# Non Opioid Pain Management

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# Opioid Epidemic

Physicians are now in a catch 22- needing to manage chronic pain in patients previously treated with opioids, but now encouraged to NOT use  opioids.

This will require an approach with a strong knowledge base in non opioid analgesic medications.

# Nature of Pain

- Unpleasant sensory ***and*** emotional experience
- ***Subjective***
- Palliative care providers consider pain as ***total pain***

# Anatomy and Physiology of Nociception and Analgesia

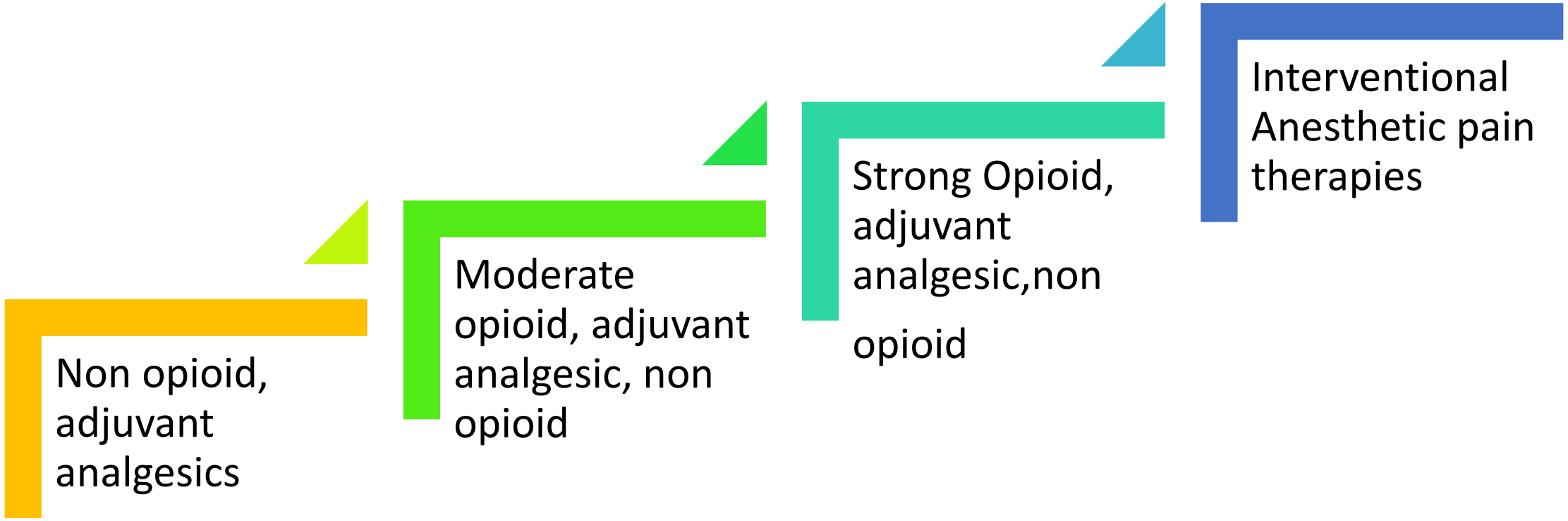
- Activation by mechanical, thermal, and chemical injury
- Nerve fibers classified as A, B, and C fibers with alpha, beta, delta, and gamma subcategories
- A Delta fibers respond to pricking, squeezing, and pinching and lead to the “fast, sharp” pain
- Polymodal C fibers respond to many noxious stimuli and produce slow, throbbing, and more diffuse pain
- Descending inhibitory neural pathways from the brain to the spinal cord involve ***serotonin and norepinephrine***

# Types of Pain

- Acute versus Chronic
- Nociceptive versus Neuropathic
- Somatic versus Visceral
- Cancer versus Non-Cancer

Knowing the type of pain, the location, and severity will guide the therapy needed.

