Chronic Pain and Psychiatric Comorbidities: A Clinical Update

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Disclosure

- I have no relevant financial relationships with ineligible companies.

Background

- Consultation-Liaison psychiatrist invited to run a chronic pain department despite no (minimal?) pain mgmt training; quickly appreciated CL psychiatry is well-prepared for the work
  - Eventually became pain and medicine boarded
- Offered biopsychosocial evals/treatment of patients in 3 settings:
  - CL inpatient setting ("Pain-Psych" consults blending psych, pain, addiction)
  - Admission to and during chronic pain day program (medical oversight, detox/meds, etc)
  - Individual outpatient cases for ongoing detox/med mgmt

Objectives

- Defining pain
- Biopsychosocial Dimensions of Chronic Pain
  - BIO: pain neurobiology
  - PSYCHOSOCIAL: pain psychology
- Management
  - Biopsychosocial Staging
  - Pain Psychopharmacology

- Discussion/Q&A

Defining Pain

Behavioral health in managing pain???

- Firstly, the target is more so **chronic** pain…
- Secondly, recognizing/managing psych comorbidities is critical
- Thirdly, psychopharmacology and detox is highly relevant

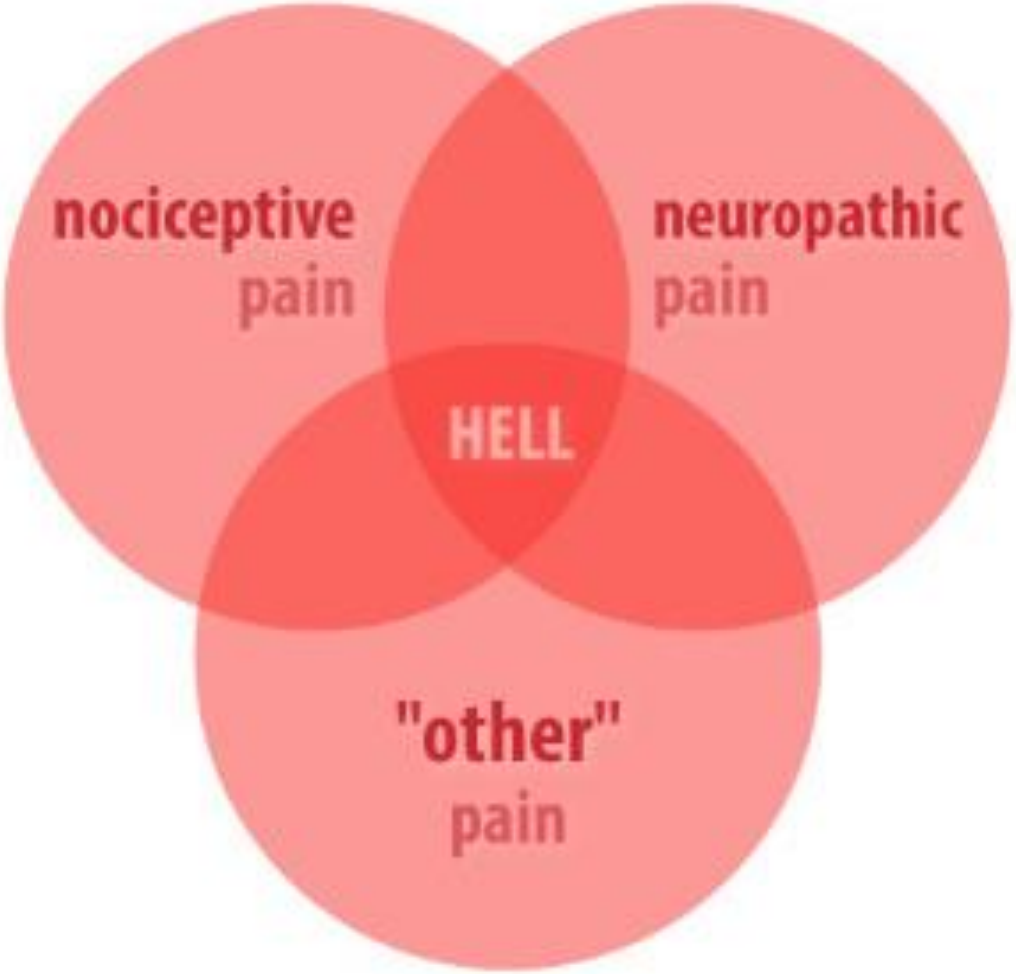
DEPRESSION
Spinal pain 2%-56%, Fibromyalgia 21%-83%, Pelvic pain 19%-22%
Abdominal pain 9%-54%, Arthritis 3%-39%
ANXIETY
Spinal pain 1%-26%, Neuropathic pain 5%-27%, Fibromyalgia 18%-60%
Pelvic pain 12-41%, Abdominal pain 21%-51%, Arthritis 1%-35%

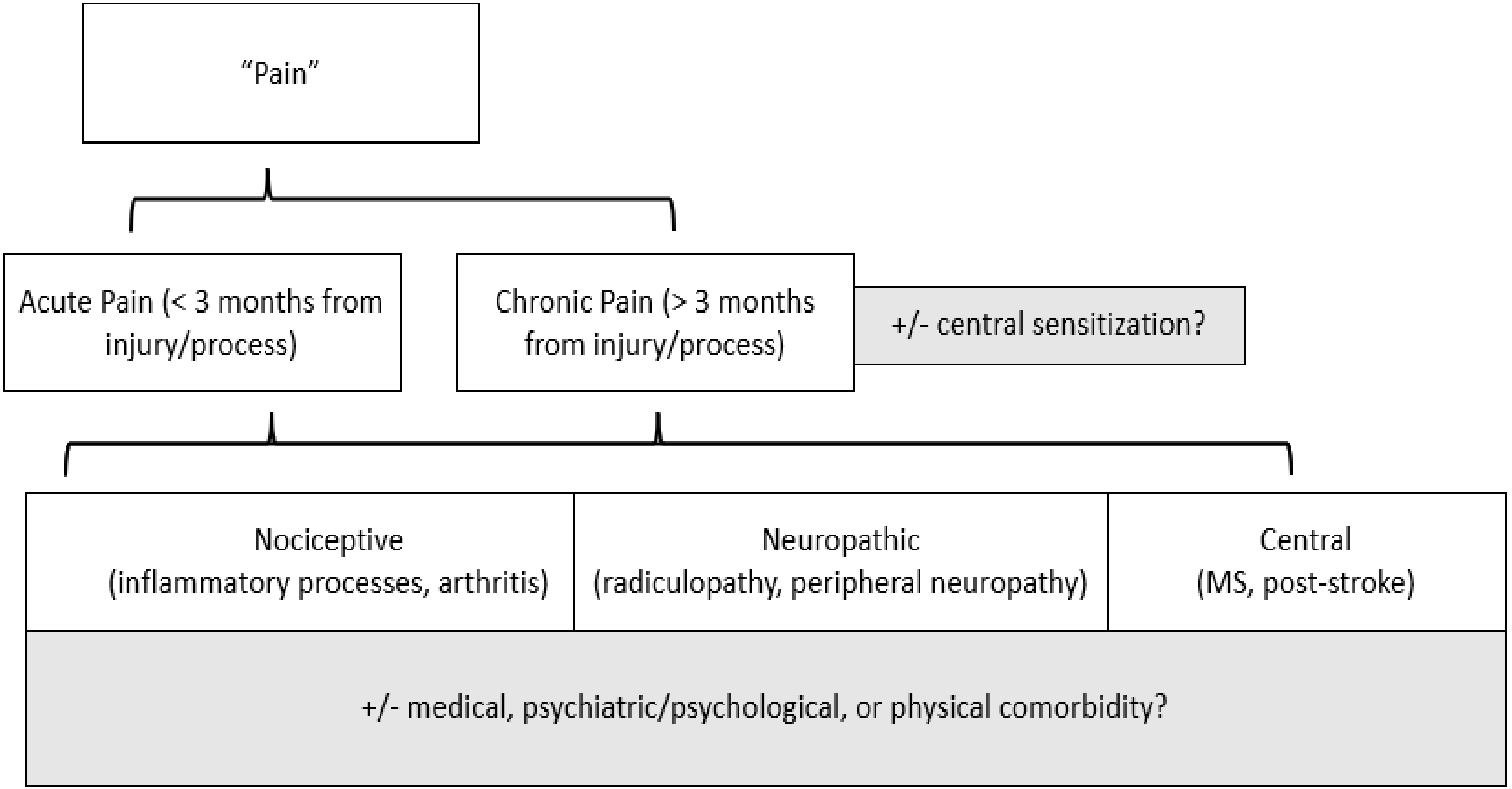
Hooten, 2016

Pain defined…

- Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.
- The function of pain is to protect us against injury and create a pain "memory" so we don't repeat a potentially harmful action.
- The intensity of pain that we experience is based not only on the information between the body part and the brain, but also upon our emotional/psychological reaction to the event.

How most clinicians classify pain…




"Pain"
Acute Pain (< 3 months from injury/process)
Chronic Pain (> 3 months from injury/process)
+/- central sensitization?
Nociceptive (inflammatory processes, arthritis)
Neuropathic (radiculopathy, peripheral neuropathy)
Central (MS, post-stroke)
+/- medical, psychiatric/psychological, or physical comorbidity?

