Pain Management in HIV

Rebecca Donald, MD

Assistant Professor of Anesthesiology and Pain Medicine

Vanderbilt University Medical Center

Disclosures

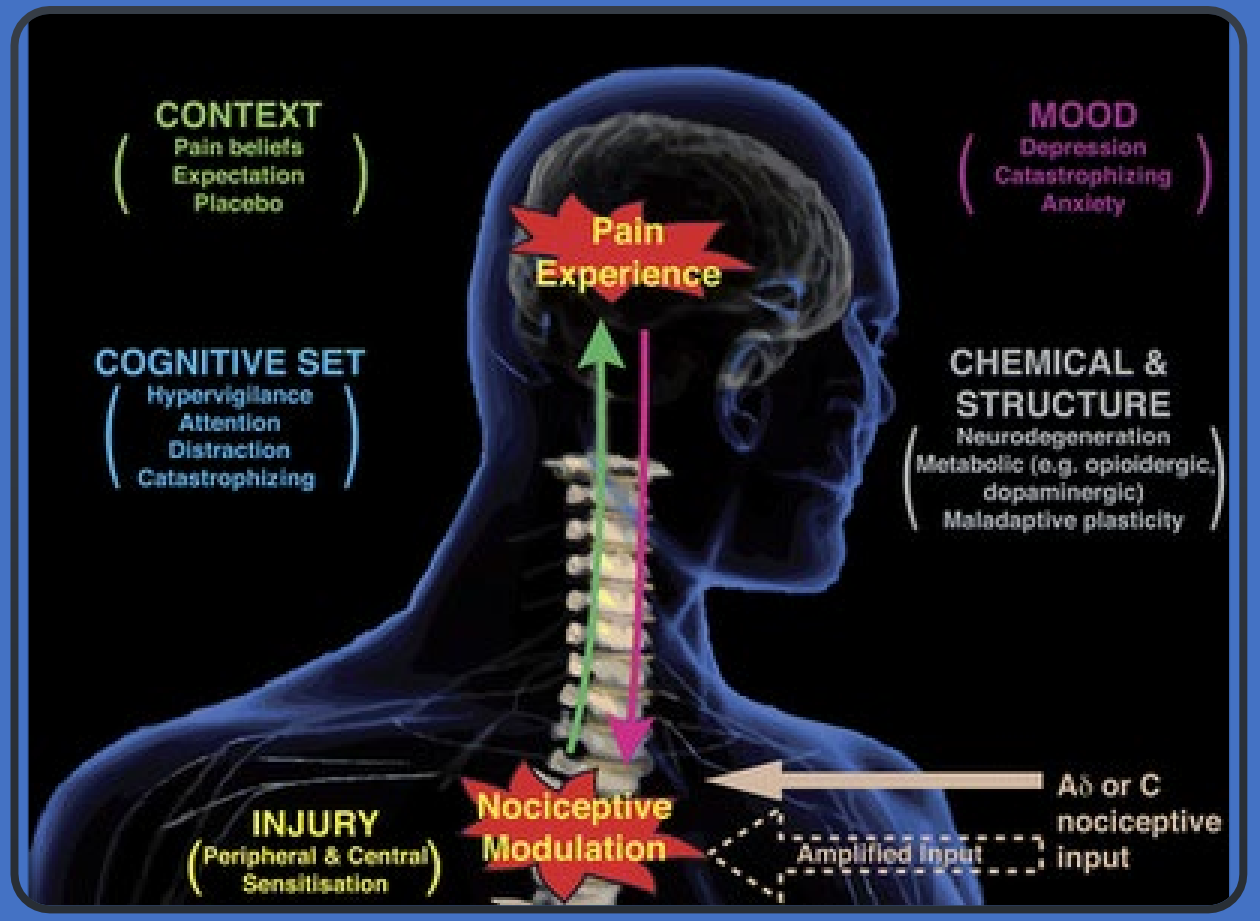
- None
- I haven't studied HIV in a really long time – you all are the experts!

Learning Objectives

- Understand the difference between acute and chronic pain
- Appreciate the epidemiology of chronic pain in HIV
- Understand the mechanisms of chronic pain in HIV
- Understand the multimodal treatment options for pain management in people with HIV

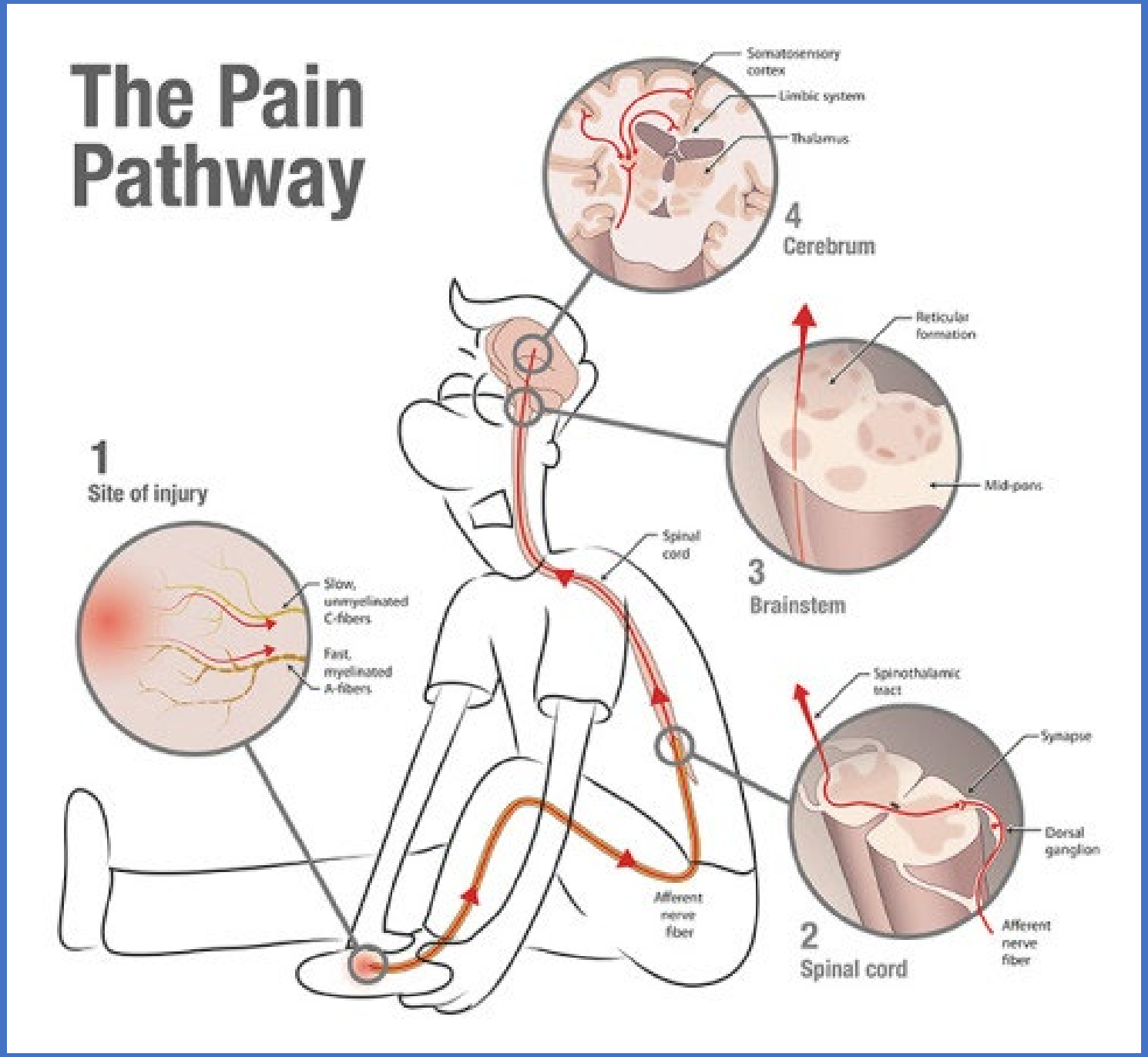
“An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.”

- revised definition by the International Association for the Study of Pain, 2020



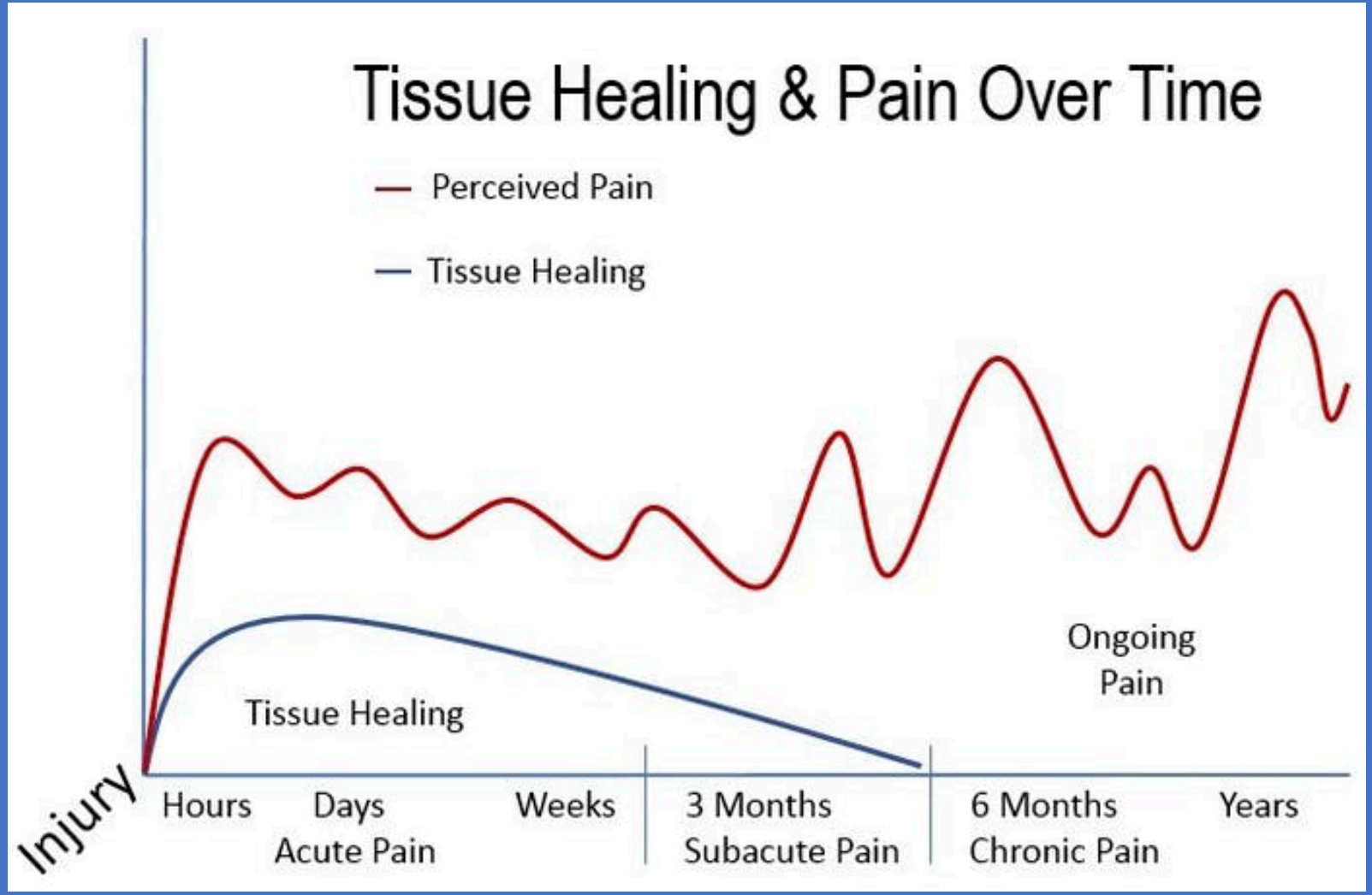
Acute pain

- Pain evoked by a specific stimulus, usually disease or injury
- Associated with tissue damage & sympathetic nervous system activation
- Serves a biological purpose & confers evolutionary survival
- Self-limited