# Four Step Analgesic Ladder



# Non Opioid Analgesic Management

- NSAIDS
- Acetylsalicylic acid (ASA)
- Paracetamol (acetaminophen)
- Corticosteroids
- Adjuvant analgesics or what is now called co-analgesics
- Interventional pain modalities
- Including acupuncture, TENs unit, counseling, PT/OT, and other non-pharmacological interventions

# NSAIDS indications

Pain due to bony metastases

Inflammatory pain (pleuritic chest pain, pericarditis)

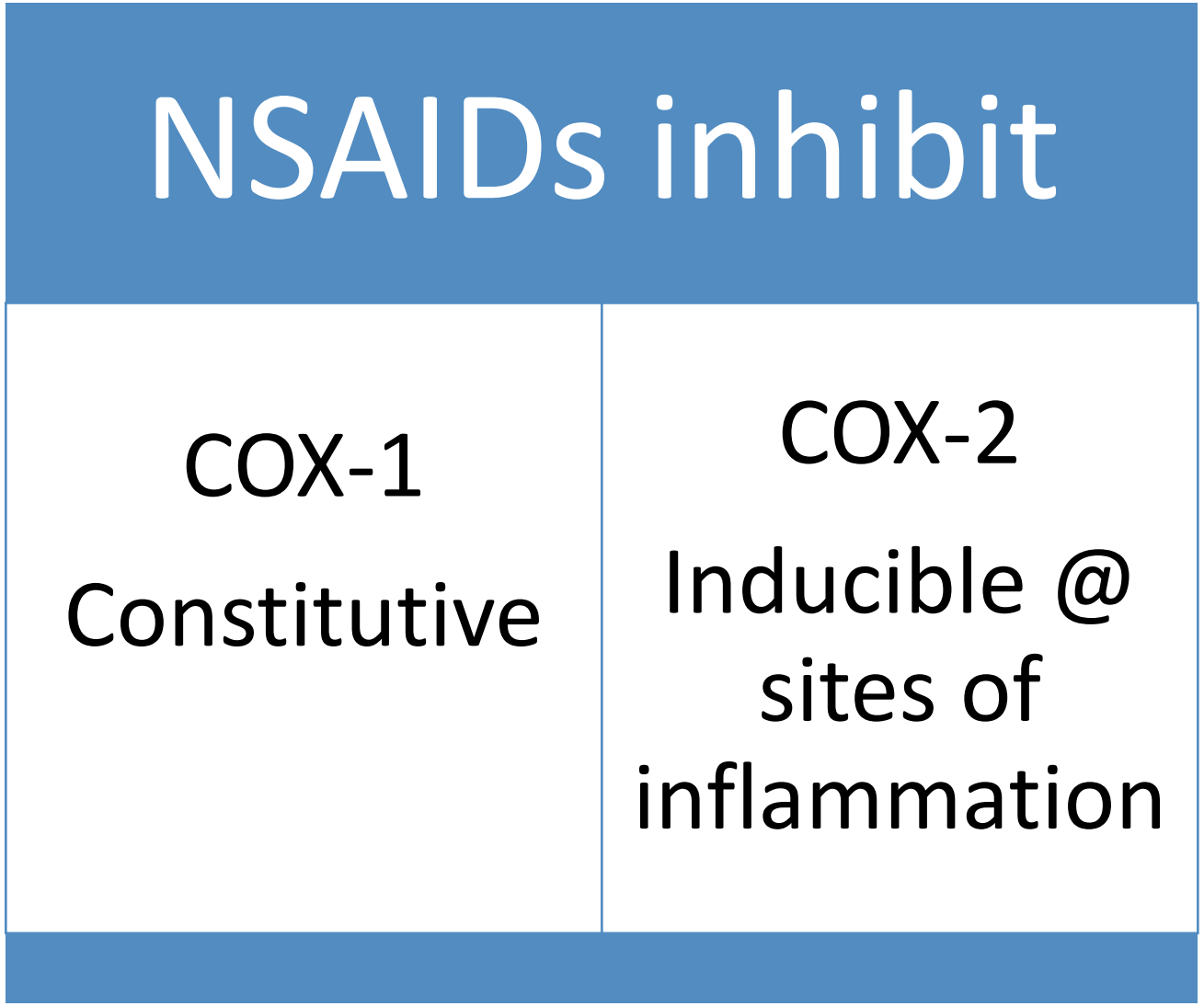
Musculoskeletal pain

Soft tissue injuries, dysmenorrhea, dental pain, Headache

# NSAIDS mechanism and types

Work by inhibiting the enzyme cyclooxygenase (COX) and that prevents the production of prostaglandins