Nociceptive (inflammatory processes, arthritis)	Neuropathic (radiculopathy, peripheral neuropathy)	Central (MS, post-stroke)

This is the most common type of physical pain and refers to harmful or noxious stimuli (an injury) which activate receptors (nociceptors) in the body that send a warning signal of potential or actual harm.

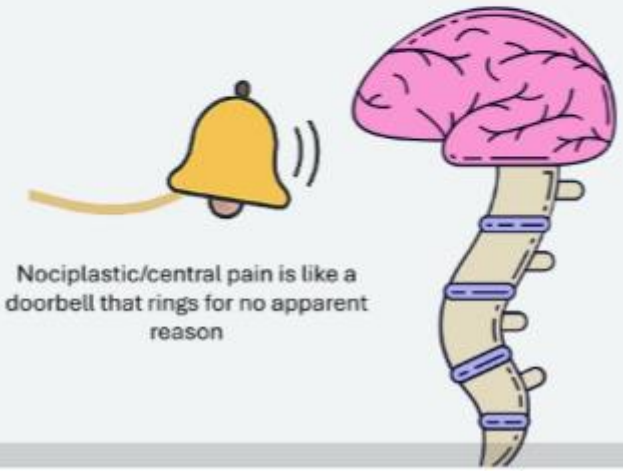
Nociceptive pain is like pressing the doorbell - there is a physical trigger

Neuropathic pain involves abnormal nerve function (diabetic neuropathy, complex regional pain syndrome, etc.).

Neuropathic pain is usually described as shooting, burning in sensation, particularly along the affected nerve. It is also common to have numbness and a tingling sensation.

Neuropathic pain is like a damaged doorbell wire

Noninflammatory/Nonneuropathic (Nociplastic) pain involves abnormal nerve signal processing where there is no known tissue or nerve injury (e.g., fibromyalgia, irritable bowel syndrome).



Nociplastic/central pain is like a doorbell that rings for no apparent reason

Chronic Pain ≠ Acute Pain

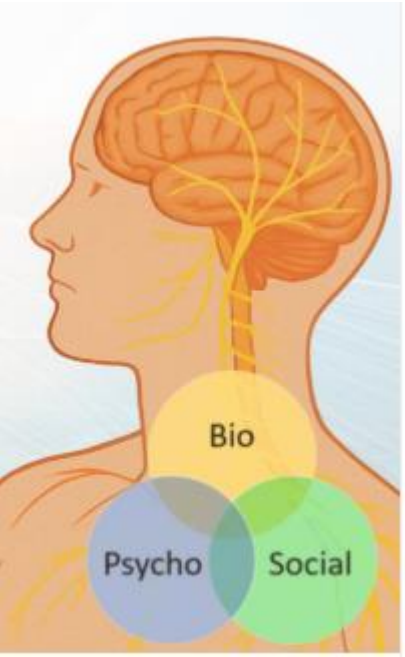
- Chronic Pain = Pain lasting greater than 3-6 months from acute incident, insult, injury, etc
- Acute pain resolves with the expected healing process.
- Chronic pain is maintained by something unexpected…

- Chronic Pain ≠ Acute Pain…
- Chronic Pain ≠ Acute Pain…
- CHRONIC PAIN ≠ ACUTE PAIN…

Chronic Pain as a cross-section only…

- Failure of most pain management: a cross-sectional, focal approach
- Patient presents with pain, and natural approach is to assess/treat in that moment
  - Numeric Rating Scale: 0-10/10 approach
  - Emphasis becomes acute relief
  - Acute relief = analgesics
  - Only “true” analgesics = opioids
  - Back to square one…
- Consider a broader understanding of pain

Biopsychosocial Dimensions to Chronic Pain



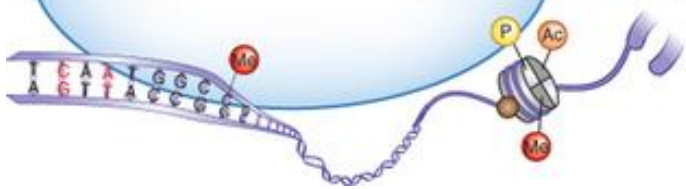
Risk for chronic pain

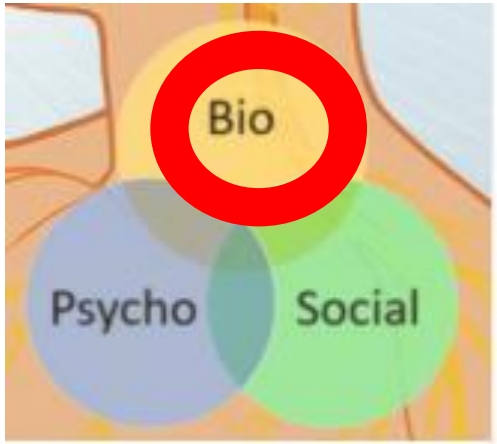
Hardware at birth
- Gender, genotype and epigenetic profile

Environmental influences
- Acute injury or disease at critical developmental periods
- Stressful life events

Gene × environment interactions
- Personality and psychology (for example, pessimism, neuroticism, anxiety, catastrophizing, reward bias)

Innate mechanisms ↔ Acquired mechanisms ↔ Brain vulnerable networks





Central sensitization

Cognitive emotional sensitization (forebrain products)

Brain

Hyperalgesia

Allodynia

Diffuse noxious inhibitory control dysfunction

Spinal cord

Astrocyte proliferation

Neurotrophic factors

Macrophage activation and migration into the nerve and the dorsal root ganglion

Cytokines

Neuropathic pain

Peripheral sensitization

Nerve damage

Maintained nociceptive input

Nitric oxide

TNF-α
IL-1β
IL-6

Lipids

Prostanoid

ATP

NGF

Chemokines

Nociceptive pain

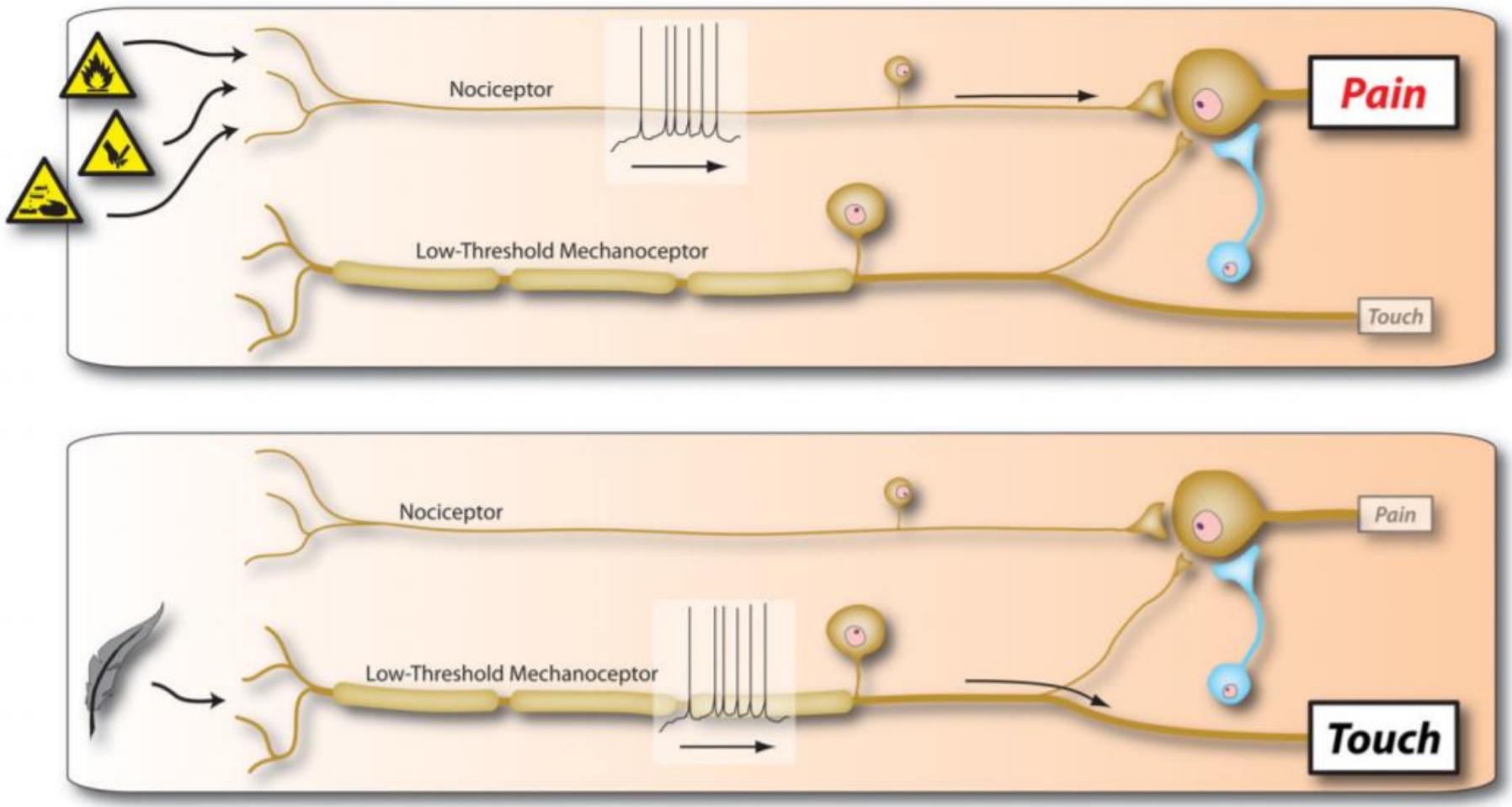
"Neuroinflammatory environment"