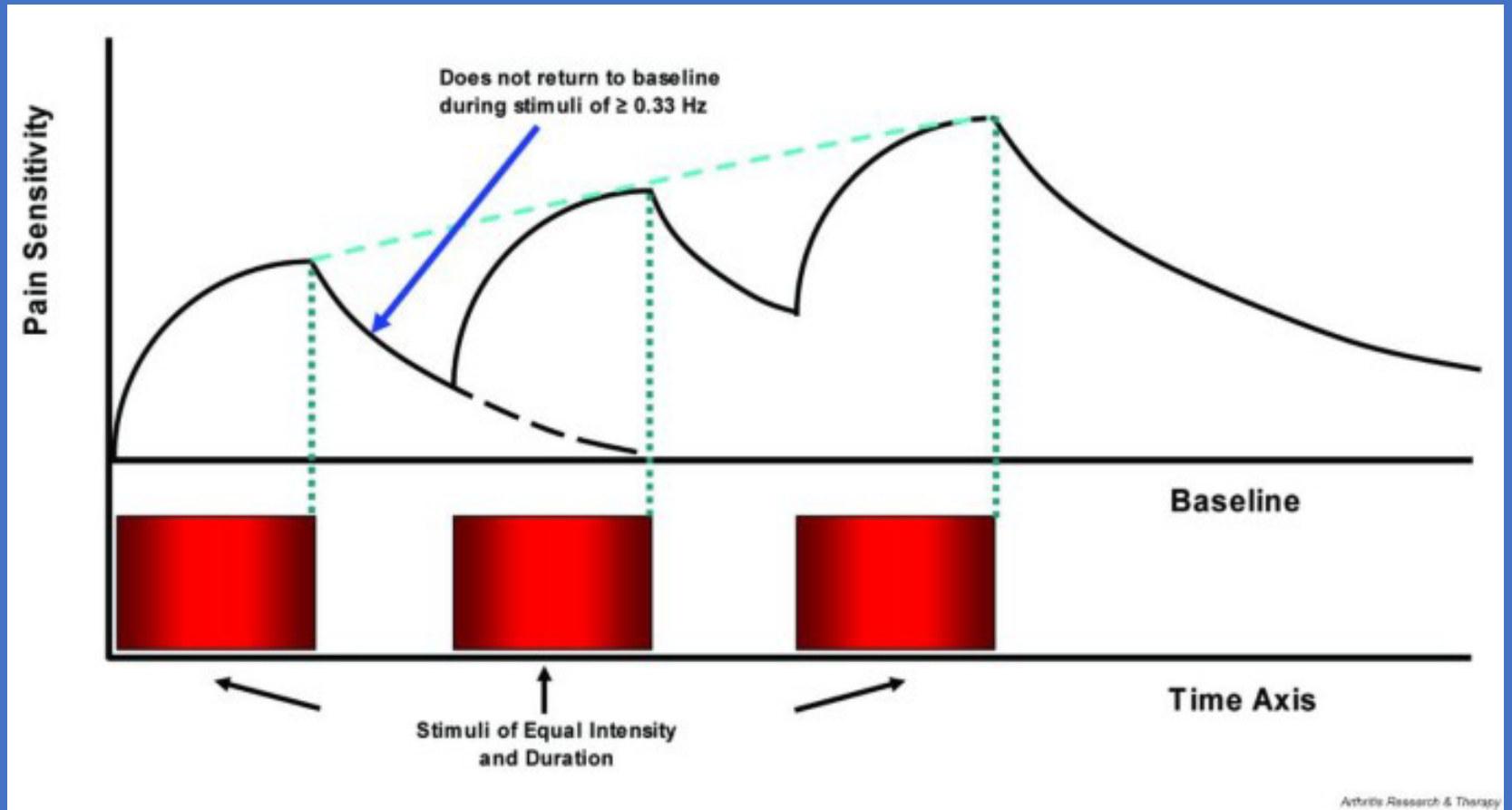
Chronic Pain

- Pain that outlasts the normal time of healing
- Generally considered pain lasting > 3 months
- Chronic pain is pathological - serves no biological purpose



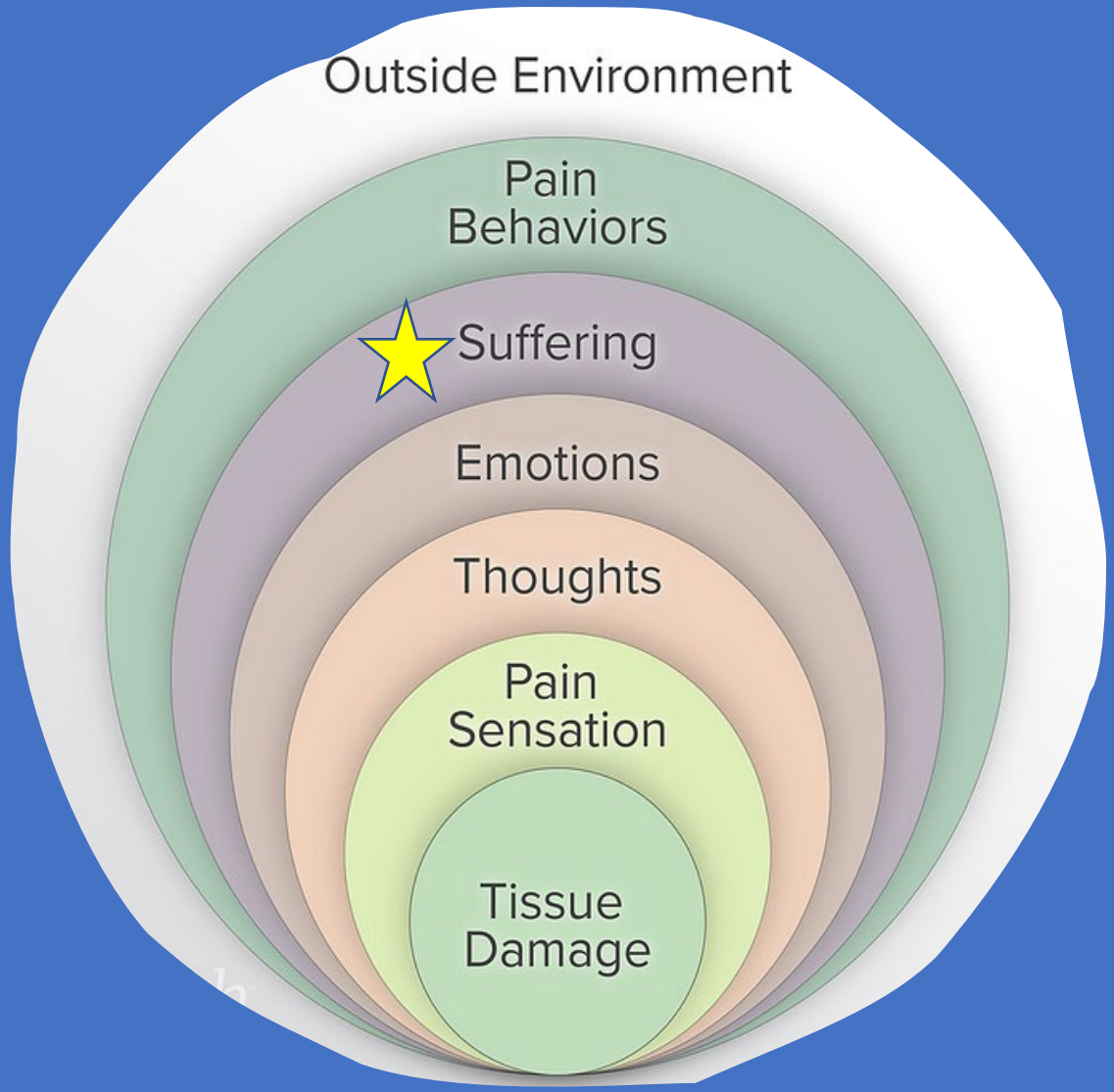
Development of Central Sensitization

- Mediated by neuroplasticity in the CNS
- Repetitive noxious stimulation of unmyelinated C-fibers results in prolonged discharge of dorsal horn cells → things that should not be painful can become extremely painful and thing that should be painful are even more painful



The Pain EXPERIENCE is complex

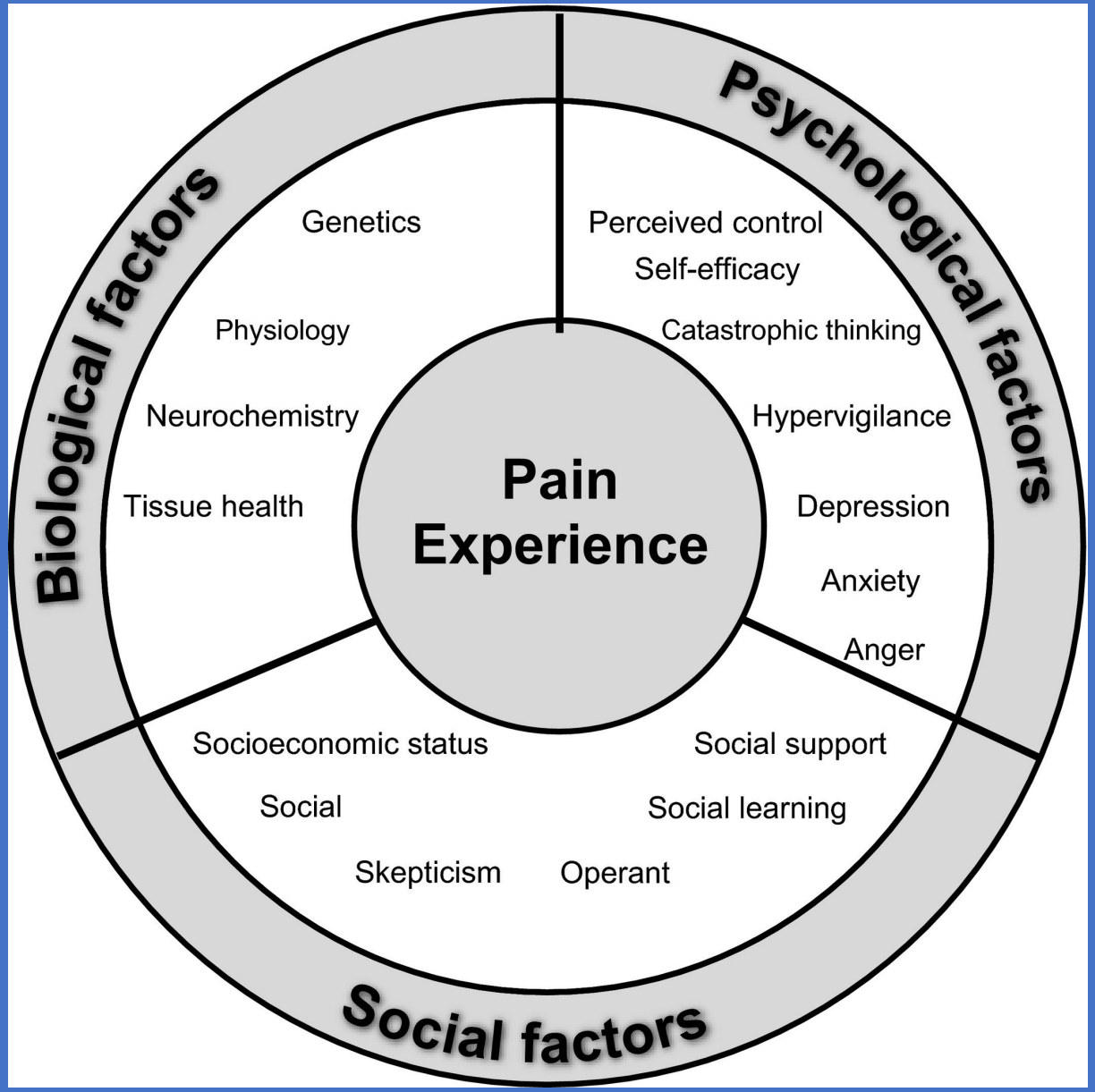
Involves the physical, psychological, emotional, social, and existential experience of suffering