Two types of COX, constitutive (COX-1) and inducible form (COX-2)



# NSAIDS

Non selective Cox-1 + Cox 2

- Ibuprofen
- Naproxen
- Diclofenac
- Indomethacin
- Meloxicam

Selective Cox -2

- ***Celecoxib***
- Valdecoxib
- Etoricoxib

# Which Route for NSAIDs

Oral-most common

IV  useful in hospital settings  (ketorolac)

Topical (diclofenac or Voltaren gel)

# Adverse events and side effects with NSAIDs

# Side Effects/Complications/Contraindications of NSAIDS

| Where | What |
|---|---|
| GI tract | Pain, Nausea, Gastric erosion and ulceration, GI bleedings, perforation<br>(up to 20% of patients will develop this side effect)<br>Celebrex best, followed by Naproxen and ibuprofen |
| Kidney | Water and sodium retention, edema, hyperkalemia, decreased efficacy of antihypertensive medications and diuretics (sulindac considered more safe) |
| CNS | HA, confusion, vertigo, depression, dizziness |
| Platelets | Inhibition of activation, increased risk of bleeding<br>(Risk continues for 2 days after discontinuation of NSAIDS and 7 days after ASA discontinued) |
| Other-Hypersensitivity | Rhinitis, Bronchial Asthma, Urticaria, Flushing, Hypotension, Shock and hepatoxicity |

# Cardiovascular toxicity of NSAIDS

- ***Naproxen*** thought to have less risk for this
- Absolute risk is ***small*** (2 events per 1000 persons per year in patients with low risk and 7 to 8 per 1000 persons  per year , including 2 fatal events in persons with high risk)
- Risk worse when NSAIDs thought to impact blood pressure as well as pro-thrombotic effects

# GI toxicity

Guidelines for risk stratification—

- History of ulcer or GI hemorrhage
- **Age>60** (increased risk 5 to 6 times)
- **High dose** of the NSAID, which increases risk 10 fold
- Concurrent use of ***glucocorticoids***
- Concurrent use of ***anticoagulants***

***High Risk***: history of previous complicated ulcer or 2 or more of risks (rec not using)

***Moderate Risk***: 1 or 2 risk factors

Rec using low dose and with PPI

***Low Risk:*** no risk factors, okay to use without PPI

# NSAIDs take home points

- ***<u>Useful for bone pain and inflammation, not as useful for neuropathic pain</u>***
- Relative contraindication in patients at high risk for peptic ulcer disease (advanced age, history of PUD or prior NSAID gastroduodenopathy, advanced illness, concurrent corticosteroids use)
- Relative contraindication in patients with CV disease or hypercoagulability
- Contraindicated in renal disease, multiple myeloma, or low perfusion states
- Naproxen thought to be less likely to increase risk of CV events
- Celebrex, then ibuprofen or naproxen less likely to cause GI toxicity
- **Potency of maximum doses of NSAIDs equivalent to 5 to 10mg IV morphine in studies**

# Cases for NSAIDs-why or why not

- 60 yo female with ovarian cancer and bowel obstruction w/ history of PUD
- 55 yo male with ischemic cardiomyopathy with comorbid gout and osteoarthritis presents w/ knee pain
- 64 yo male with newly diagnosed glioblastoma multiforme currently on corticosteroids
- 67 yo female with metastatic breast cancer with bone metastasis and brain metastasis w/ comorbid CKD
- 55 yo male with PMHx of PUD presenting with newly diagnosed prostate cancer with bone metastasis

# *Acetaminophen*

- Analgesic and antipyretic, not considered an anti-inflammatory
- Mechanism is poorly understood
- Used in various combination products
- Preferred over NSAIDs for pediatric and elderly patients

