celecoxib	Codeine	Methadone
Codeine	Flurbiprofen	Diazepam	
Desipramine	Ibuprofen	Fentanyl	
Diazepam	Meloxicam	Hydrocodone	
Hydrocodone	Piroxicam	Oxycodone	
Imipramine		Methadone	
Methadone			
Nortriptyline			
Oxycodone			
Tramadol			
Venlafaxine			

Table 3. Clinical Consequences of Opioid Cytochrome P450 Drug Interactions

Opioid	CYP2D6 Inhibition or Patient is PM	Patient is CYP2D6 UM (enzyme not inducible by other drugs)	CYP3A4 Inhibition	CYP3A4 Induction	CYP2B6 Inhibition or PM
Codeine	Decreased analgesia (less morphine produced); UDS may show no metabolite present	Increased analgesia and toxicity (more morphine produced)	Increased analgesia and toxicity (more codeine and possibly more morphine)	Decreased analgesia (decreased codeine and morphine)	N/A
Hydrocodone	Possible decreased analgesia and/or increased toxicity (more hydrocodone and less hydromorphone produced); UDS may show fewer or absent metabolite present	Possible increased analgesia and toxicity (more hydromorphone produced); UDS may show fewer or no parent molecules present	Increased analgesia and toxicity (more hydrocodone and possibly more hydromorphone)	Decreased analgesia (decreased hydrocodone and hydromorphone)	N/A
Methadone	Increased analgesia and toxicity risk	Decreased analgesia risk	Increased analgesia and toxicity risk	Decreased analgesia risk	Increased toxicity (QTc prolongation risk)
Oxycodone	Possible decreased analgesia and/or increased toxicity (more oxycodone and less oxymorphone produced); UDS may show fewer or absent metabolite present	Possible increased analgesia and toxicity (more oxymorphone produced);UDS may show fewer or no parent molecules present	Increased analgesia and toxicity (more oxycodone and possibly more oxymorphone)	Decreased analgesia (decreased oxycodone and oxymorphone)	N/A
Tramadol	Decreased analgesia and increased risk of pro-serotonergic side effects, including a decrease in seizure threshold	Increased analgesia and toxicity	Slight increased analgesia and risk of toxicity	Possible decreased analgesia	Slight increased analgesia and risk of toxicity
Hydromorphone	N/A	N/A	N/A	N/A	N/A
Morphine	N/A	N/A	N/A	N/A	N/A
Oxymorphone	N/A	N/A	N/A	N/A	N/A
Tapentadol	N/A	N/A	N/A	N/A	N/A

NA, not applicable, PM, poor metabolizer; UDS, urine drug screen; UM, ultra rapid metabolizer

Fibromyalgia Guidelines



- Non-pharmacological with active patient participation
  - Aerobic exercise, Tai Chi, Yoga
  - CBT, Mindfulness
  - Possible acupuncture, chiropractor, and therapeutic massage
  - FDM??
- Other triggers: mood or sleep disorders (CPAP??)
- Duloxetine or milnaciprin
- Amitriptyline and cyclobenzaprine
- Pregabalin or gabapentin
- Recommend AGAINST opioids- often makes it worse
- Tramadol- only 1 RCT with positive results-short-term?
- Avoid BZD or zolpidem, etc

Myofascial Pain

- WORK IT OUT
- NSAIDs
  - Oral
  - Diclofenac patch
  - Cox-2 inhibitors
- Lidocaine patch/cream
- Tizanidine, cyclobenzaprine, and BZD
- Duloxetine
- Sumatriptan
- Tramadol?
- TENS, Trigger point inj, manual therapy, US, steroid injections

Neuropathic Pain

	Recommended Drug and Dose	Not Recommended
Level A	Pregabalin, 300–600 mg/day	
Level B	Gabapentin, 900–3600 mg/day Sodium valproate, 500–1200 mg/day Venlafaxine, 75–225 mg/day Duloxetine, 60–120 mg/day Amitriptyline, 25–100 mg/day Dextromethorphan, 400 mg/day Morphine sulphate, titrated to 120 mg/day Tramadol, 210 mg/day Oxycodone, mean 37 mg/day, max 120 mg/day Capsaicin, 0.075% qid Isosorbide dinitrate spray Electrical stimulation, percutaneous nerve stimulation x 3–4 weeks	Oxcarbazepine Lamotrigine Lacosamide Clonidine Pentoxifylline Mexiletine Magnetic field treatment Low-intensity laser therapy Reiki therapy