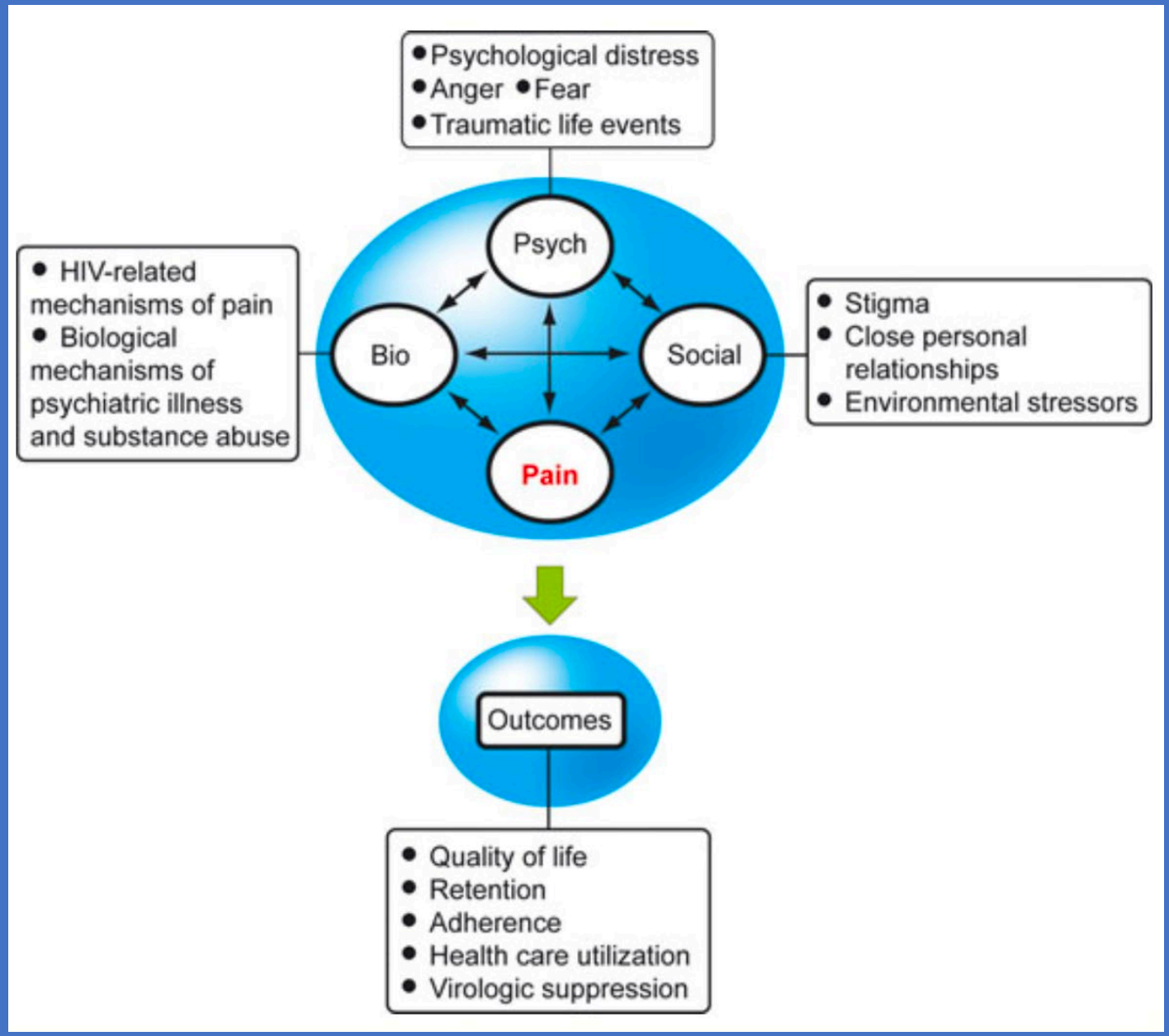
BIOPSYCHOSOCIAL MODEL OF PAIN

Pain is a result of a dynamic relationship between biological, psychological, and social factors, which modulate the patient's report and experience of the symptom.

- Biologic: tissue damage causing pain
- Psychological: pain can lead to psychological stress or having psychological comorbidities, poor coping mechanisms, being a catastrophizer can increase one's experience of pain.
- Social: past and present social factors impact the pain experience



An adapted biopsychosocial framework for chronic pain in HIV



A Conceptual Framework for Understanding Chronic Pain in Patients with HIV

Jessica S. Merlin, MD, MBA*,†; Anne Zinski, PhD*; Wynne E. Norton, PhD‡; Christine S. Ritchie, MD, MSPH§; Michael S. Saag, MD*; Michael J. Mugavero, MD, MHSc*; Glenn Treisman, MD, PhD¶,‖; W. Michael Hooten, MD**,‖

Epidemiology of Chronic Pain in HIV

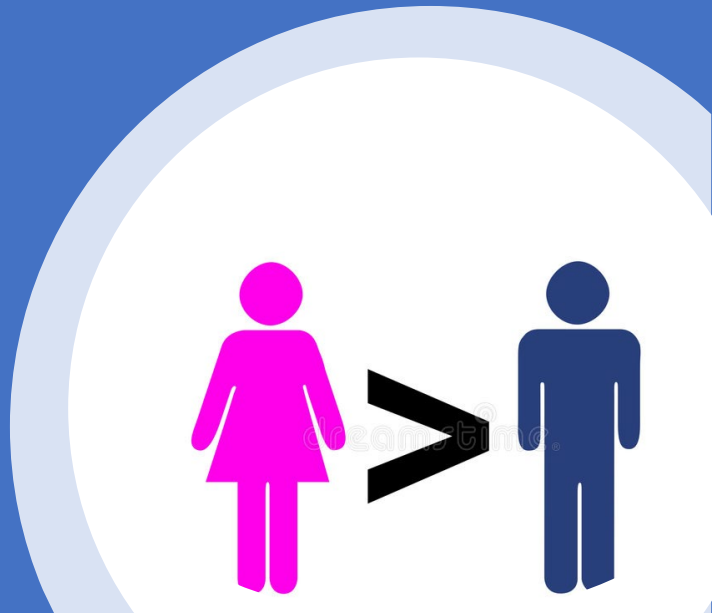
- Prevalence: 25% to 90% depending on the cohort
- 53.7% rate their pain as severe
- Prevalence has not decreased since the 1980s despite
  - creation of the International Task Force on Pain and AIDS in 1994 and combination antiretroviral therapy (cART)
  - Implication: cART and pain management strategies are not sufficient to prevent pain
- Types of pain:
  - Neuropathic pain
  - Regional and widespread MSK pain
  - Inflammatory pain
- Pain locations: joints, head, legs, back
- Other common pain syndromes: pain due to widespread Kaposi sarcoma, headache, abdominal pain

Epidemiology of Chronic Pain in HIV

- Increased prevalence in those with:
  - Lower socioeconomic status and educational attainment,
  - Comorbid psychological illness
  - Previous or recent use of illicit drugs /Comorbid substance use issues
  - Treatment with cART
    - those on a PI-based (vs. a non-PI-based) cART regimen
    - those receiving NRTIs (vs. those not receiving NRTIs).
  - Increasing age
  - Longer time since diagnosis

- Studies have found variable association with CD4 counts and viral loads

- Women > men



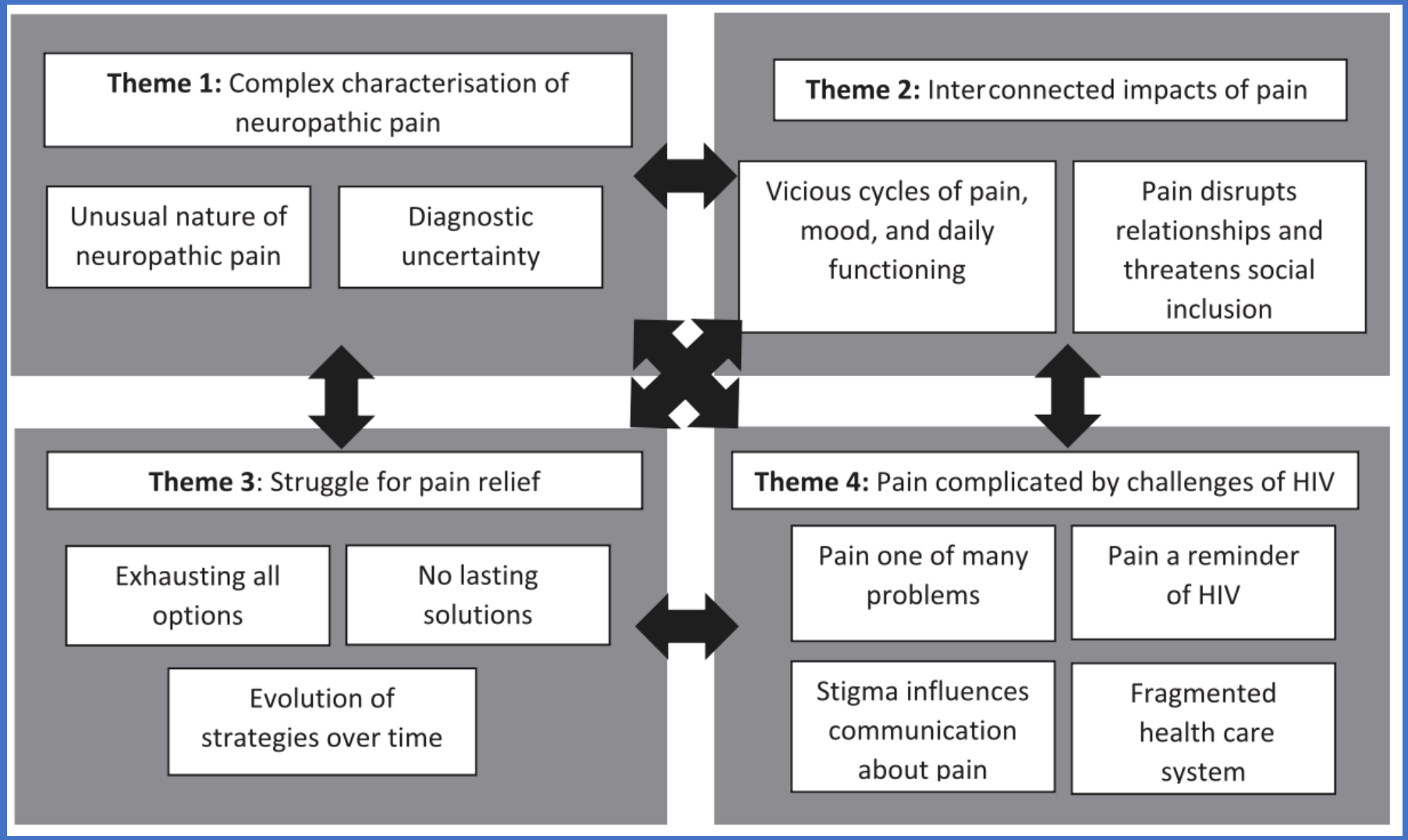
Pain and Psychiatric illness

- Commonly co-occur
  - Depression/Anxiety
  - PTSD
  - Sleep disturbances
  - Unemployment
  - Substance use
- Affect retention, adherence, disease progression, and virologic suppression
- Health consequences of chronic widespread pain:
  - 10x greater odds of functional impairment