# *Acetaminophen*

- Hepatotoxicity is greatest concern with Acetaminophen
- Suggested maximal dose of 650mg and maximal total dose of 3 grams or less  in a 24 hour period
- No more than 325mg in combination opioid/APAP drugs

# Cases for Tylenol-why or why not

- 60 yo female with ovarian cancer and bowel obstruction with escalating pain requiring more frequent Lortab for pain
- 55 yo male with ischemic cardiomyopathy with comorbid gout and osteoarthritis
- 64 yo male with newly diagnosed glioblastoma multiforme with comorbid cirrhosis
- 67 yo female with metastatic breast cancer with bone metastasis and brain metastasis with current etoh abuse disorder
- 55 yo male with PMHx of PUD presenting with newly diagnosed prostate cancer with bone metastasis

# *Adjuvant Analgesics*

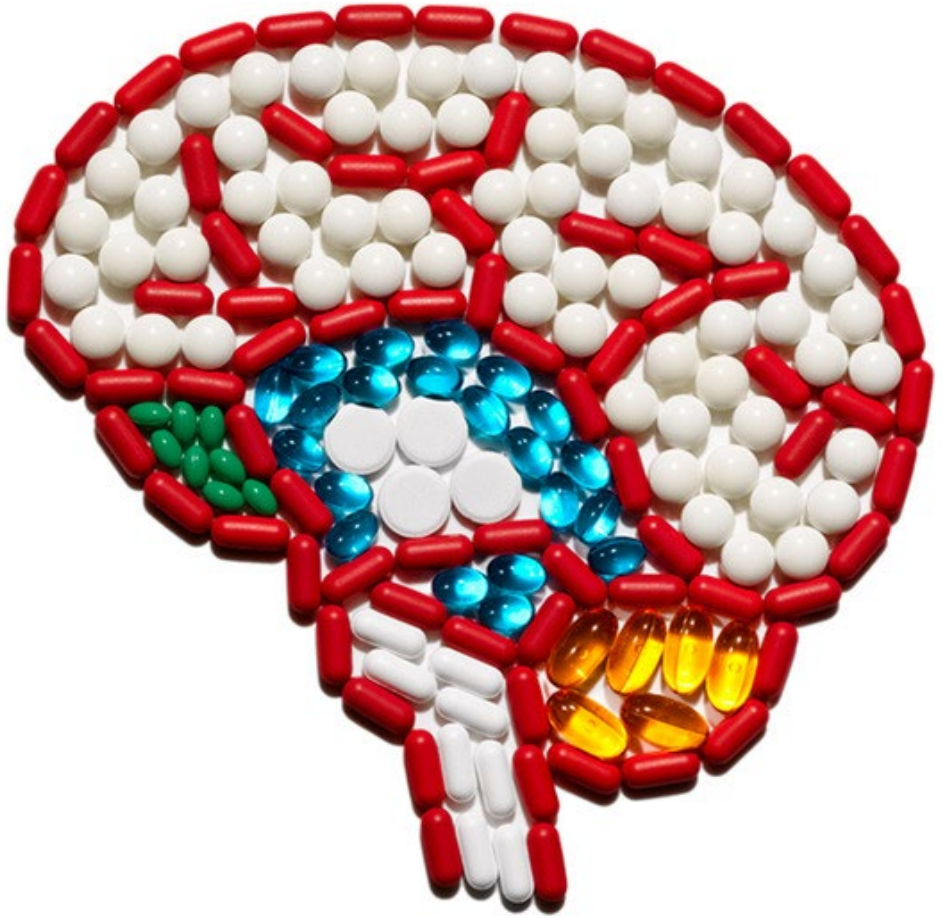
- A drug that has a primary indication other than pain, but is analgesic in some painful conditions

- Sometimes called “co-analgesic”