Central Sensitization

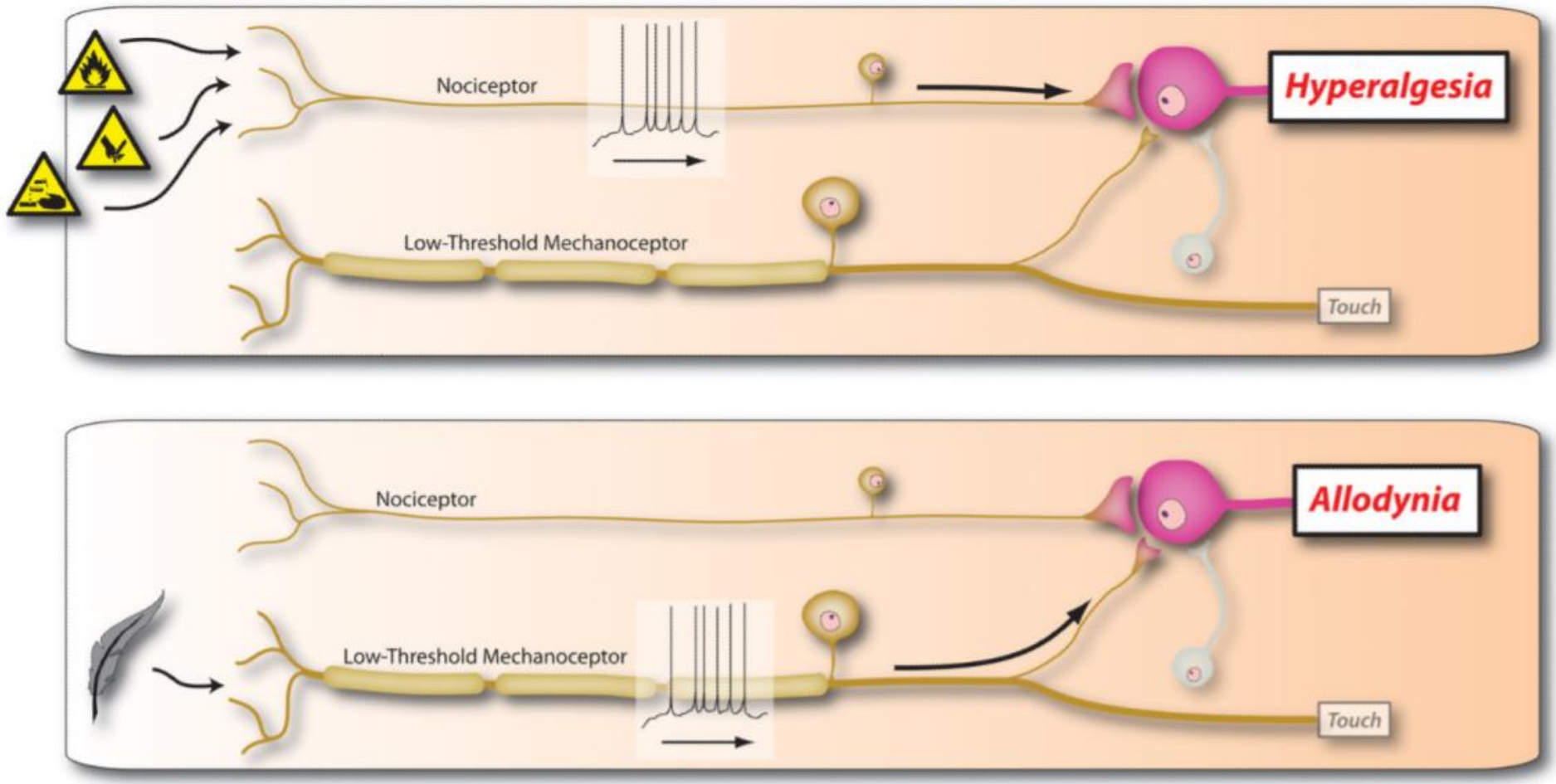
- Central sensitization (CS) involves abnormal and intense enhancement of pain in the central nervous system, characterized by both hyperalgesia and allodynia.
  - Hyperalgesia: excessive pain sensation caused by stimulus meant to cause pain (e.g. light bump hurts excessively/for prolonged state)
  - Allodynia: pain sensation caused by stimulus not meant to cause pain (e.g. light touch/clothes activates pain)
- Windup: progressive increase in pain perception with second-order neural response to repetitive stimulation (more often than every 3 seconds) of peripheral C fibers – AKA temporal summation