PAIN®
161 (2020) 970–978

A qualitative study of the experience and impact of neuropathic pain in people living with HIV

Whitney Scott[a,b,*], Maite Garcia Calderon Mendoza del Solar[a], Harriet Kemp[c], Lance M. McCracken[d], Amanda C de C Williams[e], Andrew S.C. Rice[c]

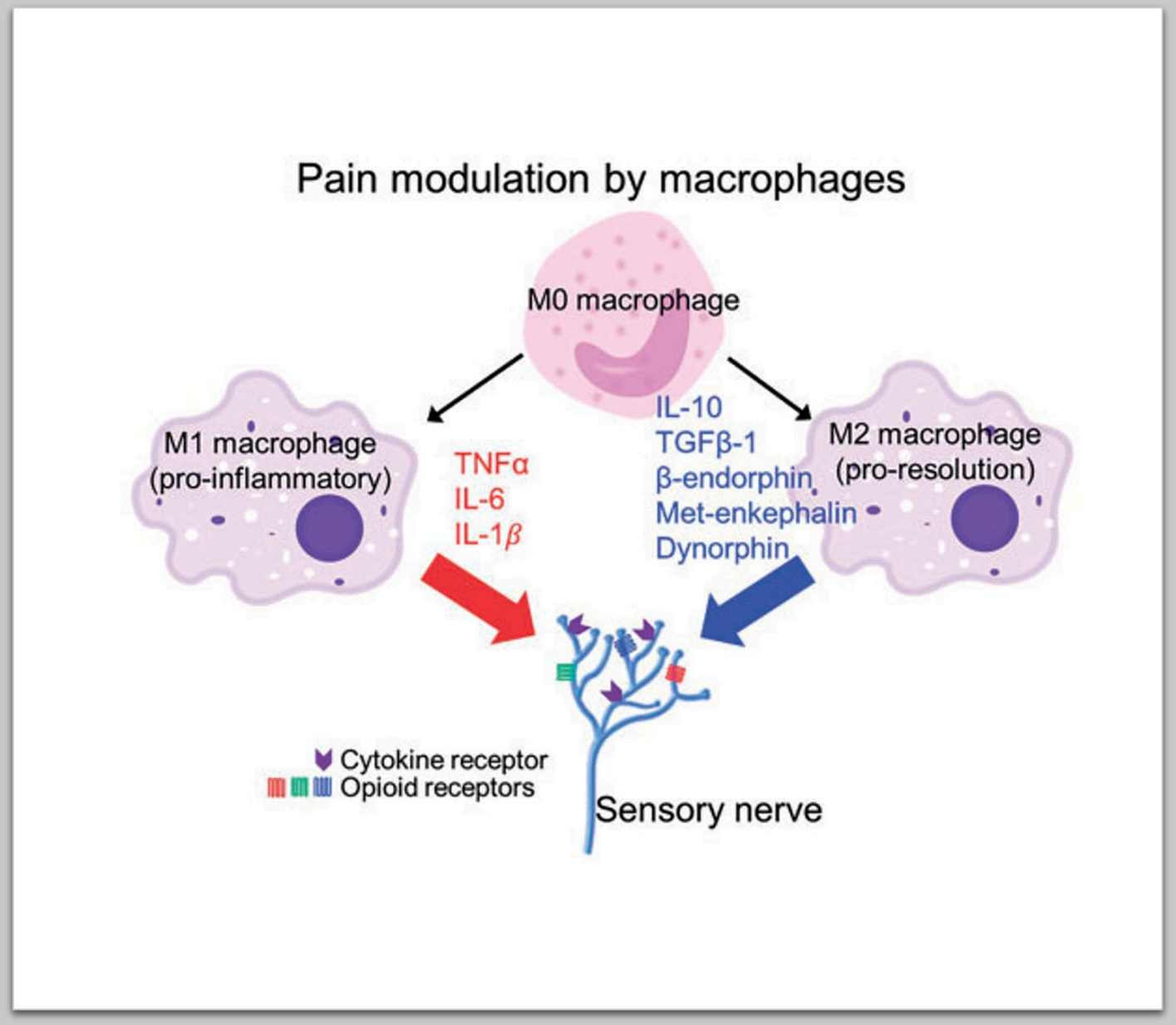


Mechanisms of Chronic Pain In HIV

- Macrophages
- HIV proteins: Glycoprotein 120 (gp120), Trans-activator of transcription (Tat), Viral Protein R (Vpr)
- Antiretroviral drugs
- Much of the work has been done in mice

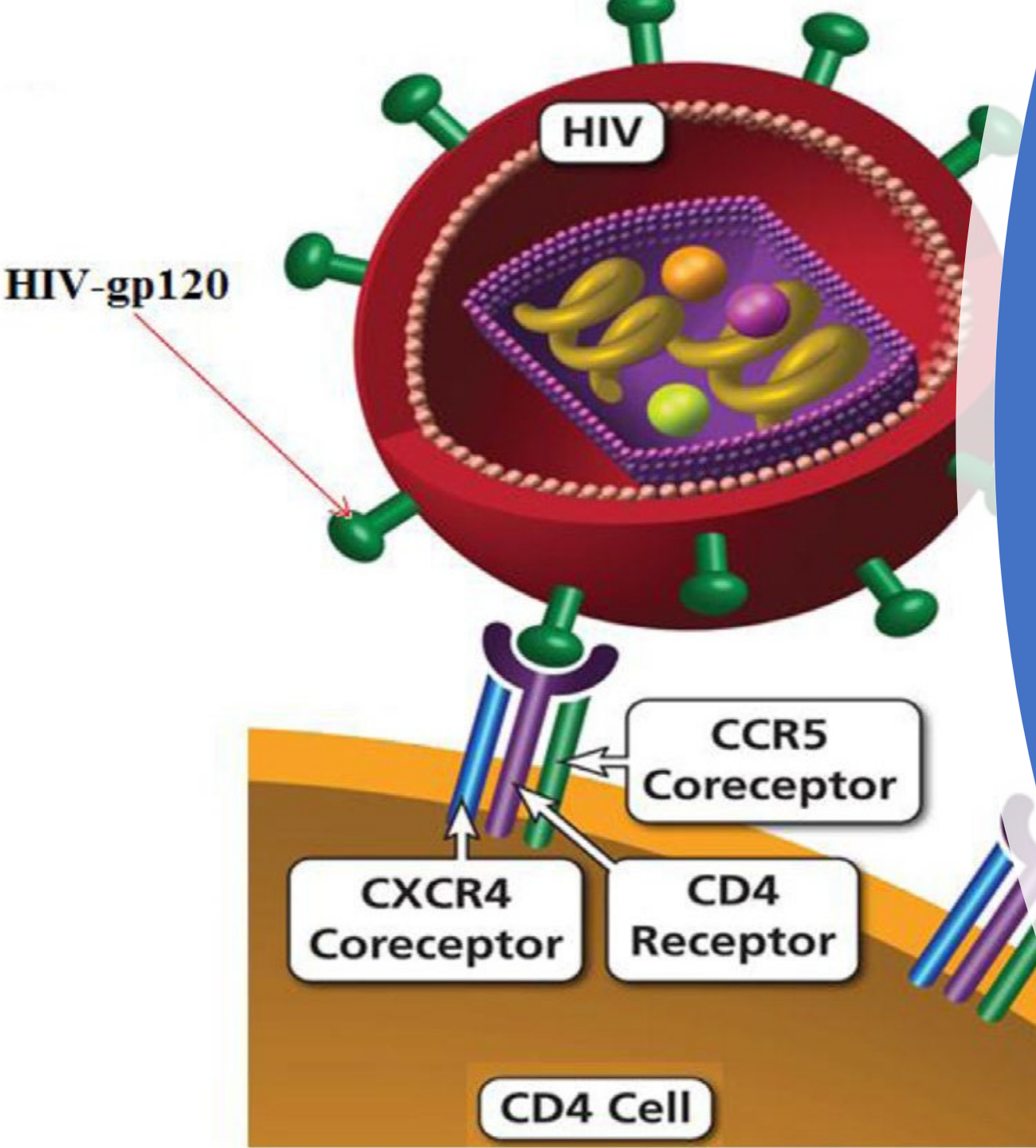
Macrophages

- Infection with HIV --> activation of pro-inflammatory pathways --> changes in afferent nociceptive signaling --> hypersensitivity to pain.
- Macrophages express inflammatory cytokines IL-1B, IL-6, TNF-a which enhance local neuroinflammation --> neuropathic pain --> peripheral and central sensitization
- Macrophages also recruit other inflammatory cells, including neutrophils and lymphocytes
  - --> release chemicals that cause oxidative stress on the DRG
- Failure of endogenous inhibitory systems both centrally and peripherally
  - M2 Macrophages release endogenous opioids (enkephalins, B-endorphins, dynorphins)



HIV-1 proteins: Glycoprotein 120 (gp120), Trans-activator of transcription (Tat), Viral Protein R (Vpr)

- Each has a unique downstream signaling pathway capable of inducing peripheral neuropathic changes and pain.
- Despite low viral count and nearly normal CD4 level, the circulating or cellular levels of HIV-1 proteins remain high.
- Currently no known genetic manipulations or pharmaceutical drugs to reduce the burden of HIV-proteins in humans
  - Lifestyle modifications aimed at lowering chronic inflammation may be the best option for reducing long-term pain and morbidity.



Glycoprotein gp120

- Activates macrophages --> downstream neurotoxic effects
- Establishes an inflammatory state --> neurotoxicity --> axonal degeneration
  - Up-regulation of pro-inflammatory genes in macrophages
  - TNF-a mediated neuronal apoptosis
- Can exert an effect on cells even in the absence of viral infection of neuronal cells
- Interactions between gp120 and cART
  - Neuropathic pain models showed that combined administration of HAART and gp120 resulted in greater neuropathic pain than cART alone.
- Interactions between gp120 and Opioid Exposure
  - IT administration of gp120 and morphine for 5 days induced greater persistent mechanical allodynia compared to gp120 or morphine alone

Trans-activator of Transcription (Tat)

- First protein released by infected host cells after HIV infection
- Continues to be expressed from host cells in the CNS despite cART & irrespective of viral load--> neuro-inflammation --> neurotoxicity
- Induces neurotoxicity through
  - DNA double strand breaks
    - NMDA receptor-mediated alterations in intracellular calcium hemostasis and glutamate excitotoxicity
    - Increased expression of inflammatory cytokines IL-6 and TNF-a
    - Induces hyperexcitability and apoptosis of primary DRG neurons
- Also implicated in modification of opioid tolerance and physical dependence
  - Loss of morphine-induced antinociception (i.e. morphine doesn't provide analgesia)
  - Increased tolerance for morphine

Viral Protein R (Vpr)

- Mediates viral replication
- Triggers apoptotic pathways, stimulates inflammatory cytokine release, interferes with ATP production --> accumulation of ROS and increased oxidative stress.

Antiretroviral drugs

- Reduced HIV-related mortality --> HIV is a chronic disease
- Patients must take cART for a long time --> acute and chronic side effects
- Nucleoside reverse transcriptase inhibitors (NRTIs) implicated
  - mitochondrial dysfunction leading to disruptions in calcium homeostasis and pro-apoptotic state
  - Exposure to zalcitabine induced macrophage infiltration into the DRG--> downstream effects
  - Combination of alcohol consumption and NRTI exposure produced mechanical hyperalgesia at doses that do not independently cause nociception
- Protease inhibitors elicit neuropathic changes and potentiate the neuropathic actions of NRTI therapy

Treatment options

Data is limited

Direct acknowledgment of the complexity of HIV-associated chronic pain syndrome when communicating with patients may help in setting expectations and discussion options for treatment.