# Adjuvant Analgesics/ Co-analgesics

| Multipurpose | Neuropathic pain | Topical | Bone Pain | Bowel obstruction | Musculo-skeletal/Misc |
|---|---|---|---|---|---|
| Antidepressants | Anticonvulsants | Capsaicin | Calcitonin | Octreotide | Muscle relaxants |
| Corticosteroids | Sodium Channel Blockers | Local anesthetics | Bisphosphonate | Anticholinergics | Psychostimulant |
| Alpha-2 adrenergic agonists | N-Methyl-D Aspartate Receptor blockers | NSAIDS | Radio-pharmaceuticals | Corticosteroids | |
| Neuroleptics | Cannabinoids | | NSAIDs and corticosteroids | | |
| | Misc. (baclofen, calcitonin) | | | | |

# Antidepressants



# Analgesic Antidepressants

- Used primarily for neuropathic pain, sometimes in chronic pain
- Mechanism based on enhanced availability of monoamines at synapses within the descending inhibiting pain modulating nervous system
- Best established with SNRIs and TCAs  (bupropion and SSRI used less)
- Preferred SNRI is  duloxetine, preferred TCA is nortriptyline or despiramine
- Benefit of bupropion has been suggested in some studies and is more activating (but contraindicated with history of seizures)
- First line without depression→ gabapentin or pregabalin
- First line with depression→ SNRIs or tricylics

# Corticosteroids

- ***Multipurpose*** medication-nausea, pain, anorexia, malaise/fatigue, pain
- Pain uses related to neuropathic pain, bone pain, pain associated with capsular expansion or duct obstruction, bowel obstruction, or lymphedema, and HA associated with ICP
- ***Decadron preferred*** due to longer half life (daily dosing possible) and relatively low mineralocorticoid effects
- Decadron 1 to 2mg Po or IV BID starting (sometimes after loading dose of 10mg)– unless using for ICP or bowel obstruction
- Long term risk with myopathy, immunocompromise, steroid induced diabetes, osteoporosis, and hypoadrenalism

# Alpha-2 adrenergic agonists

- ***Clonidine*** and ***tizanidine*** used
- Clonidine can be given orally, transdermally, or intraspinally
- Spinally administered more for neuropathic than nociceptive
- Side effects→ dry mouth, hypotension (orthostatic), and somnulence

# *Anticonvulsants*

- Gabapentin and pregabalin act by binding to the alpha-2 delta protein modulator of the N type, gated calcium channel→ which then reduces calcium influx into the neuron, and lessens the likelihood of depolarization
- ***No drug-drug interactions, not metabolized by the liver (unlike other anticonvulsants)***
- ***Gabapentin has a pharmacokinetic ceiling (usually 1800mg per day), pregabalin does not***

# Dosing of anticonvulsants

## Gabapentin

Start with 100 to 300mg daily and increase dose gradually every few days to max dosing of 3600mg per day

## Pregabalin

Start at 50mg to 75 mg daily in two divided doses and titrate to 150 to 300mg twice daily over 1 week

# Bone Pain

| Bisphosphonates | Calcitonin | Denosumab | Bone Targeted Radioisotopes | Corticosteroids and NSAIDS |
|---|---|---|---|---|
| • Inhibit osteoclast activity, stimulate osteoblasts to produce osteoclast –inhibiting factor, and causing osteoclast apoptosis<br>• Renal function warnings<br>• Temporary flu like syndrome<br>• Hypocalcemia (VIT D deficient)<br>• Osteonecrosis of the jaw<br>• Typical dosing of zometa: 4mg IV<br>• Ibandronate has oral and IV forms | • Conflicting evidence of efficacy | • Inhibits osteoclast activity by targeting receptor activator of nuclear factor Kappa B ligand (RANKL)<br>• Compared to zoledronic acid<br>• Same side effects as bisphosphonates<br>• One advantage over zometa is quick infusion and lack of renal function impairment | • Examples include strontium-89 and samarium-153<br>• Provides a short lived radiation source to bisphosphonate molecule<br>• Usually limited in use as causes myelosupression (12 weeks after)<br>• Can cause a transitory pain flare immediately after (5 to 10% of patients) | • Lack of evidence based literature for use of corticosteroids in pain |