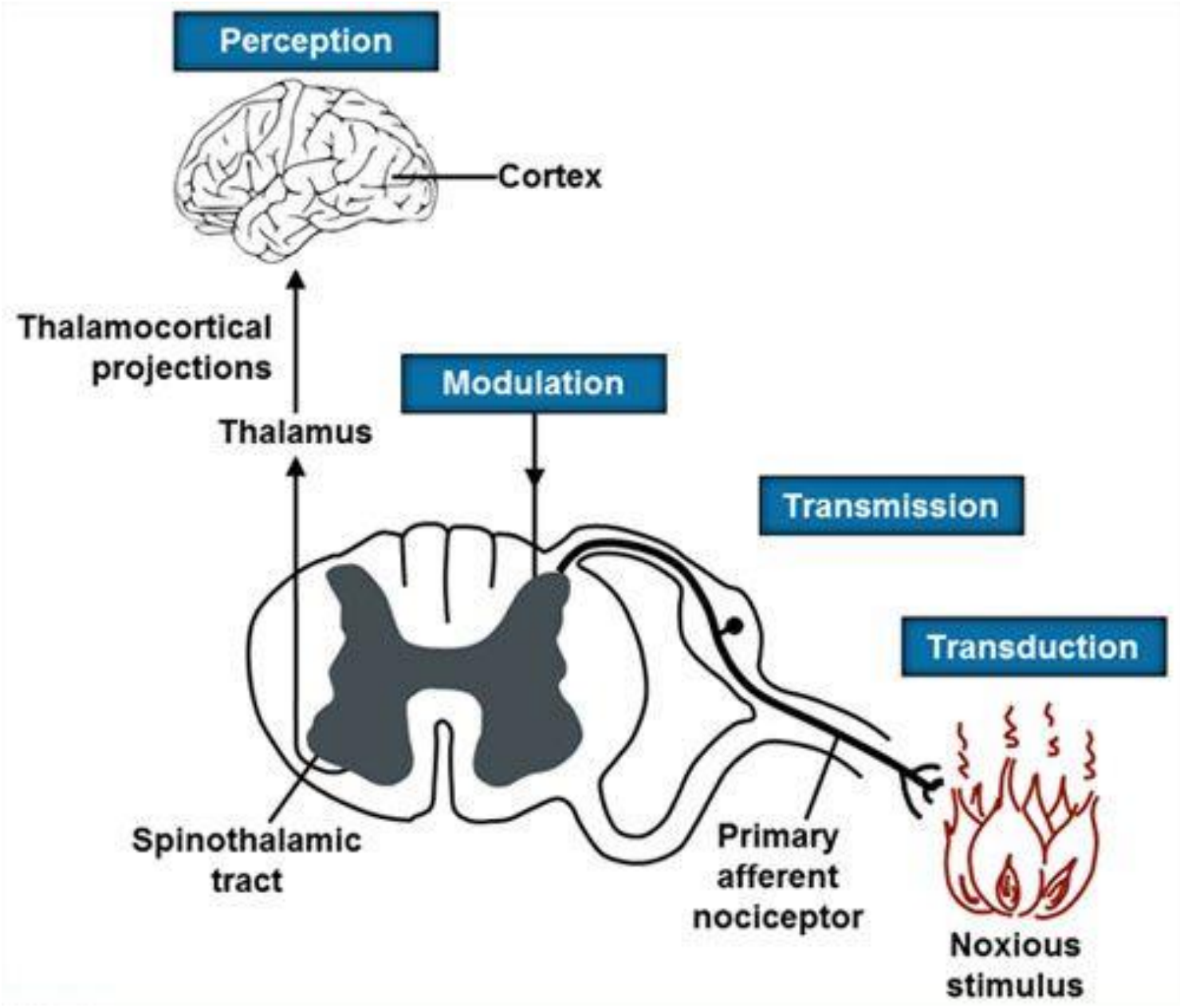
Woolf, 2011; Staud et al, 2007

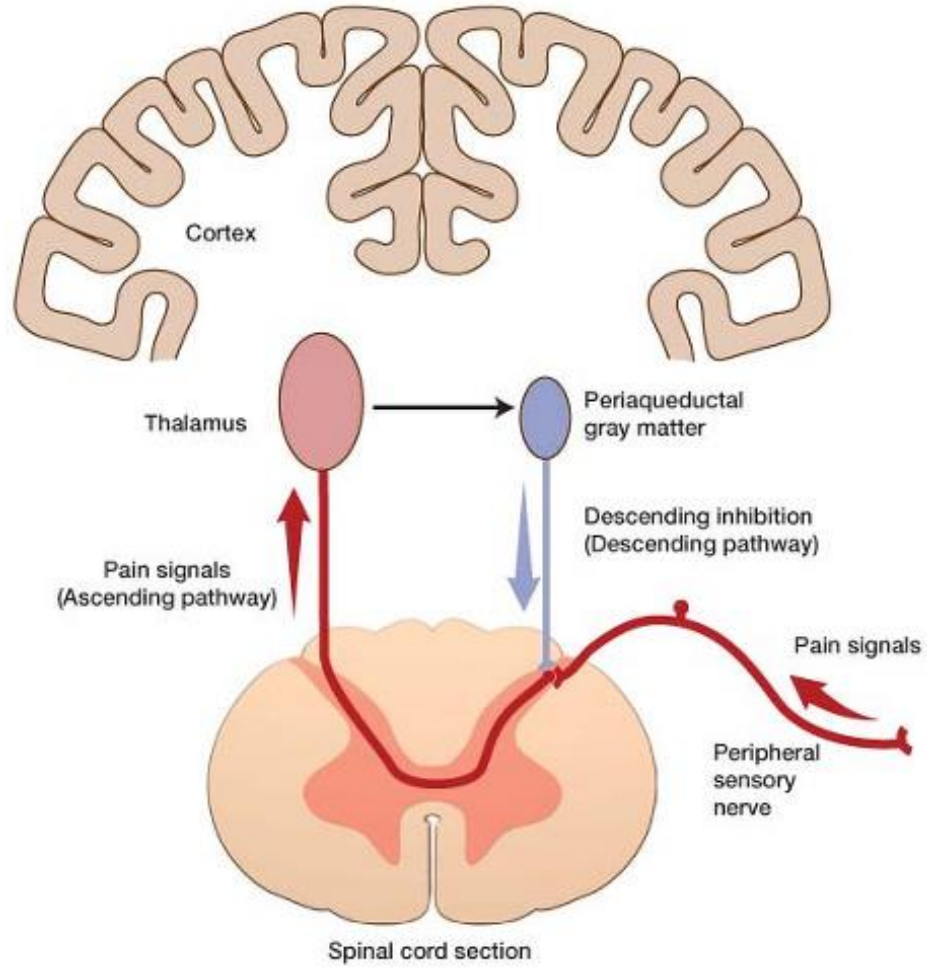
Normal Sensation

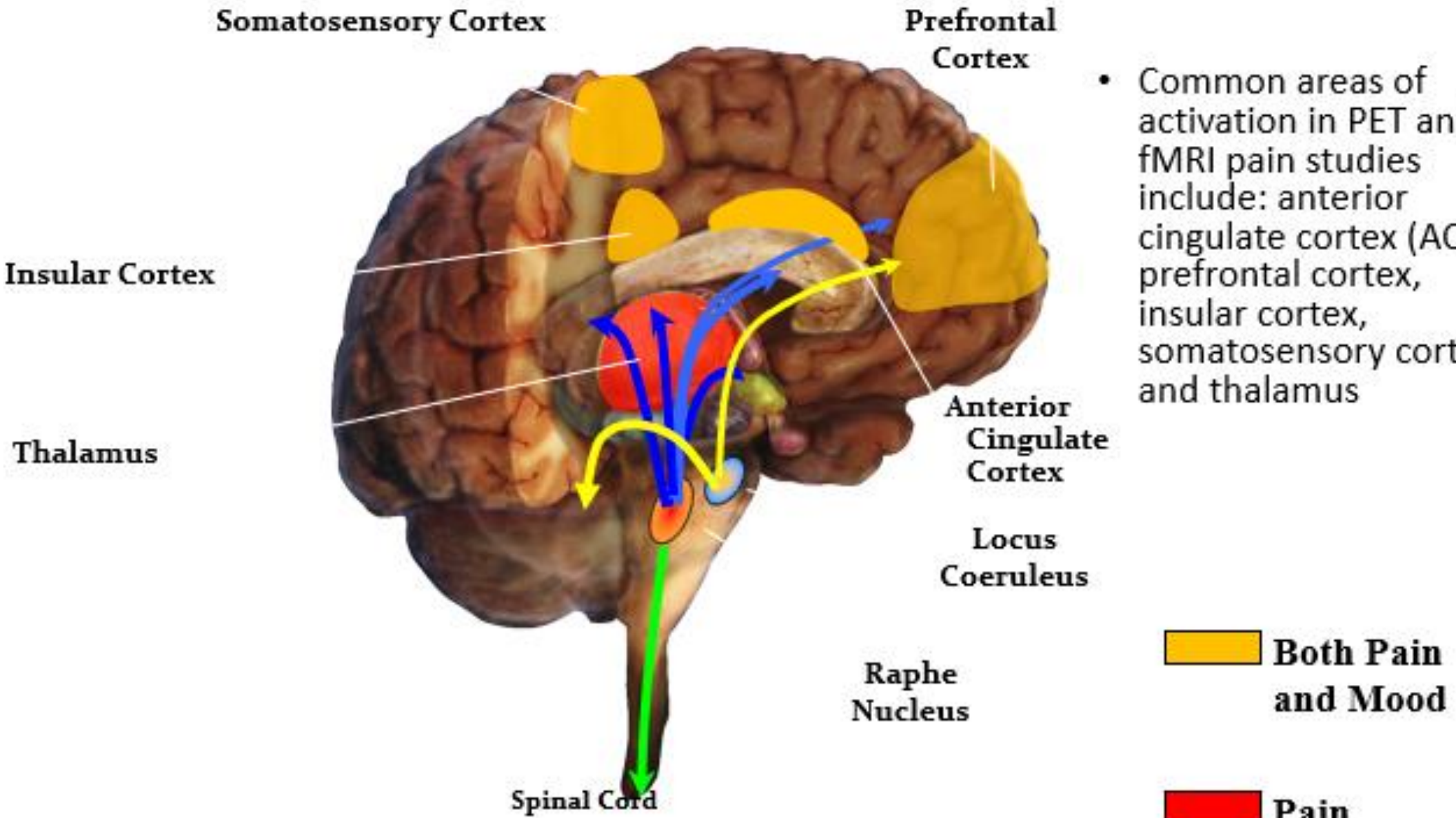


Central Sensitization




Perception
Cortex
Thalamocortical projections
Thalamus
Modulation
Transmission
Transduction
Spinothalamic tract
Primary afferent nociceptor
Noxious stimulus


Cortex
Thalamus
Periaqueductal gray matter
Descending inhibition (Descending pathway)
Pain signals (Ascending pathway)
Pain signals
Peripheral sensory nerve
Spinal cord section

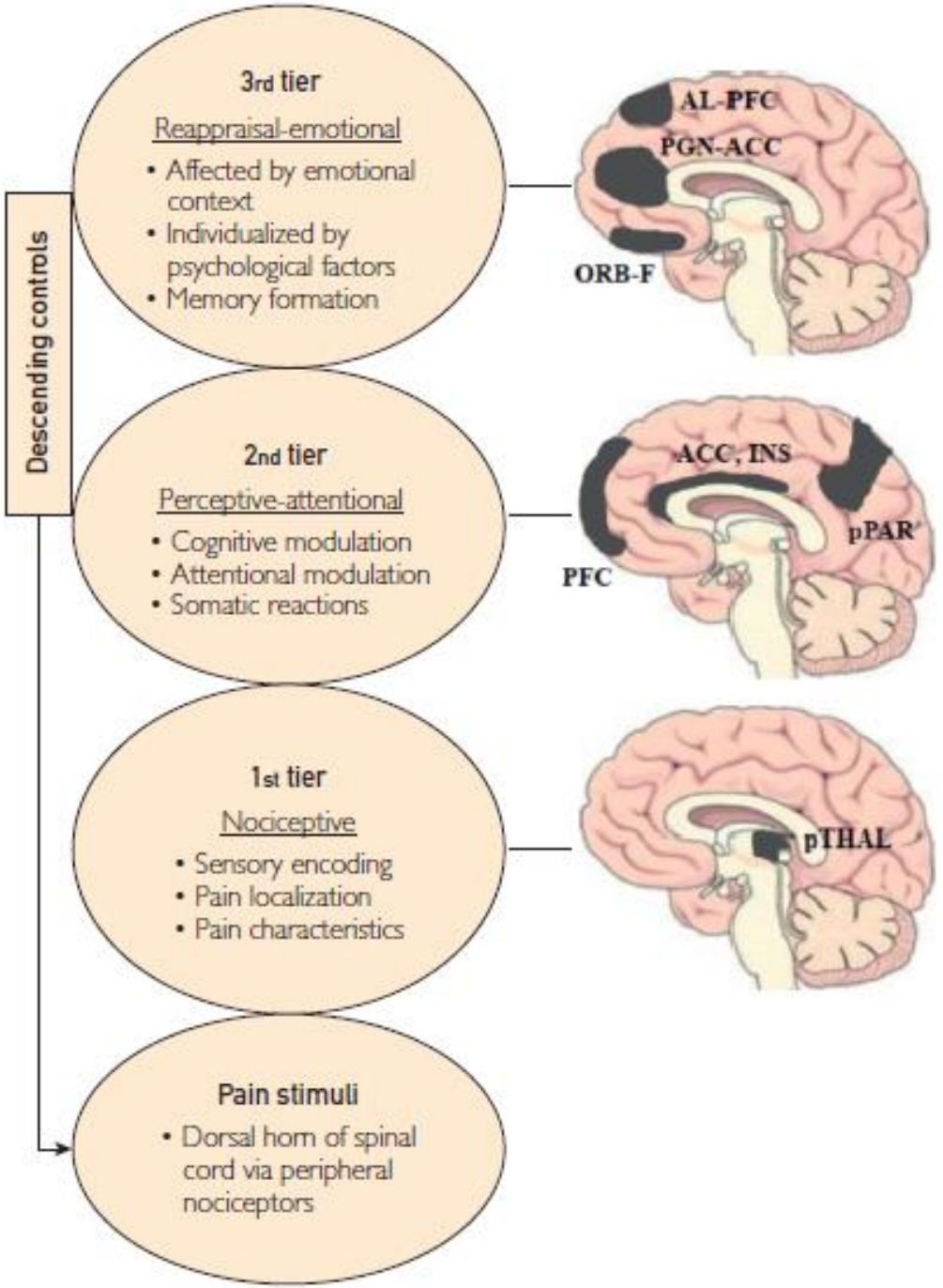


- Common areas of activation in PET and fMRI pain studies include: anterior cingulate cortex (ACC), prefrontal cortex, insular cortex, somatosensory cortex, and thalamus