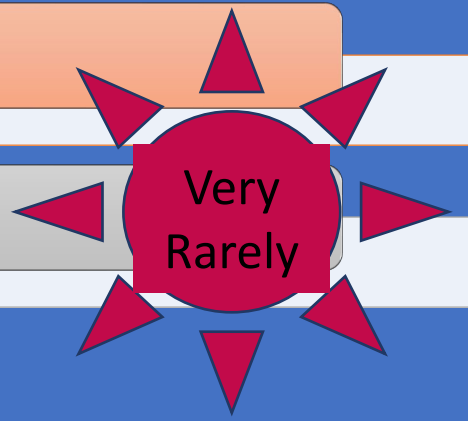
2017 Clinical Practice Guideline for the Management of Chronic Pain in Patients Living with HIV, recommended a biopsychosocial strategy

- opioid analgesics should not be the first line of

- non-opioid drugs as well as non-pharmacological methods should be first- line approaches.

Treatment for Chronic Pain

- RICE
- NSAIDS
- Acetaminophen
- Muscle relaxants
- Gabapentinoids
- Interventions
- Opioids



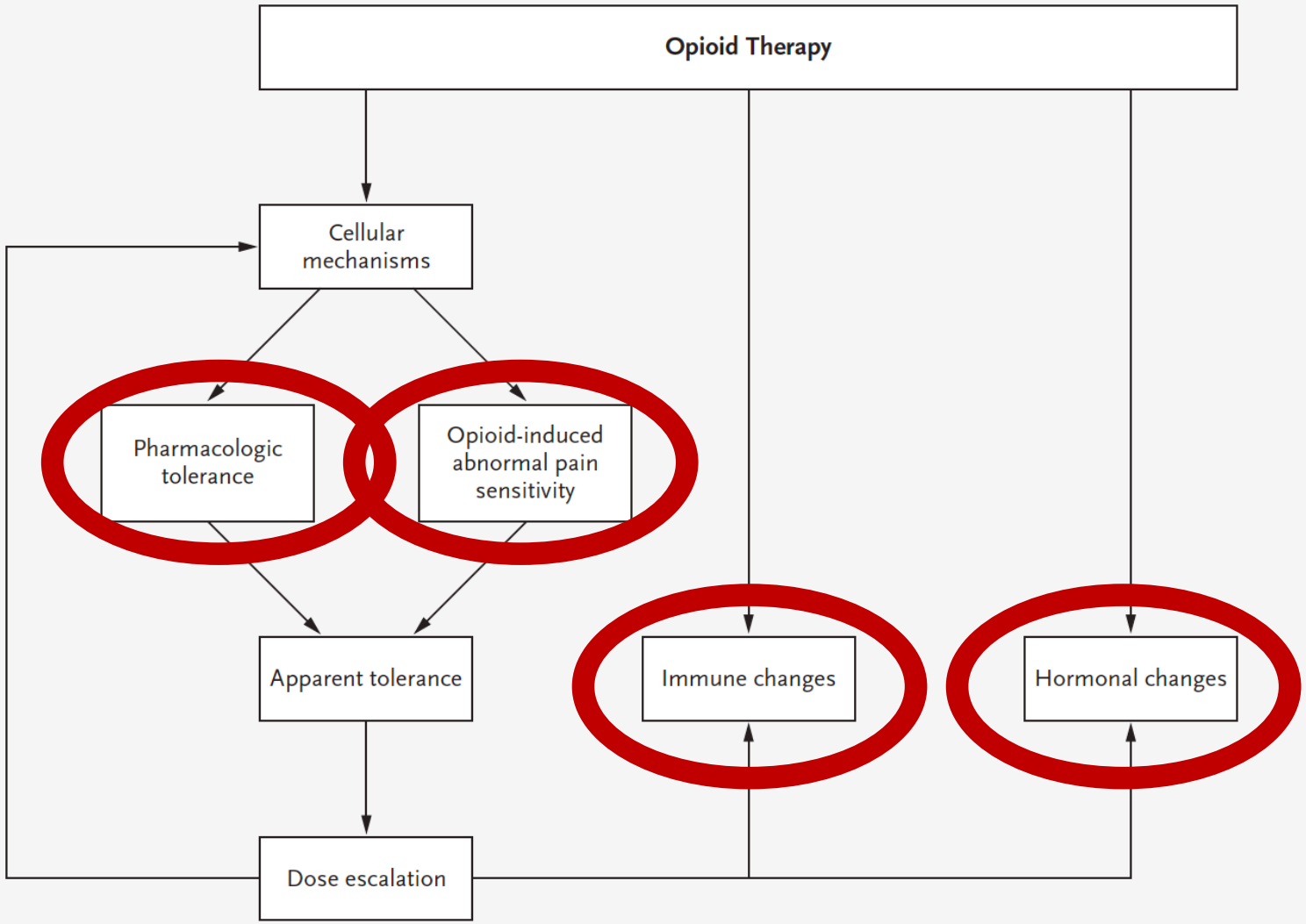


Figure 1. Possible Adverse Effects of Prolonged Opioid Therapy.

Prolonged opioid therapy can lead to cellular and intracellular changes, including activation of *N*-methyl-D-aspartate receptors. Such changes may contribute to pharmacologic opioid tolerance, increased sensitivity to pain (manifested as "apparent" opioid tolerance), or both and the need for dose escalation. Prolonged opioid treatment may also result in hormonal changes and may alter immune function. These effects may be exacerbated by dose escalation in some circumstances.

Ballantyne JC, Mao J: Opioid Therapy for Chronic Pain. NEJM 2003; 349: 1943-53.

HIV Pain and Opioids

- "within the HIV patient population, those with a history of illicit substance abuse are statistically more likely to report pain"
- "comorbid illicit substance abuse increases pain symptoms in persons with HIV"
- Translational evidence suggest opioid agonism may enhance HIV-induced allodynia.

Krashin DL, Merrill JO, Trescot AM. Opioids in the management of HIV-related pain. *Pain Physician*. 2012;15(3):ES157-ES168. http://proxy.library.vanderbilt.edu/login?url=https://www.proquest.com/scholarly-journals/opioids-management-hiv-related-pain/docview/2655995094/se-2.

Gabapentinoids: Anti-neuropathic agents

(*structurally derived from GABA but do not bind GABA receptor)

Membrane Stabilizers: Stop injured nerves from firing

Gabapentin	Pregabalin	Risks/Side Effects
• Absorption 3-4h • Bioavailability 33-66% (bioavailability decreases with increasing doses) • Not metabolized • Excreted in urine • Dose: 300-1200mg tid, Max: 3600mg/d • Cheaper	• Absorption 1h • Bioavailability 90% (bioavailability increases with increasing doses) • Minimal metabolism • Excreted in urine • Dose: 50-300mg q8-12h, Max: 600mg/d	• Lower extremity swelling • Weight gain • Dizziness • Somnolence • Visual disturbances • Gait disturbances • Withdrawal • Respiratory depression • ? Suicidal ideation

Renal failure: These agents don't CAUSE kidney injury, but side effects can be greater in patients with AKI/CKD. UpToDate has recommendations for dosing for renal dysfunction

Gabapentinoids: Gabapentin & Pregabalin

- Dosing– Gabapentin
  - Initial 100-300mg/d → therapeutic 600-1200mg/d → max 3600mg/d

CrCl (mL/minute)[c]	Approximate Maintenance Dose Adjustment	Maximum Maintenance Dose
>79	No dose adjustment necessary	3,600 mg/day in 3 divided doses
50 to 79	No dose adjustment necessary	1,800 mg/day in 3 divided doses
30 to 49	~50% reduction	900 mg/day in 2 to 3 divided doses
15 to 29	~75% reduction	600 mg/day in 1 to 2 divided doses
<15	~90% reduction	300 mg/**day** in 1 dose

https://www.uptodate.com/contents/gabapentin-drug-information?sectionName=Renal%20Impairment%20(Adult)&topicId=8483&search=gabapentin%20&usage_type=panel&anchor=F50991466&source=panel_search_result&selectedTitle=1~148&kp_tab=drug_general&display_rank=1#F50991466

  - Hemodialysis– Initial 100mg 3x/wk after HD → max 300mg 3x/wk after HD

Gabapentinoids: Gabapentin & Pregabalin

- Dosing– Pregabalin
  - Initial 50-100mg/d → therapeutic 150-300mg/d → max 400-600mg/d

CrCl[b] (mL/minute)	Immediate release				
	Usual recommended dose (mg/day)				Dosing frequency
≥60 (normal renal function)	150	300	450	600	2 to 3 divided doses
30 to <60	75	150	225	300	2 to 3 divided doses
15 to <30	25 to 50	75	100 to 150	150	1 to 2 divided doses
<15	25	25 to 50	50 to 75	75	Single daily dose

https://www.uptodate.com/contents/pregabalin-drug-information?sectionName=Renal%20Impairment%20(Adult)&topicId=9473&search=lyrica%20&usage_type=panel&anchor=F50991155&source=panel_search_result&selectedTitle=1~143&kp_tab=drug_general&display_rank=1#F50991155

  - Hemodialysis– 25mg qd (on HD days give after HD) or 25-75mg 3x/wk after HD

Gabapentinoids: Gabapentin & Pregabalin

- Toxicity/side effects
  - Lower extremity swelling
  - Weight gain
  - Dizziness
  - Somnolence
  - Visual disturbances
  - Gait disturbances
  - Withdrawal
  - Respiratory depression
  - ? Suicidal ideation

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR)

When used with CNS depressants or in patients with lung problems

Antidepressants: SNRIs and TCAs

- MOA: Inhibition of serotonin and norepinephrine reuptake in synaptic cleft enhances descending modulation of pain

TCA's :	SNRI's:	Risks/Side Effects

• Amitriptyline, Nortriptyline, Desipramine
• Anti-cholinergic Side Effects
  • Sedation
  • Dry mouth
  • Blurred vision
  • Urinary retention
	• Duloxetine, Milnacipran, Venlafaxine
	• Additional Risks:
	  • May impair platelet aggregation
	  • Hyponatremia
	  • Severe skin reaction
		• sedation
		• sexual dysfunction
		• weight gain
		• may increase suicidal thinking in children/adolescents/young adults
		• serotonin syndrome
		• *relative contraindication in patients with bipolar d/o due to risk of inducing mania

Start low and increase dose over the next several weeks to reduce risk of side effects. May not be effective to help with pain until higher dose is used.