# *Cannabinoids*

- Derived from the cannabis plant, which contains over 400 compounds, including more than 60 cannabinoids.
- Primary psychoactive cannabinoid is delta-9-tetrahydrocannabinol (THC, also known as dronabinol)
- Mechanism is related to endogenous system that includes cannabinoid-like ligands (endocannabinoids) as well as multiple receptors in the CNS and periphery
- Sativex =nabiximols (approved in Canada) is an oromucosal spray which includes THC and cannabidol, approved for neuropathic pain in MS and cancer
- Nabilone is started at 0.5mg to 1mg qhs and titrated up to 3mg BID
- THC (Dronabinol) is started at 2.5mg daily or twice daily
- Side Effects: dizziness, somnulence, and dry mouth

# *Ketamine, NMDA receptor antagonist*

- N-methyl-D-aspartate receptor antagonist, Ketamine involved in the CNS (sensitization of the central neurons and the functioning of the opioid receptor and possible analgesic properties)
- Used primarily in ***refractory pain (neuropathic suspected) at end of life***
- Extensive list of side effects, including ***delirium/hallucination*** and as such ***usually given with benzodiazepine or neuroleptic***
- Dose- 0.05 to 0.4mg/kg/h infusion after initial 0.1 to 0.5mg/kg bolus dose or IV burst doses 0.25 to 0.5mg/kg or oral doses 0.3 to 0.5mg/kg tid

# Topical Agents

| Capsaicin | Lidocaine patch or gel | EMLA | NSAIDs/other |
|---|---|---|---|
| • Constituent of chili pepper<br>• Depletes substance P form afferent C fibers<br>• Available as cream or patch<br>• Used for focal areas of neuropathy or arthropathy<br>• Must use for several weeks/4 times a day | • Lidocaine 5% patch<br>• Can use q 24 hours<br>• Patches expensive, may be less expensive to use gel<br>• Can cut patches and can apply up to 3 or 4 | • Eutectic mixture of local anesthetics (1:1 mix of prilocaine and lignocaine<br>• Used to prevent pain at incision or puncture sites<br>• Short lived anesthetic that is expensive | • Diclofenac patch 1.3% or 1% gel available<br>• Patch is applied BID<br>• Gel dose is 2 to 4 gm qid for 7 days<br>• Other- cream with tricylic (amitriptyline 2% with or without ketamine1%) for neuropathic pain with conflicting evidence<br>• Topical doxepin for pruritis |

# Bowel Obstruction Analgesics

| Corticosteroids | Octreotide | Anticholinergics |
| --- | --- | --- |
| • Various dosing regimens have been recommended, tend to use decadron 4mg q6 or q 8hour<br>• Risk of perforation concerning<br>• Mechanism unknown, suspected to decrease edema surrounding tumors and obstruction | • Mechanism is the inhibition of secretion of gastric, pancreatic, and intestinal secretions and reduced GI motility<br>• Usually dose 50 to 100mcg subcutaneously TID for short course (usually 3 to 5 days) | • Scopolamine and Glycopyrrolate used primarily<br>• Decreases secretions and decreases GI motility as well |

# Acupuncture and TENS

**Acupuncture**

- Very old procedure for pain management
- In category with cupping, scarification, cauterization
- Acupuncture releases multiple endogenous substances (Beta-endorphin, metenkephalin, and dynorphins which activate opioid receptors; releases serotonin and oxytocin, endogenous steroids. It also up regulates opioid gene production

**TENS**

- Historically used, dating back to 2500 BC
- Mechanism thought to be due to the “gate theory”, selective electrical stimulation of the certain nerves block the pain impulses to the brain

# Generals…

- 60 yo female with ovarian cancer and bowel obstruction
- 55 yo male with ischemic cardiomyopathy with comorbid gout and osteoarthritis
- 64 yo male with newly diagnosed glioblastoma multiforme
- 67 yo female with metastatic breast cancer with bone metastasis and brain metastasis
- 55 yo male with PMHx of PUD presenting with newly diagnosed prostate cancer with bone metastasis

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