Sensitization of CNS/brain

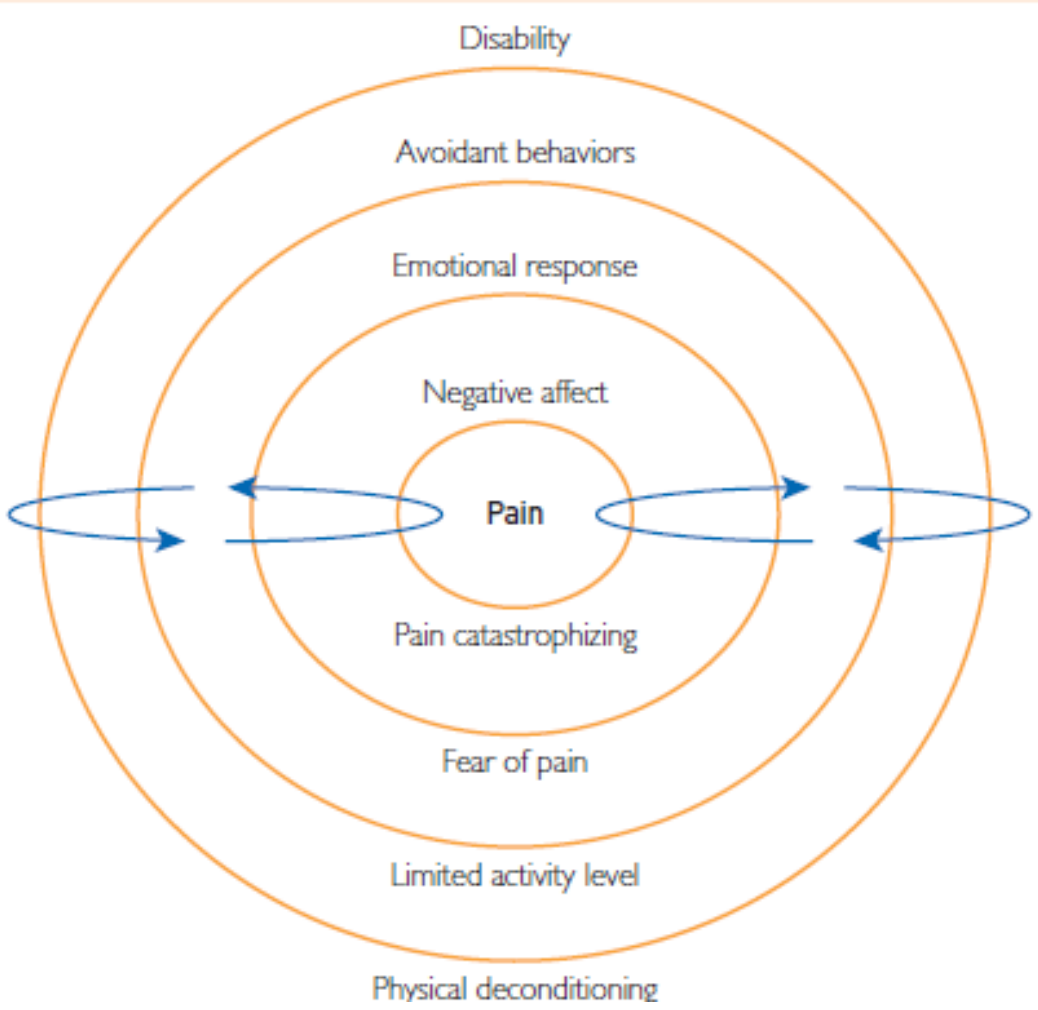
- Repeated hits/traumas sensitize brain structures exacerbating pain experience
- PTSD model: pain/injury/trauma activates amygdala, results in hypervigilance (so more attention directed at pain), sympathetic output (adrenergic fuel to the fire), and avoidance (to escape intolerable sensation)
- Strong neurobiological similarities in PTSD and chronic pain (central sensitization)

Moeller-Bertram et al, 2014;
Hooten 2016.

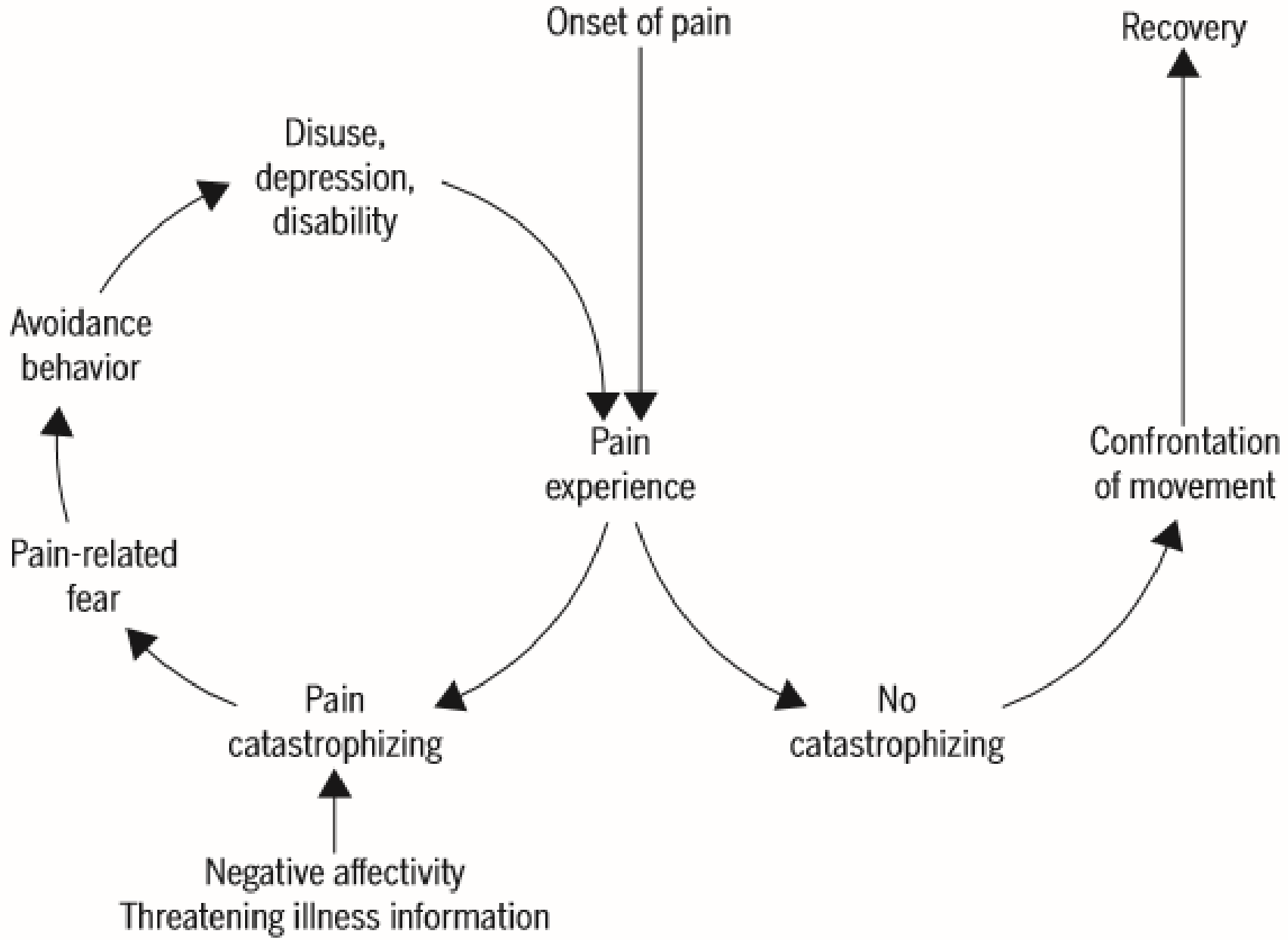


Pain as experience

- Pain experienced as visceral threat to bodily integrity
- Activates vigilance and worry
- Leads to cascade of psychological features



Hooten 2016


Onset of pain
Recovery
Disuse,
depression,
disability
Avoidance
behavior
Pain
experience
Confrontation
of movement
Pain-related
fear
Pain
catastrophizing
No
catastrophizing
Negative affectivity
Threatening illness information