Geriatric Pain

- APAP (For ALL…except liver failure)
- NSAIDs- risk vs benefit (+ PPI)
  - PRECISION study- celecoxib similar CV risk to IBU
- Opioids
- Gabapentin, Pregabalin (decrease dose for renal dysfunction)
- Topical lidocaine, diclofenac, capsaicin, menthol
- AVOID cyclobenzaprine, metaxalone, orphenadrine, methocarbamol, carisoprodol, chlorzoxazone
- AVOID TCAs, if possible (amitriptyline, nortriptyline, doxepin)
- Adequate therapeutic trial before D/C

ESRD

- APAP
- Antidepressants
- TCAs
- Savella (increased half-life?)
- Tapentadol
  - highly protein bound
  - larger molecular weights
  - higher lipophilicity
- <u>It is recommended to avoid duloxetine and venlafaxine.</u>

Liver Dysfunction

- APAP – 2-3 g per day
  - Prolonged t ½
  - No accumulation if stable disease
- AVOID NSAIDs
- Gabapentin and pregabalin
- TCAs-low dose and gradually titrate
- AVOID carbamazepine
- Fentanyl and hydromorphone
- Methadone-avoid with alcohol

Pregnancy

- Best time to consider non-pharmacologic approaches
- APAP
- NSAIDs-first and early second trimester
- Opioids
- Sumatriptan
- Low-dose naltrexone NOT recommended
- Pregabalin and gabapentin-risk vs benefit
- Duloxetine and TCAs- risk vs benefit
  - Avoid paroxetine, fluoxetine, clomipramine
- AVOID valproic acid

Other Potential Lab Work

- Vitamin D
- Hormone Testing
  - Testosterone
    - Low levels decrease efficacy of opioids, reduce energy, strength, motivation, libido, sleep, and appetite
  - Pregnenolone
    - Opioids suppress this
    - CNS protection and regeneration properties
  - early AM cortisol
    - High-uncontrolled pain
    - >1mcg/dL may be life-threatening
  - ACTH-uncontrolled pain
    - Biomarker for centralized pain (high or low)
  - DHEA
    - precursor for testosterone, progesterone, and estrogen
    - Neurosteroid with CNS regenerative properties
  - Progesterone-reduces pain and symptoms of centralized pain
- Replace and recheck every 2-4 weeks, increase daily dose over 6-8 weeks

MOST COMMON REPLACEMENTS

HORMONE	USUAL DAILY DOSAGES
Hydrocortisone	5 to 15 mg
Pregnenolone	100 to 300 mg
Testosterone	Male:10 – 100 mg Female: 2.5 – 25 mg
Dehydroepiandrosterone (DHEA)	100 to 300 mg

- Medroxyprogesterone
  - ✓ 20 to 40 mg a day

Hormones & Pain Care Information Network

Patient Empowerment

- www.PainToolkit.org
- What is their responsibility?
- Maintain a pain diary or log
  - Apps
  - Chart
- Bullet journaling and bullet journal charting
- "Tell me what you have learned"
- Active involvement in medication options
- Encourage development of other tools
- Explain everything in detail
- Encourage further education (reputable sources)
- Join support groups-get involved
- Celebrate successes
- Dietary and lifestyle changes (FODMAP diet=anti-inflammatory)
- Learn something new from every provider

Handout

- AZPDMP Tips and Tricks
- Resources- Providers and Patients
- American Chronic Pain Association-Include in after visit summary?

Conclusions

- Pain management is subjective
- Do your research
- Listen to your patients
  - Work through problems and concerns
  - Get buy-in
  - Give options when possible
- Treat the cause – look outside the box
- Use appropriate drug for source of pain
- Need functional and measureable goals
- Treatment plans should include all pharmacologic and non-pharmacologic options AND INDIVIDUALIZED
- Assign responsibility.
- Re-evaluate the plan regularly – Did they do their part?
- No room for excuses! (Free apps, Youtube, internet-FIND SOLUTIONS)
- Regular visits-every week, if necessary
- Controlled Substance Agreements
- LABS
  - urine drug screens-often and random
  - cortisol, pregnenolone, and testosterone- early morning fasting blood draw
  - Vitamin D
- Refer – Pain psychology, psychiatry, addictionology, PT, OT, Massage
- Documentation is the key
- Provide after-visit summary
- Continued education for you and your patients
- YOU ARE NOT ALONE-know your resources

Congratulations…WE MADE IT TO THE END

- Thank you for your dedication to your patients
- Contact information: JoAnna.Harper@PainPartnersLLC.com

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