ACUTE VERSUS CHRONIC PAIN:

	Acute pain	Chronic pain
Cause	• Generally known • Physiologic response to tissue damage	• Often unknown • May be present without an identifiable injury
Duration	• Short and well-localized • Purpose to protect from further harm (warning system) • Intensity of pain is proportional to degree of tissue damage	• Persists ≥ 3 months or after healing • Serves no physiologic function (involved altered anatomy and neural pathways) • Intensity of pain is not proportional to the severity of tissue damage
Treatment	• Resolution (healing) of underlying cause • Usually self-limited • Respond to traditional analgesics	• Adversely affects pt's well-being • Restore function and sleep • Treatment may provide transient relief but does not resolve underlying pathology • Pain continues after txt is stopped

NEUROPATHIC PAIN:

- Spontaneous pain (continuous or intermittent)
  - Burning
  - Electric shocks (shooting)
  - Lancinating (cutting, stabbing, piercing)
- Stimulus (evoked pain)
  - Allodynia (normally non-painful)
  - Hyperalgesia (increased pain to something normally painful)
  - Hyperpathia (exaggerated pain even once stimulus ceased)
  - Paresthetic (pins and needles, numbness)

TREATMENT PRINCIPLES:

- Select pharmacologic classes with efficacy demonstrated (ideally) in multiple RCTs
  - Consider SEs, drug interactions, cost, and abuse potential
- Be aware that response will vary between patients
- Start with very low doses and titrate slowly to effective or acceptable pain relief (30-50% reduction)
  - If not tolerated, or is ineffective, slowly taper off medication
- Consider adding 2nd agent with different MOA if the 1st agent is providing partial relief yet pain remains ≥ 4/10
- Be aware of comorbidities such as depression, anxiety, and insomnia
- Design a future plan to slowly taper off most medications for chronic pain (exit plan)
- Educate pts about their medications

GOALS FOR TREATMENT OF CNCP:

- Improve physical function
- Improve general function status
- Increase self-management of pain
- Improve vocational/disability status
- Reduce/discontinue opioids and sedatives
- Reduce healthcare utilization
- Reduce pain level

ACETAMINOPHEN:

MOA	• Inhibits prostaglandin (COX-3) synthesis in CNS • Analgesic, antipyretic (not anti-inflammatory)
Role in therapy	• Monotherapy for mild pain • Combined with opioids and other adjuvants
Precautions	• Hepatotoxic (liver disease, chronic & binge alcohol use) ○ Max safe dose = 2.6 gm??? • Do not exceed 4 g daily (avoid OTC combo products)
Advantages	• No effect on platelet function or stomach lining

NSAIDS:

MOA	• Inhibit synthesis of prostaglandin (COX) • Anti-inflammatory, analgesic, antipyretic • COX-2 selective or non-selective inhibitors	
Role in therapy	• Monotherapy for mild-moderate pain • Monotherapy for inflammatory conditions • Combination therapy with opioids • Available topical (diclofenac), injectable (ketorolac, ibuprofen)	
GI effects	Nausea, dyspepsia, GERD, erosions, ulcers, bleeding	
	Management	• Reduce dose / stop therapy • Change to celecoxib • Cytoprotective therapy with PPI or H2RA • H. pylori eradication
	Risk factors for ulcers	• Advanced age > 70 yo • History of ulcer • Concomitant use of steroids or anticoagulant • High doses or use of more than one NSAID
	Other probable risk factors	• H. pylori infection • Cigarette smoking • Alcohol consumption

ANTICONVULSANTS (adjuvant treatment)

MOA	• Binds to presynaptic α2δ subunit of voltage-gated calcium channels in dorsal horn • Decrease glutamate & substance P (excitatory) • Analogue to GABA but doesn't bind to receptors		
Gabapentin	Role	• Variety of neuropathic pain states (diabetic, postherpetic, mixed states)	
	Dose	• Start 100 mg hs and increase q3d to 1800-3600 mg daily as tolerated (divided tid) • Adjust in renal impairment (↓ clearance)	