Pain Psychology 101

- Psychology = ABCS
  - Affect - *feelings*
  - Behavior - *actions*
  - Cognitions – *thoughts*
  - Social - *environment*
- Corresponding pain psychology phenotypes:
  - Affect: Pain Distress
  - Behavior: Pain Avoidance
  - Cognitions: Pain Catastrophizing
  - Social: Enabling, stressors and Incentives

Pain Psychology Assessment

- ABCS
  - **A**ffect: distress
    - Resultant feelings of low mood/depression, anxiety/panic, and/or frustration/anger
    - Scale: PHQ-9, GAD-7
  - **B**ehavior: avoidance
    - Social isolation, decreased physical activity (fear of pain/reinjury) and/or avoiding pain sensation itself (excessive medications/drugs: CNS suppressing opioids, benzos, illicits)
    - Scale: Pain Disability Index (PDI)
  - **C**ognitions: catastrophizing
    - Catastrophic/worst-case-scenario thinking distortions (and other irrational thinking)
    - Scale: Pain Catastrophizing Scale (PCS)
  - **S**ocial: Development, stressors, enabling and incentives
    - Think beyond the patient: examine context
    - Scale: Adverse Childhood Experiences Scale (ACES)

Pain Behaviors: Avoidance

Pain Disability Index

Name: _____ **Date:** _____

Rate each category listed below. The rating scale measures the current impact of chronic pain on your everyday life, i.e. how much your pain is preventing you from doing normal activities. CIRCLE the number that best reflects your CURRENT level of disability. If category does not apply to you, circle 0. Your rating should reflect the current, overall impact of pain on your life, not just when the pain is at its worst.

►**Family and Home Responsibilities:** *Refers to activities related to home and family; includes chores or duties performed around the house (e.g. yard work) and errands for other family members (e.g., driving children to school)*

0	1	2	3	4	5	6	7	8	9	10
No disability			Mild		Moderate			Severe		Total Disability

►**Recreation:** *Includes hobbies, sports, and other leisure-time activities*

0	1	2	3	4	5	6	7	8	9	10
No disability			Mild		Moderate			Severe		Total Disability

►**Social Activity:** *Includes parties, theater, concerts, dining-out, and other social activities attended with family and friends*

0	1	2	3	4	5	6	7	8	9	10
No disability			Mild		Moderate			Severe		Total Disability

►**Occupation:** *Refers to activities related to one's job; includes nonpaying jobs, such as homemaker or volunteer worker*

0	1	2	3	4	5	6	7	8	9	10
No disability			Mild		Moderate			Severe		Total Disability

►**Sexual Behavior:** *Refers to the frequency and quality of one's sex life*

0	1	2	3	4	5	6	7	8	9	10
No disability			Mild		Moderate			Severe		Total Disability

►**Self Care:** *Includes personal maintenance and independent daily living activities (e.g. taking a shower, driving, getting dressed)*

0	1	2	3	4	5	6	7	8	9	10
No disability			Mild		Moderate			Severe		Total Disability

►**Life Support Activities:** *Refers to basic life-supporting behaviors such as eating, sleeping, and breathing*

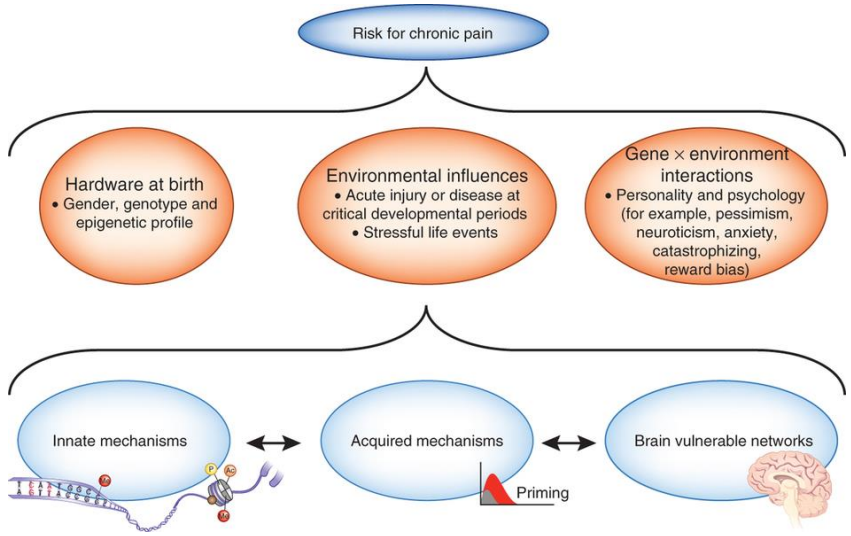
0	1	2	3	4	5	6	7	8	9	10
No disability			Mild		Moderate			Severe		Total Disability

Pain Cognition: Catastrophizing

	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
I worry all the time about whether the pain will end	0	1	2	3	4
I feel I can't go on	0	1	2	3	4
It's terrible and I think it's never going to get any better	0	1	2	3	4
It's awful and I feel that it overwhelms me	0	1	2	3	4
I feel I can't stand it anymore	0	1	2	3	4
I become afraid that the pain will get worse	0	1	2	3	4
I keep thinking of other painful events	0	1	2	3	4
I anxiously want the pain to go away	0	1	2	3	4
I can't seem to keep it out of my mind	0	1	2	3	4
I keep thinking about how much it hurts	0	1	2	3	4
I keep thinking about how badly I want the pain to stop	0	1	2	3	4
There's nothing I can do to reduce the intensity of the pain	0	1	2	3	4
I wonder whether something serious may happen	0	1	2	3	4

ACES

- Could consider this as a screener for adverse/traumatic developmental events (in early childhood)
- Captures self-reported sexual and physical abuse
- Also captures emotionally neglect, bullying, mentally-ill and/or chemically-dependent parents/caregivers, etc.
- May open up dialogue about role of trauma, PTSD, central sensitization, etc.



Psychodynamics of Chronic Pain

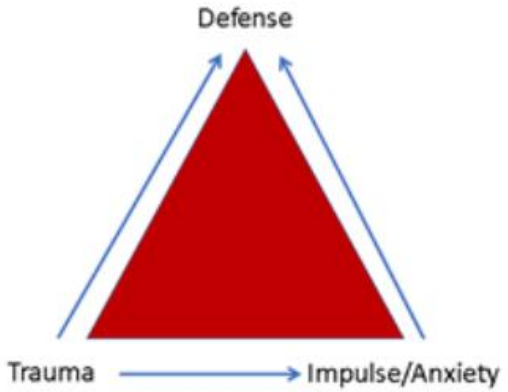
Parallel Pains and Dynamic Dilemmas: Psychodynamic Considerations in Approaching and Managing Chronic Physical Pain

Xavier F. Jimenez

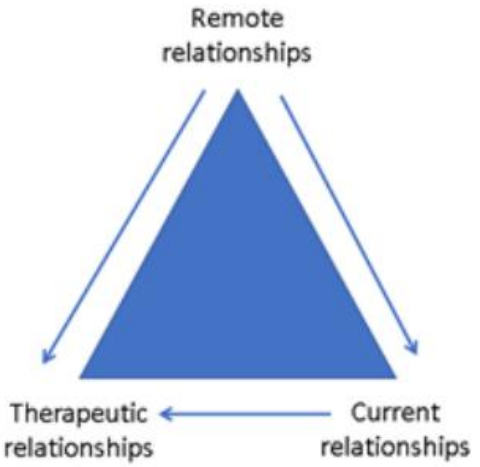
Abstract: Chronic physical pain is prevalent condition and has gained considerable attention in the wake of the opioid crisis and epidemic. As a medical phenomenon, it has highlighted significant gaps in healthcare training, finances, clinical service, and administration. The psychodynamic determinants of pain symptoms or the need for analgesia are rarely considered in the medical management of this problem. The specific objective of this article is to offer a general psychodynamic understanding of chronic physical pain. As a psychodynamically oriented, medically informed psychiatrist practicing in a multidisciplinary pain management program, I propose a clinical construct of psychologically rich "parallel pains" to chronic physical pain, and that these pains inform important interpersonal issues dubbed "dynamic dilemmas." Chronic physical pain is defined, clinical examples are provided, and general implications are considered.