Hint: when in doubt, start with the lowest dose suggested in Epic and titrate up from there

Antidepressants: TCAs

- Rarely first line for depression→ now w/ many alternative applications
- Primarily used for neuropathic pain, central-sensitization, CRPS
- Old, “dirty” drugs → many mechanisms!
  - Inhibit reuptake of norepinephrine/serotonin (primary mechanism; like SNRIs)
  - NMDA antagonism (like ketamine, memantine)
  - Sodium channel blockade (like lidocaine, AEDs)
  - Inhibit adenosine reuptake

Antidepressants: TCAs

Medication	Dosing	Metabolism	Excretion	Notes
Amitriptyline (Elavil)	25-100mg qhs	Liver, CYP2C19, 3A4	Urine, feces	↑↑ ↑ anticholinergic side effects
Nortriptyline (Pamelor)	25-150mg qhs	Liver, CYP2D6	Urine, feces	↑↑ anticholinergic side effects
Desipramine (Norpramin)	100-200mg qhs, <300mg/d	Liver, CYP2D6	Urine	↑ anticholinergic side effects

- Additional toxicities:
  - arrythmias (avoid in cardiac disease)
  - hepatotoxicity (avoid in liver disease)

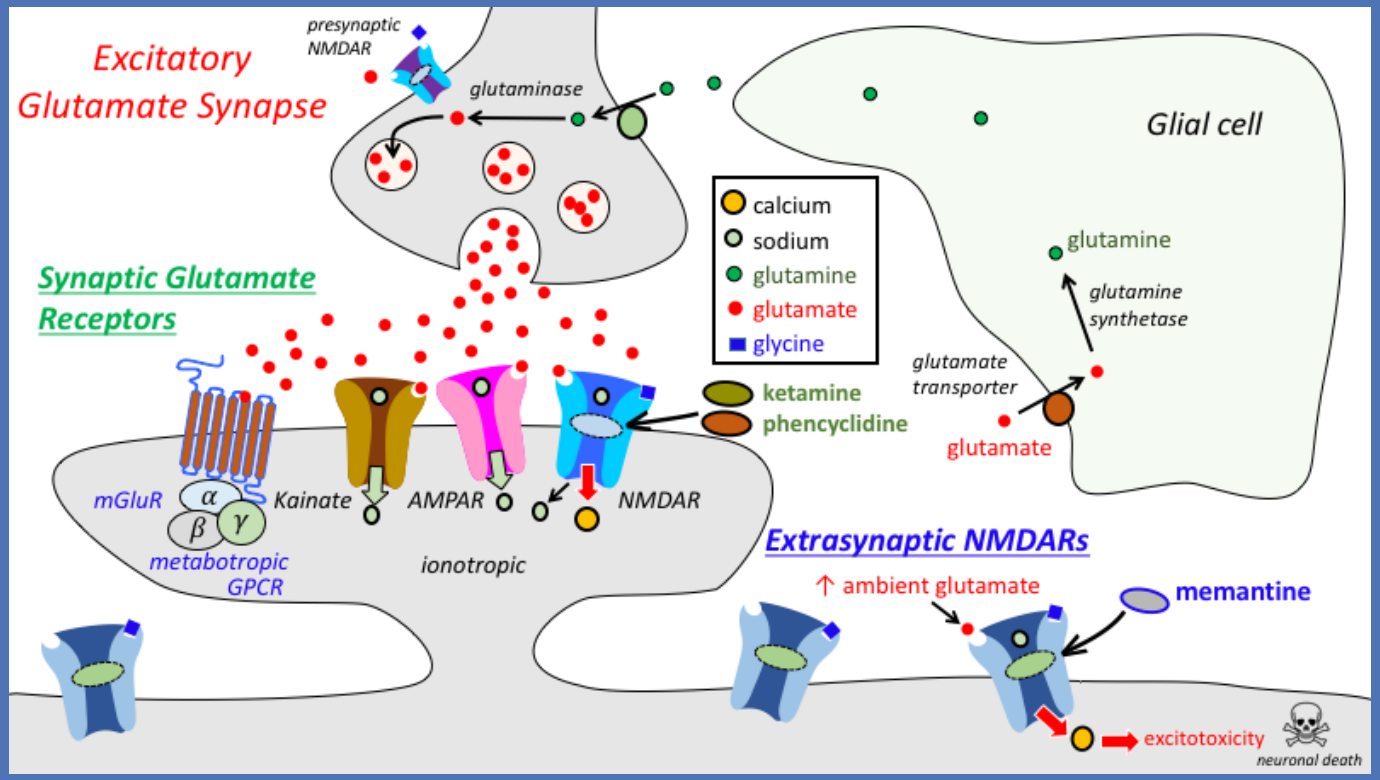
Antidepressants: SNRIs

- Newer medications, fewer side effects than TCAs
- Mechanism: serotonin/norepinephrine reuptake inhibition
- Primarily used for neuropathic pain, central-sensitization, CRPS
- Side effects: hyponatremia, severe skin reaction

	Dose	Metabolism	Excretion	Notes
Duloxetine (Cymbalta)	30-60mg qd	Liver, CYP2D6, 1A2	Urine, feces	- First line for neuropathic pain - No analgesic benefit of higher doses (e.g. 120mg qd)
Venlafaxine (Effexor)	75-225mg qd	Liver, CYP2D6	Urine	
Milnacipran (Savella)	50mg q12h, <200mg/d		Urine	- Approved for fibromyalgia - Causes significant nausea

- Lamotrigine: sodium channel blocker
  - Requires slow titration (up to 2 months) to reduce risk of CNS side effects and serious toxicity (Stevens-Johnson Syndrome)
- Carbamazepine
- Oxcarbazepine

Memantine (Namenda)



- NMDA receptor antagonist
- Start at 5mg BID and titrate to 10mg BID

Muscle Relaxant

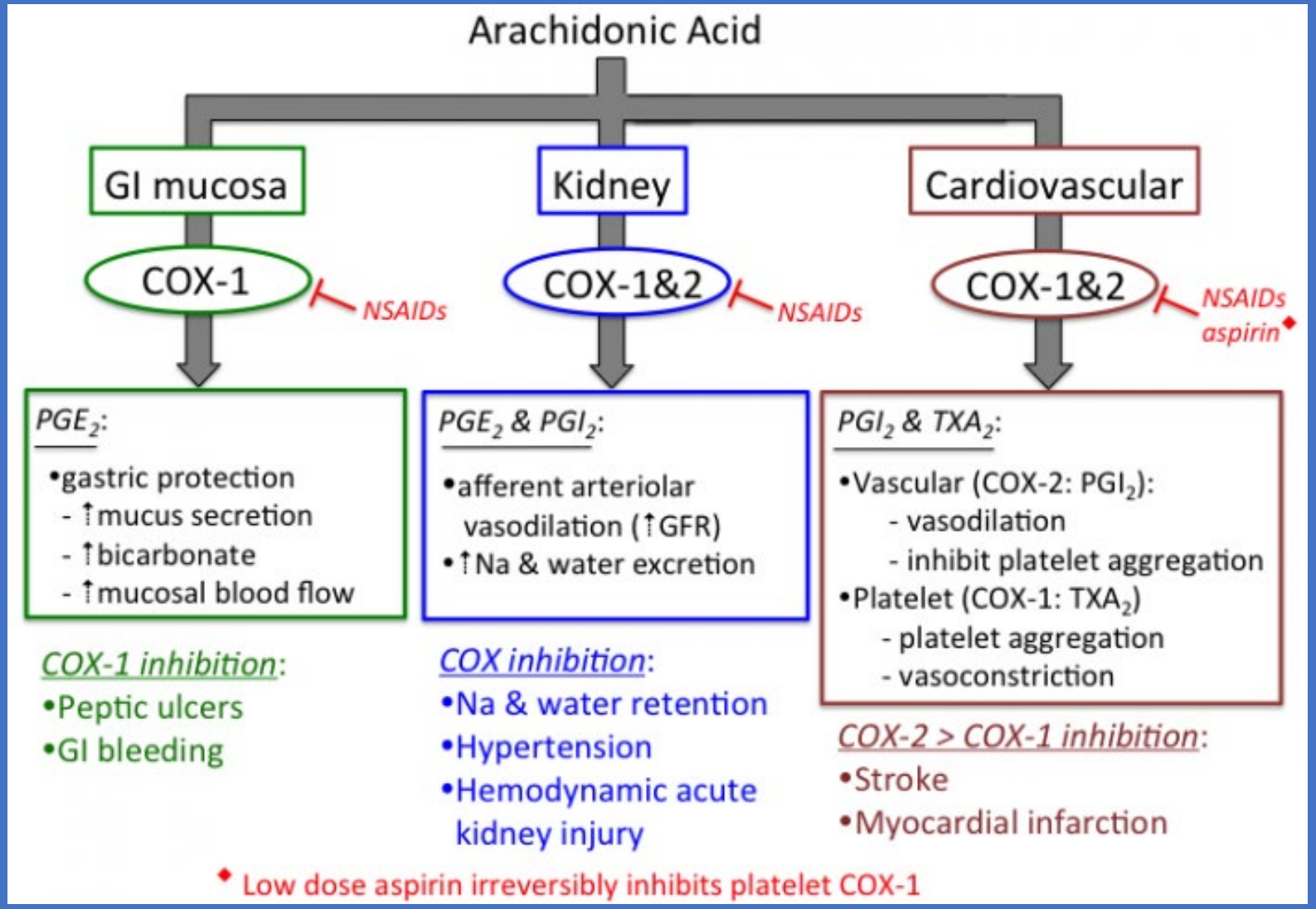
- Robaxin is usually well-tolerated with few side effects
  - Can order 500mg, 750mg, or 1000mg up to 4x/day depending on how “robust” the patient is
- Flexeril is usually well-tolerated too, but can cause more somnolence (TCA-like properties)
- Tizanidine
  - Will lower BP (good if patient has HTN, bad if hypotensive)
  - Causes somnolence (good if pt has difficulty sleeping at night, bad if causes sleepiness during the day)
  - Can cause urinary retention in older adults
- Avoid Valium due to highly addictive nature of benzodiazepines and increased risk of sedation and death if taken in conjunction with opioids

Acetaminophen (Tylenol)

- Dosing:
  - No liver disease– 3g/day in divided doses
  - CLD, no EtOH use-– 2g/day in divided doses
  - CLD and EtOH use OR acute hepatitis– AVOID
  - Renal disease– no adjustments

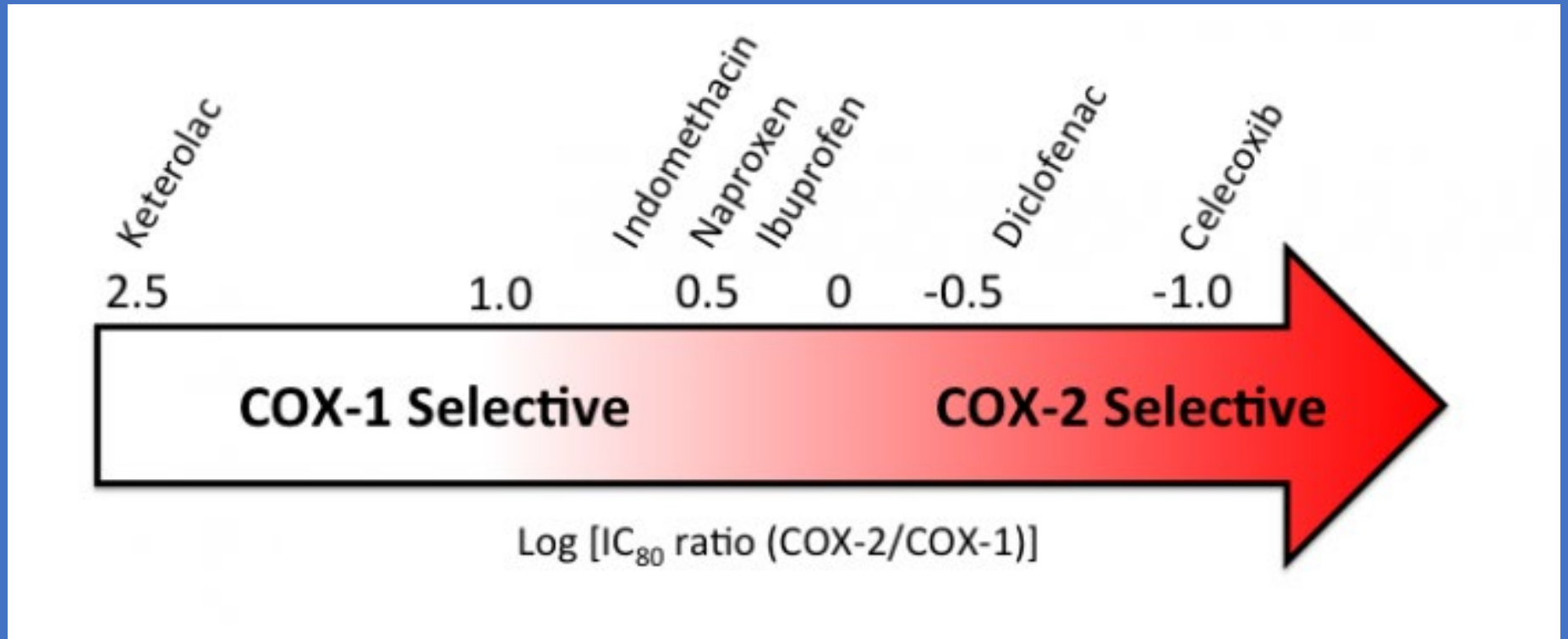
- Metabolism/toxicity:
  - Normal doses– hepatic conjugation
  - Toxic doses– minor (CYP) pathway generates large amounts NAPQI → hepatic necrosis
    - NAPQI normally conjugated/inactivated easily
    - High doses/EtOH overwhelm this process