	Notes	• Absorption variable with non-linear PK
		  ○ 80% bioavailable with 100 mg tid
		  ○ 27% bioavailable with 1600 mg tid
		• Analgesia seen at 2-3 wks of therapeutic dose	

Pregabalin	Dose	• Start with 25 mg qhs and increase q3-7d as tolerated to 150 mg daily or bid (max 600 mg)	
	Notes	• Linear PK (dose-response more predictable) • Analgesia seen w/in 1 wk of therapeutic dose	
Tapering	• Taper to elimination to avoid seizures even with no history of convulsive disorder		
AEs	• Somnolence • Dizziness/ • Ataxia • ↓ concentration	• Dry mouth • Peripheral edema • Blurred vision • Aggression	
Risk of suicide	• Twice the risk of suicidal thinking or behavior • Evident as early as 1 week after starting treatment • Risk is highest in epileptic cases		
Combo therapy	• Gabapentin + nortriptyline or morphine provided better efficacy in PDN & PHN without increase in SEs • Gabapentin + oxycodone > gabapentin alone in diabetic neuropathic pain		

SNRIs (adjuvant treatment)

MOA	• Increase levels of norepinephrine (and serotonin) to stimulate the descending pain pathway	
Duloxetine	Dose	• Start at 15 mg once daily (mix 30 mg capsule with apple sauce) and titrate slowly up to 60 mg daily • Caution with hepatic insufficiency
Venlafaxine	Dose	• Start at 37.5 mg once daily and titrate slowly up to 150 mg (225 mg) daily
	AEs	• Nausea, headaches, stimulation/sedation, sweating, increased BP • Minimal anticholinergic side effects

OTHER ANTIDEPRESSANTS: (adjuvant treatment)

SSRIs	• Very weak analgesic potential
Bupropion	• Dopamine/noradrenaline reuptake inhibitor • Single trial of analgesic benefit at 150 – 300 mg daily • Insomnia, psychosis, seizures ○ NO sexual dysfunction or weight gain
Trazodone	• Serotonin-2 antagonist/reuptake inhibitor • No analgesia but very sedating (useful as sleep aid) • Rare but can cause priapism (50 – 150 mg dose)

TRICYCLIC ANTIDEPRESSANTS (adjuvant treatment):

MOA	• Inhibit reuptake of norepinephrine & serotonin of descending pain pathway	
Role	• Diabetic neuropathy, PHN, central post-stroke pain, neuropathic pain, fibromyalgia, headache • Useful in co-morbid conditions (insomnia, depression, anxiety) • Nortriptyline (2° amine; > NE reuptake inhibition) preferred over amitriptyline (3° amine) due to fewer (esp. anticholinergic) SEs	
AEs	• Anticholinergic side effects: dry mouth, constipation, urinary retention, blurred vision, tachycardia, cognitive impairment • Sedation, postural hypotension • Cardiac arrhythmias (especially in overdose) • Weight gain	
Pre-caution	• Benign prostatic hypertrophy, closed angle glaucoma, CVD • Screening EKG for cardiac conduction abnormalities if > 40 yo • Risk of suicide by overdose (>750 mg or 15-20 mg/kg)	
Dose	• Start with 10 mg at bedtime and titrate slowly • Analgesic response typically within 10-75 mg daily	
Monitoring	• Efficacy for improved sleep (immediate) • Efficacy for improved pain control (102 weeks) • EKG baseline prior to initiation in pts over 40 years old • Must taper off to avoid antidepressants discontinuation syndrome ○ FINISH: flu-like sx, insomnia, nausea, imbalance, sensory disturbances and hyperarousal	
Drug interactions	Codeine	TCA blocks hepatic CYP2D6 isoenzyme, so inhibits conversion of codeine to morphine
	Tramadol	TCA blocks hepatic CYP2D6 isoenzyme, so inhibits conversion to active metabolite
	CNS depressants	Increased sedation with alcohol, opioids, etc
	Other anticholinergics	Paralytic ileus
	SSRI (SNRI) or + triptan or tramadol	Serotonin syndrome