Keywords: chronic pain, psychodynamic psychotherapy, biopsychosocial, consultation psychiatry

*Intra*personal (triangle of conflict)



*Inter*personal (triangle of persons)



Jimenez, 2019

Social: Stressors, enabling and incentives

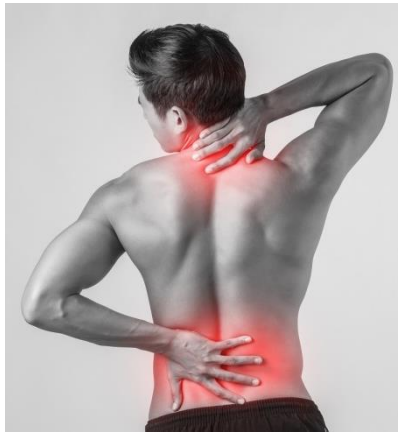
- Beyond scales: think contextually about family, work, etc.
  - Stressors/challenges: generally strained relationships, financial/legal difficulties, etc
  - Enabling: social contacts calling the person off from work, making excuses for him/her, performing household or family responsibilities, allowing the person to avoid stressful situations
  - Incentives: disability, lawsuits, avoiding responsibilities/work, avoiding conflicts with family/people

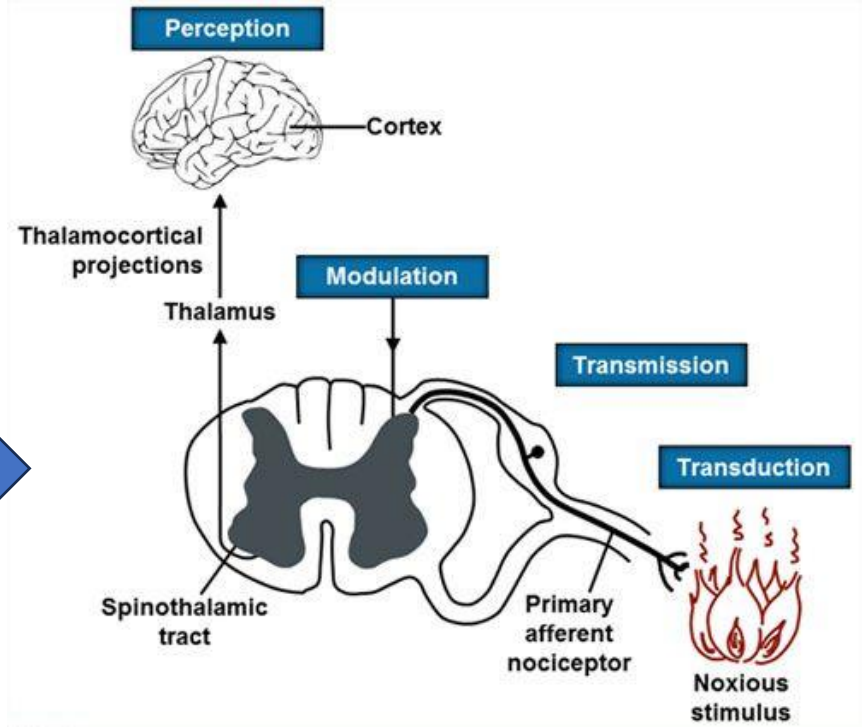
- Be curious about patient
- Observe behaviors, responses, openness vs vagueness
- Review the record
- Practice skepticism re: patient motives, yet avoid cynicism

Management:
Setting the (Biopsychosocial) Stage

Altering the focus…

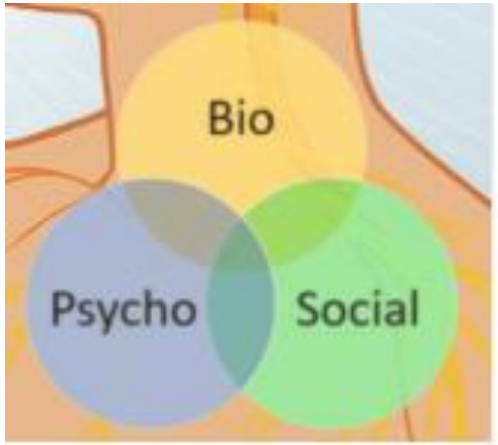
- Patient perception/agenda: “my body hurts; treat my pain”
  - “peripheralist” perspective
  - Leads to emphasis on analgesia, peripheral specialists, etc
- Physiologic reality: “my nervous system is sensitized; lets calm it down”
  - “integrative” perspective
  - Leads to consideration/inclusion of interventions for CNS, not just peripheral





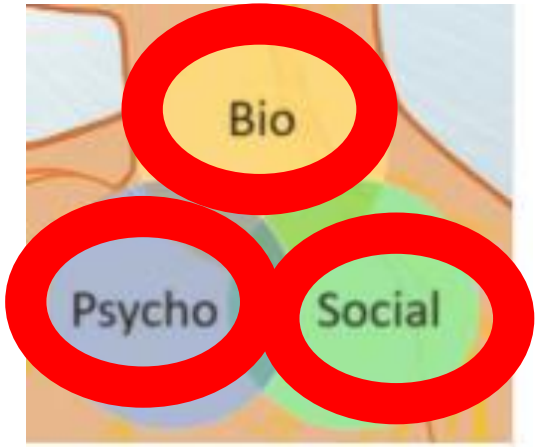
Chronic Pain Treatment: Functional Restoration and Rehabilitation

- Emphasis on *acceptance* and chronic *management*
- Target is **not cure**, but rather is **rehabilitation**
  - Medical (pharmacological, graded detox, proper psychiatric dx/tx, education)
  - Physical (reconditioning, graded exposure to movement, aerobic work, diversion, occupational tx)
  - Psychological (MI → acceptance → coping, relaxation, biofeedback, counseling/CBT/DBT, family, dynamic/process groups, emotional awareness, desensitization)



“ICU” for chronic pain: interdisciplinary chronic pain rehabilitation programs

- Interdisciplinary chronic pain rehabilitation programs (iCPRPs) utilize a **functional restoration** and a **biopsychosocial** model in treating the most refractory chronic pain patients with multiple modalities including (but not limited to):
  - medical management of comorbidities
  - detoxification from opioids/benzodiazepines
  - psychiatric/psychological assessment
  - PT/OT (land/aquatic, mirror, graded work, yoga/Tai Chi, etc)
  - biofeedback sessions
  - individual therapy/counseling
  - group therapy work
  - skills training/education
  - family therapy sessions



Stanos, 2012

ICPRPs

- iCPRPs treat diagnostic heterogeneity in terms of pain/disorders:
  - musculoskeletal (low back pain, spinal stenosis, failed back surgery syndrome/post-laminectomy syndrome, osteoarthritis, DJD)
  - diffuse/widespread (fibromyalgia, somatic symptom disorder)
  - neuropathic (neuropathy, radiculopathy, complex regional pain syndrome/reflex sympathetic dystrophy)
  - migraine/headache
  - abdominal (IBS, visceral hyperalgesia, stable IBD)
  - pelvic (vulvodynia, pudendal neuralgia, endometriosis)
  - Thoracic/atypical chest pain
  - More…
- Comorbidities: depression, anxiety, insomnia, addiction, somatic symptom disorder, PTSD/trauma, etc

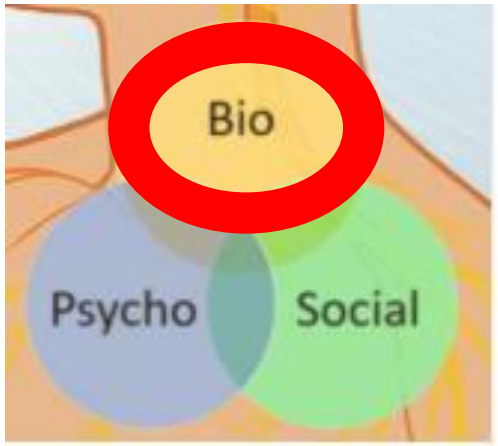
Stanos, 2012

Refer intelligently…

- Don’t scare people by saying they need some multi-week program – suggest a comprehensive chronic pain neurological evaluation first, and know your referral destinations
  - Some patients will shrug this off as psychiatric, some will not
- Use central sensitization (not psychosocial/psychosomatic/”stress” explanations) to biovalidate and suggest a comprehensive approach
- A complex/chronic problem requires a complex/layered solution (not just a quick pill or one-time PT)
  - “Would you address your 10-year hx of pain if it took a few weeks of investment?”