NSAIDs: Downstream Effects



NSAIDs: COX-1 vs COX-2 Inhibition

- COX-1: housekeeping gene, constitutively active
- COX-2: inducible (exception– kidney + CNS = constitutive)



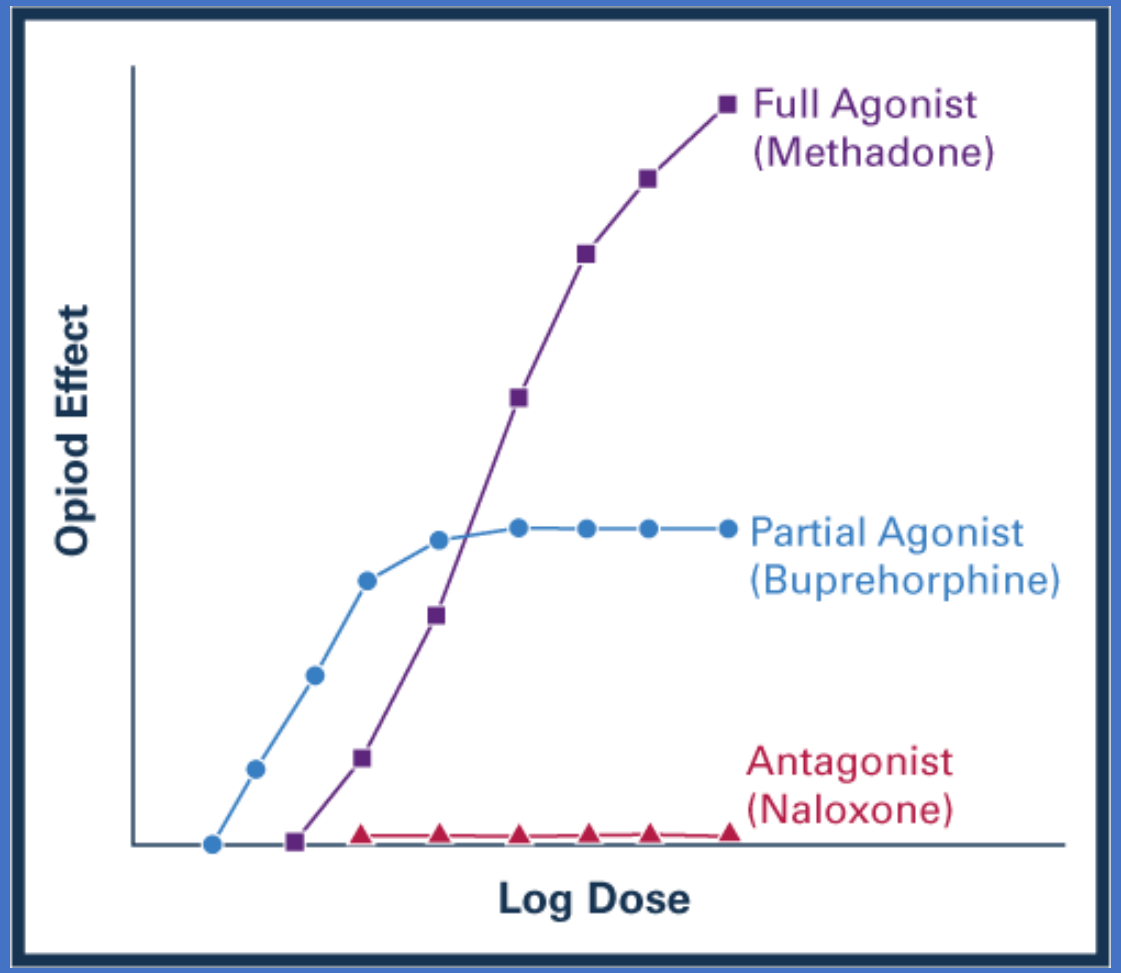
NSAIDs: COX-2 Preferential

Medication	Dosing	Metabolism	Excretion	Side effects / Toxicities	Notes
Celecoxib (Celebrex)	PO: 100-200mg BID Healthy: Max 400mg/d Cardiac disease: contraindicated	Hepatic	Feces and urine	Renal toxicity ?Increased stroke and MI risk	Slow onset (up to 3hrs) Long half life (11 hrs) No decrement in platelet function No GI symptoms
Meloxicam (Mobic)	PO: 7.5mg-15mg QD Healthy: Max 15mg/d	Hepatic	Urine	Less GI toxicity	COX-2 preferential Long half life (20 hours)

Topicals

- Benefit: minimal systemic absorption
- Benefits unclear
- Capsaicin: depletes Substance P
  - May be effective at higher concentrations (8%)
- Lidocaine patches
- Diclofenac gel: for inflammatory pain

Safer Opioid Options: Buprenorphine



- Partial agonist at μ-opioid receptor with high affinity and slow dissociation from the μ-opioid receptor
- Antagonist at the κ-opioid receptors
- "Ceiling effect" for euphoria, respiratory depression, constipation, tolerance
- May reduce hyperalgesia
- Contraindications: resp depression, acute asthma attack, hypersensitivity rxn, SBO/ileus
- Most common side effects: N/V, dizziness, somnolence, constipation

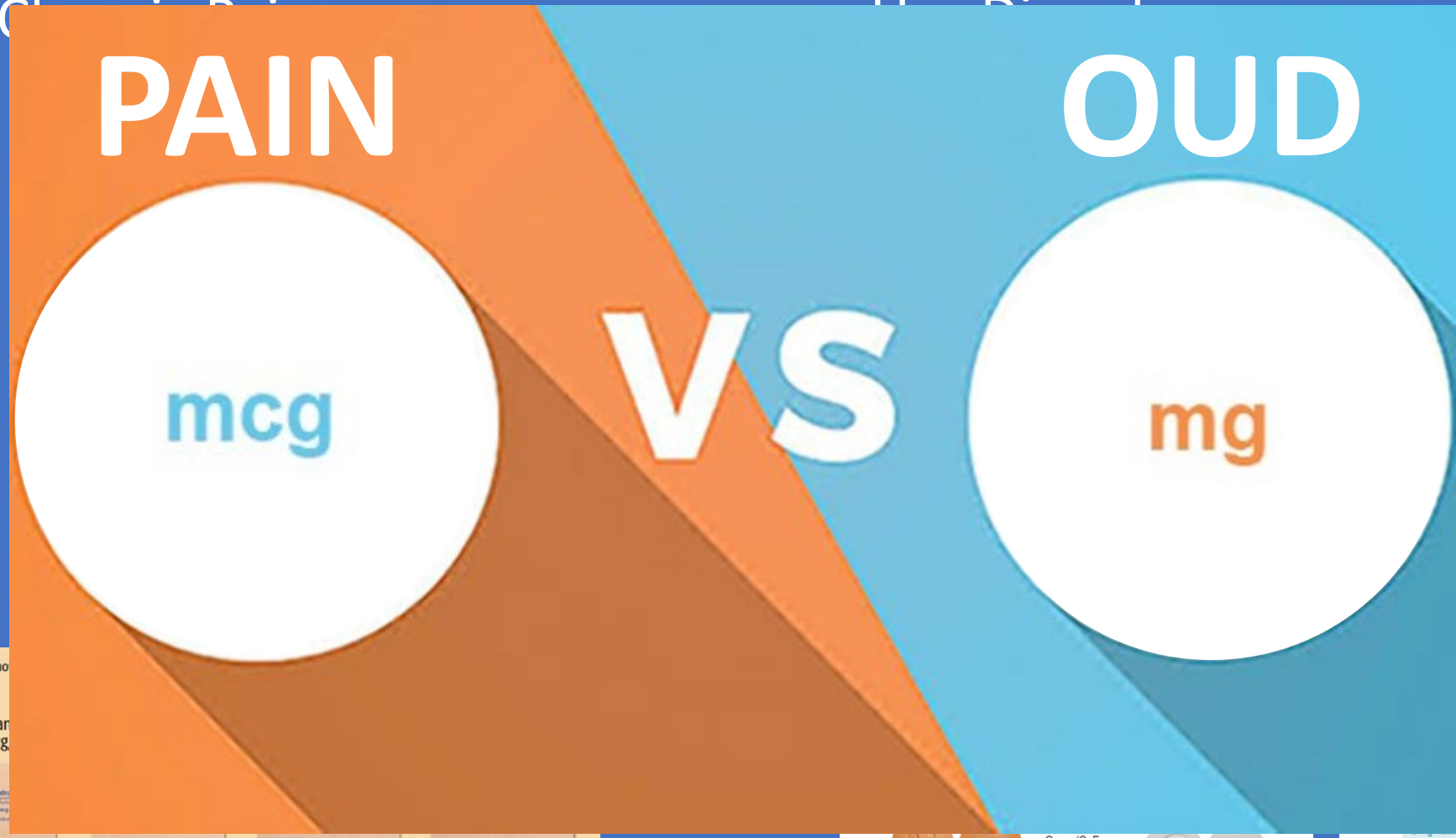
Buprenorphine

- FDA Approved for Chronic Pain:
  - Buccal: Belbuca
    - 75mcg – 900mcg BID
  - Transdermal: Butrans 7-day patch
    - 5, 7.5, 10, 15, 20 mcg/h

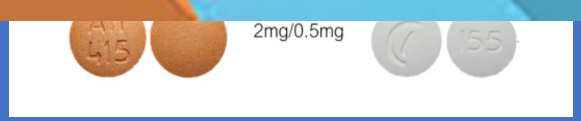
- FDA Approved for Opioid Use Disorder
  - Sublingual:
    - Suboxone or Zubsolv (buprenorphine/naloxone)
    - Subutex (buprenorphine only)
  - Buccal: Bunavail
  - Injectable: Sublocade
  - Implantable: Probuphine

Buprenorphine

- FDA Approved for
- FDA Approved for Opioid



ne)
e only)
ne



Opioids in the Management of HIV-Related Pain

Daniel L. Krashin, MD[1], Joseph O. Merrill, MD[1], and Andrea M. Trescot, MD[2]