MAINTENANCE AND MONITORING OF AE WITH LONG-TERM OPIOID USE:

CNS	• Hyperalgesia syndrome • Comorbid clinical depression (up to 38%) • Neuropsychological effects – memory,
Resp	• > 6 months of therapy, sleep disordered breathing present (in up to 75%) • Ataxic breathing • Interaction with BZD, barbiturates, alcohol
CVS	• Increased risk of CV events (similar to NSAIDs)
GI	• Constipation → obstruction
Liver/ heme	• Immunosuppression • Increased pneumonia in elderly patients
Endo	• Hyperfunctioning HPA axis • Decreased function of HPG axis • Endocrine abnormalities (decreased sex hormone levels): erectile dysfunction, hypogonadism, amenorrhea
MSK	• Increased risk of fractures

OPIOID TAPERING PROTOCOL:

- Use controlled-release products for 24-hour coverage
- Decrease by 10% of total daily starting dose (ranging from every day to every 1-2 weeks)
- Slower tapers recommended for pts who are anxious about tapering, may be psychologically dependent on opioids, have co-morbid cardio-respiratory conditions, or express preference for slow taper
- Once 1/3 of original dose is reached, decrease by 5% of original starting dose every 2-4 weeks
- Hold the dose when appropriate: if pt experiences severe withdrawal sx, a significant worsening of pain or mood, or reduced function during the taper
- Provide frequent follow-up and supportive counselling
- Taper can usually be completed between 2 weeks – 4 months

Lecture has more complete slides, notes are based on the highlighted LOs from class

DRUGS FOR INSOMNIA:

- Antidepressants are preferred for sleep:
  - Trazadone 25 – 100 mg qhs
  - TCAs 10-50 mg qhs
  - Mirtazapine 7.5 mg qhs
- Zopiclone for short-term use only
- Avoid BZDs in chronic pain
  - Pose an addiction risk
  - Impair function
  - Lack analgesic effect
  - May contribute to depression
  - BZD use predicts opioid use
  - Synergistic toxicity with opioids and alcohol
  - Increased mortality with BDZ use
  - Short-term use only in select cases
  - Taper off (very slowly) pts taking them long-term

CANNABINOIDS (3rd line treatments):

- Evidence in MS and HIV neuropathies
- SEs: euphoria, anxiety, panic, paranoia, psychosis, sedation, dizziness, depression, ataxia, tachycardia, postural hypotension

MANAGEMENT STRATEGIES FOR COMMON OPIOID ADVERSE EFFECTS:

Constipation	• PEG-3350, lactulose • Oral opioid antagonist (low-dose naloxone) • Tolerance doesn't develop overtime
Sedation	• Slow dosage titrations • Review & modify other sedating drugs • Opioid rotation
Pruritus	• Antihistamines not very helpful • Opioid rotation or dosage reduction • Not an allergic reaction
Nausea	• Initiate w/ low doses & increase slowly • Dimenhydrinate, metoclopramide or prochlorperazine may help • Change from oral route to transdermal

REASONS TO SWITCH OPIOIDS:

- Unacceptable side effects
- Unresponsiveness to a particular opioid
- Genetic (CYP2D6) – poor or ultra metabolizers of codeine to morphine
- Problematic drug-drug interactions
- Preference or need for different route of administration
- Change in clinical status
- Financial or drug availability considerations

HOW TO CONVERT OPIOIDS:

1. Calculate total daily dose of opioid products
2. Convert dose to morphine
3. Convert morphine to opioid of choice
4. Individualize new dose
   a. Decrease daily amount by about 33% to account for cross-tolerance
   b. Start daily amount as converted
   c. Slowly increase daily amount by 25-30%
5. Follow up with patient within 3-10 days
6. If dose needs to be increased, increase daily long-acting opioid by daily amount of PRN short-acting opioid