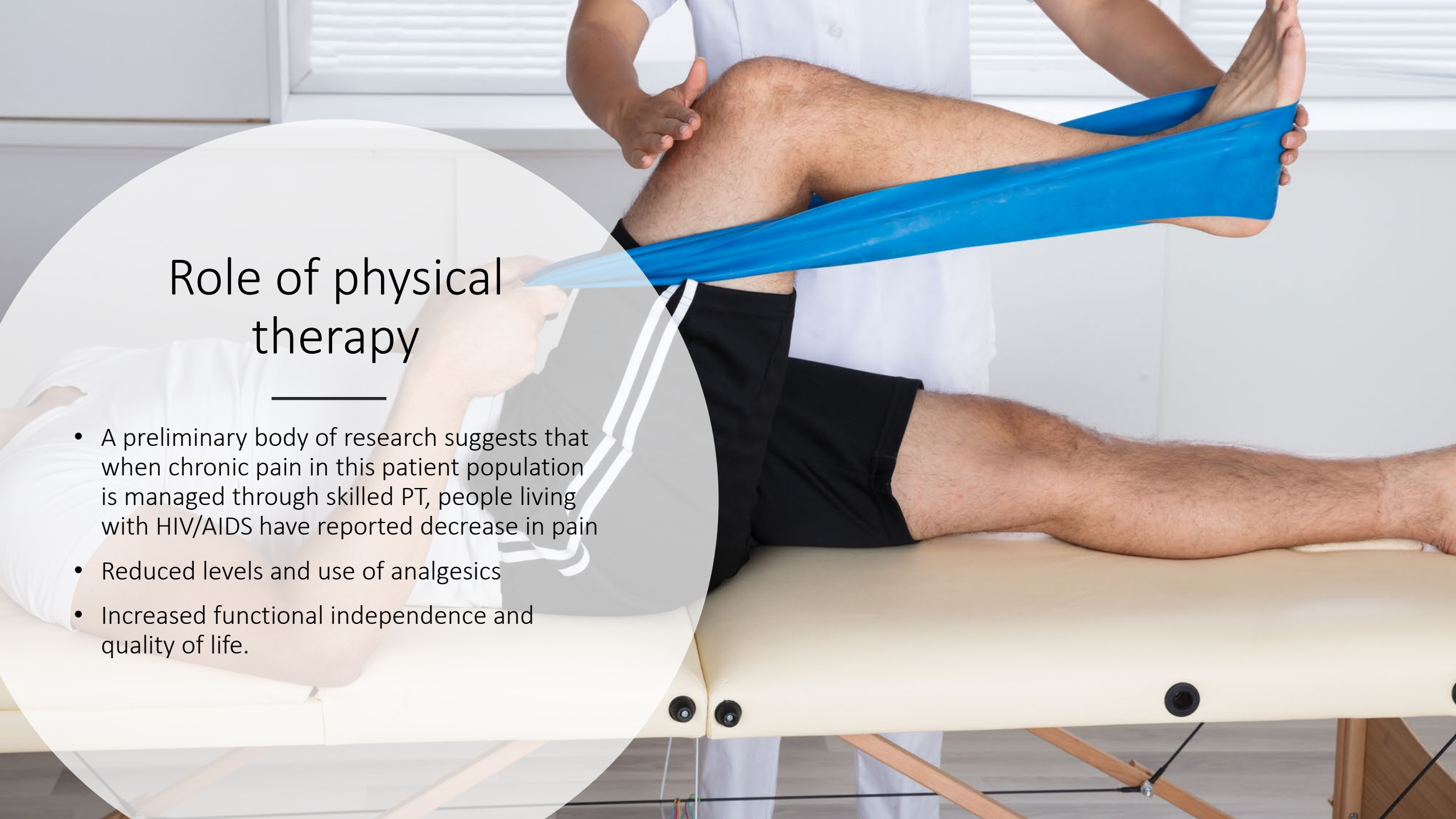
Pain Physician 2012; 15:ES157-ES168 • ISSN 2150-1149

Table 4. *Analgesic medications and clinically significant interactions with ARVs.*

Medication	Level Affected	Effect on ARV	Management
Nonopioids			
Acetaminophen		Increased doses of atazanavir and rilpivarine	No adjustment needed
NSAIDs			Avoid piroxicam with ritonivir or indinavir
Celecoxib		May increase efavirenz level	May raise risk of renal injury with tenofovir
Amitriptyline	Increased by ritonavir		Use decreased dose of amitriptyline, monitor for side effects
Cannabis		Decreases atazanvir levels	Monitor clinical response
Lamotrigine	Decreased by lopinavir/ritonavir		May need to increase lamotrigine dosage
Gabapentin	No direct interaction, but antacid in didanosine decreases gabapentin absorption		Stagger diadanosine and gabapentin dosing
Pregabalin			
Opioids			
Tramadol	Metabolized to active drug by 2D6, hence less effective when given with ritonavir		Use alternate medication
Codeine			
Morphine	May be decreased by ritonavir, indinavir		Monitor for signs of withdrawal
Oxycodone	May be increased by ritonavir		
Hydrocodone	May be decreased by ritonavir		Monitor for withdrawal, rarely seen clinically
Buprenorphine	Mild decrease with efavirenz		
	Ritonavir, indinavir and iaquinavir: potential increase (3A4 inhibition)		Monitor for sedation
	Increase with atazanavir, delavirdine		Monitor for sedation
Methadone	Efavirenz and nevirapine can lower levels by 50%		Monitor for withdrawal
	Etravirine causes minor decrease in methadone level		
	Lopinavir/ritonavir and darunavir/ritonavir cause decrease in level with 2 week lag time		
		Stavudine: decreased absorption	
		Zidovudine: increased levels	
		Didanosine: decreased levels	

Role of physical therapy

- A preliminary body of research suggests that when chronic pain in this patient population is managed through skilled PT, people living with HIV/AIDS have reported decrease in pain
- Reduced levels and use of analgesics
- Increased functional independence and quality of life.

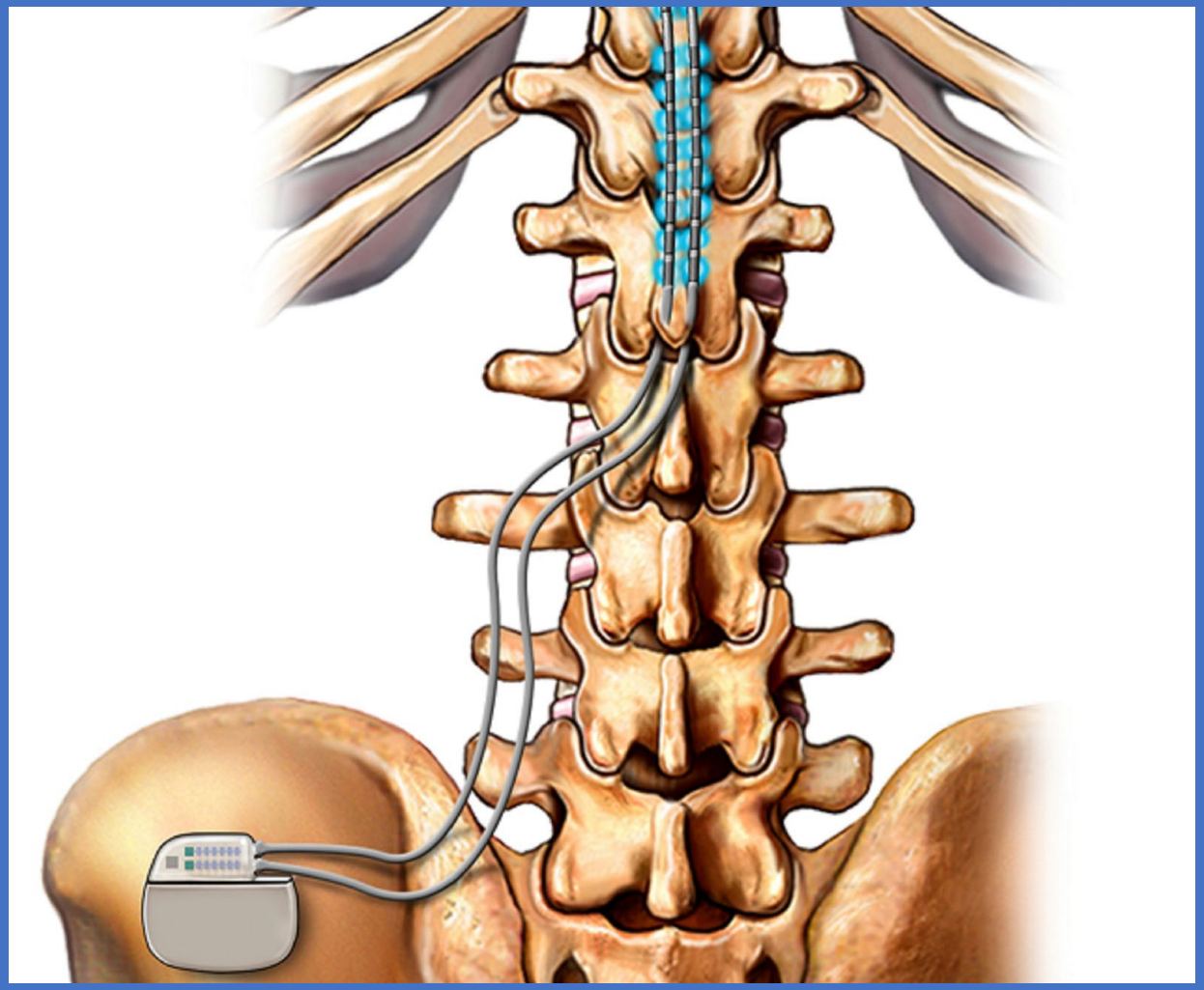


Psychosocial approaches

- Reduced perceived pain, pain behavior, and restore function
- CBT: helps patient identify and change maladaptive thoughts and behaviors regarding their health and pain problems; decreases catastrophization and helplessness; improves coping and functioning
- Hypnotherapy
- Biofeedback: decreases autonomic arousal, increase patient's sense of self-efficacy and decrease avoidance of activity.
- Empowered Relief

Neuromodulation

- Spinal cord stimulation
- Stimulation of dorsal column tract of spinal cord changes way brain interprets pain signals.
- Placed by interventional pain physicians after thorough evaluation, psych eval, and insurance approval



References

- Addis DR, DeBerry JJ, Aggarwal S. Chronic Pain in HIV. Molecular Pain. 2020;16. doi:10.1177/1744806920927276
- Ballantyne JC, Mao J: Opioid Therapy for Chronic Pain. NEJM 2003; 349: 1943-53.
- Krashin DL, Merrill JO, Trescot AM. Opioids in the management of HIV-related pain. *Pain Physician*. 2012;15(3):ES157-ES168. http://proxy.library.vanderbilt.edu/login?url=https://www.proquest.com/scholarly-journals/opioids-management-hiv-related-pain/docview/2655995094/se-2.
- Lawson E, Sabin C, Perry N, et al. Is HIV Painful? An Epidemiologic Study of the Prevalence and Risk Factors for Pain in HIV-infected Patients. *Clin J Pain*. 2015;31(9):813-819. doi:10.1097/AJP.0000000000000162
- Merlin, J.S., Zinski, A., Norton, W.E., Ritchie, C.S., Saag, M.S., Mugavero, M.J., Treisman, G. and Hooten, W.M. (2014), A Conceptual Framework for Understanding Chronic Pain in Patients with HIV. Pain Pract, 14: 207-216. https://doi.org/10.1111/papr.12052
- Pullen, Sara D. DPT, MPH, CHES. HIV and Chronic Pain: The Emerging Role of Physical Therapy. Rehabilitation Oncology 38(2):p E41-E42, April 2020. | DOI: 10.1097/01.REO.0000000000000212
- Scott, Whitneya,b,*; Garcia Calderon Mendoza del Solar, Maitea; Kemp, Harrietc; McCracken, Lance M.d; C de C Williams, Amandae; Rice, Andrew S.C.c. A qualitative study of the experience and impact of neuropathic pain in people living with HIV. PAIN 161(5):p 970-978, May 2020. | DOI: 10.1097/j.pain.0000000000001783