Management:
Pain Psychopharmacology

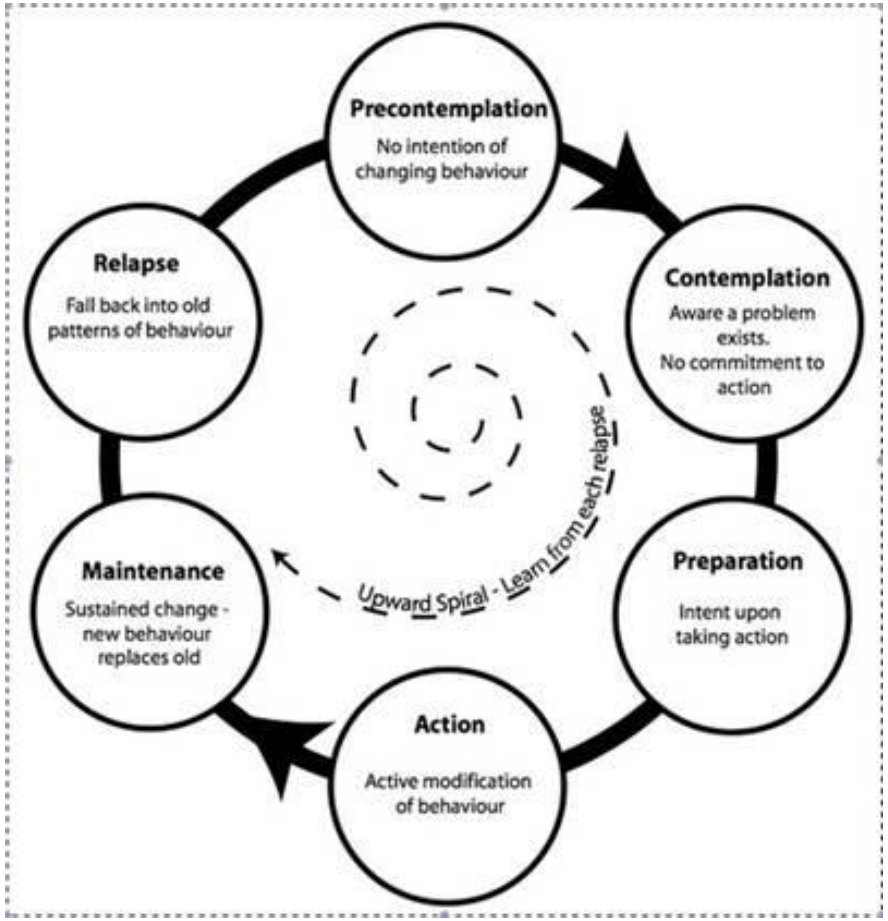
Pain psychopharmacology



- Pharmacological creativity (and off-label use) is the norm, not the exception
- Remove barriers first: benzos, opioids, MJA
- Assist in a pragmatic way: what is ego-dystonic aside from pain? Mood? Sleep? Energy?
- SNRIs
  - Duloxetine, Venlafaxine, Milnacipran, etc
- TCAs
  - Amitriptyline, Nortriptyline, Doxepin, etc
- Anticonvulsants
  - Gabapentinoids (Gabapentin, Pregabalin), Topiramate, Lamotrigine, Valproate, Carbamazepine, Oxcarbamazepine
- Antipsychotics
  - Atypicals mostly, low-dose (receptor heterogeneity)
- Sympathetic modulators
  - Prazosin, Clonidine (for sympathetically-maintained syndromes: PTSD, complex regional pain syndrome)
- Ketamine
- Suboxone

First do no harm…

- Avoid/remove chronic opioid/benzo therapy
  - Conventional concerns: dependence/addiction, risk of death
  - Patient-centered concerns: opioid-induced hyperalgesia (“obstacle to pain management”), CNS suppression (falls, cognitive, depression), systemic (GI, immune, endocrine), social/logistical (stigma, costly, time-consuming)
- Method?
  - Complicated blend of MI, pharmacology, and time…



Benzos !!!

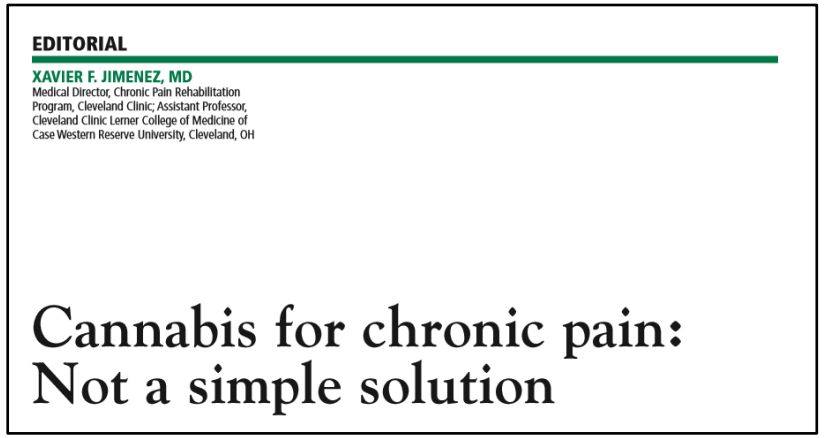
- Safety/coadministration issues, but also also *efficacy* issues!
    - **Benzos predict opioid use better than does pain itself**!
    - N = 17,074
    - Linked to Norwegian Prescription Database during 2004–2007
    - OR for moderate-high prescription frequency of opioids for previous BZ users was 7.7
    - Benzodiazepine users had more disability, CV disease and reported musculoskeletal pain

- Danish Health Survey 2010 + Danish health and socio-economic registers
    - N = 13,281
    - Patients on chronic opioid therapy had 12.5 x the odds of being prescribed long-term BZs as did pain patients not receiving opioids
- Cross sectional study
    - N = 229 patients entering pain rehabilitation
    - BZ use was associated with:
    - Worse mood, pain, and function
    - Authors speculated that BZ effect was due to impaired mood, coping, cognition, ability to tolerate pain

Skurtveit, 2010; Hojsted et al, 2013; Gauntlett-Gilbert J et al, 2016

cannabis ≠ medical marijuana ≠ CBD ≠ THC ≠ synthetic MJA ≠ "other" = chaos!

- Cannabis/CBD efficacy in pain is meager (at best), yet harms are known and certain
- Counterpoints
  - Chronic Pain is complicated (most cannabis studies: short duration/small sample sizes, cross-sectional outcome measures, exclude psychiatric/substance use patients, etc)
  - Impact on cognition/motivation (impacts true rehabilitation/behavioral activation)
  - Not all "cannabis" is the same (semantics matter: cannabis ≠ medical marijuana ≠ CBD ≠ THC ≠ synthetic MJA ≠ other; but do non-medically trained, psychiatric/substance use populations really know the difference?
  - Youth/psychiatric at risk (evidence from medical cannabis dispensaries: younger patients used more cannabis, had higher rates of using "when bored," and had higher rates of dependence than older patients; also high use among young men with low SES and psych/substance use disorders; add this to old evidence on serious psych disorders (schizophrenia, depression, bipolar disorder) unfolding in youth after cannabis exposure.

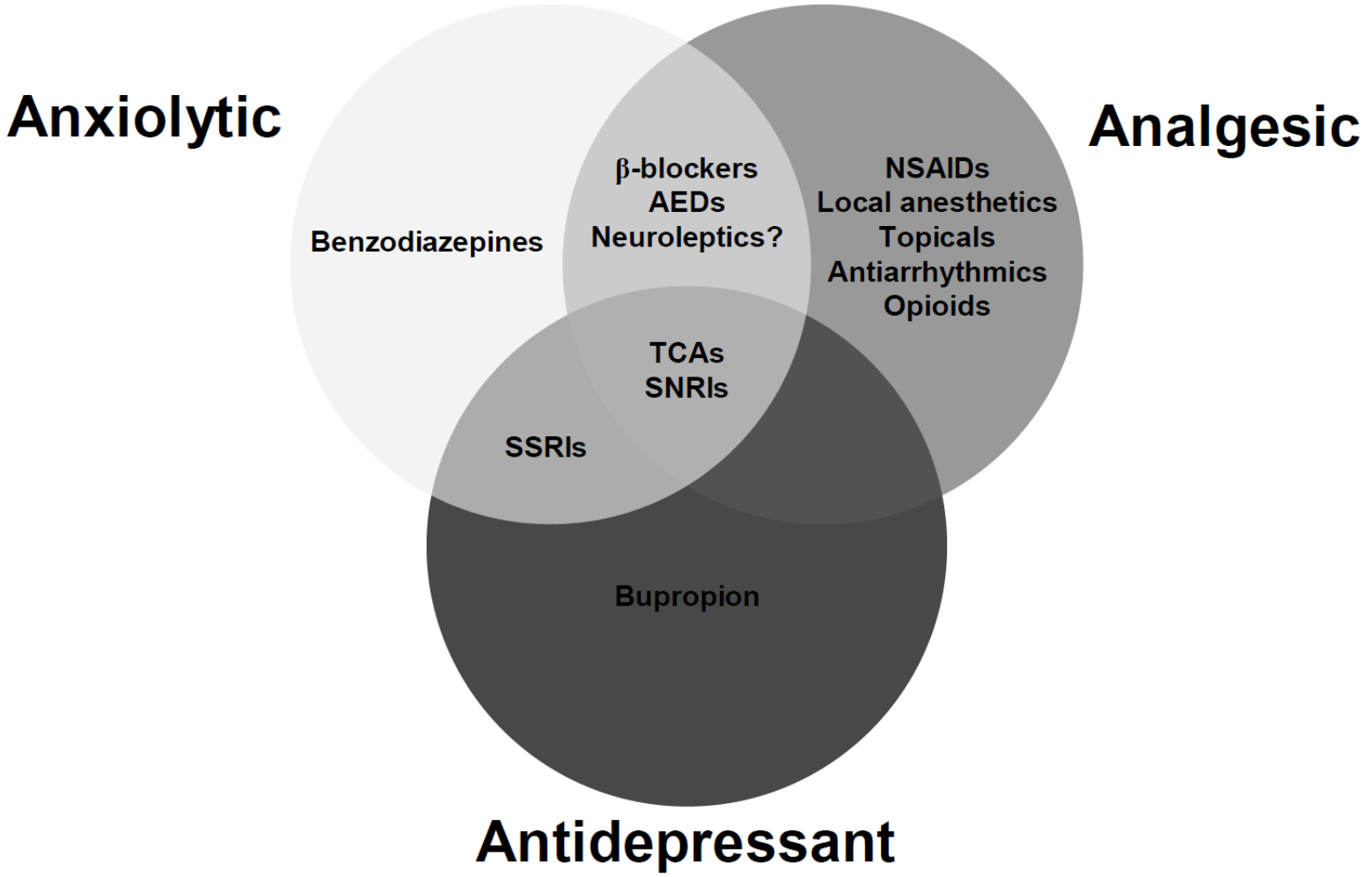

EDITORIAL

XAVIER F. JIMENEZ, MD
Medical Director, Chronic Pain Rehabilitation Program, Cleveland Clinic; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Cannabis for chronic pain: Not a simple solution

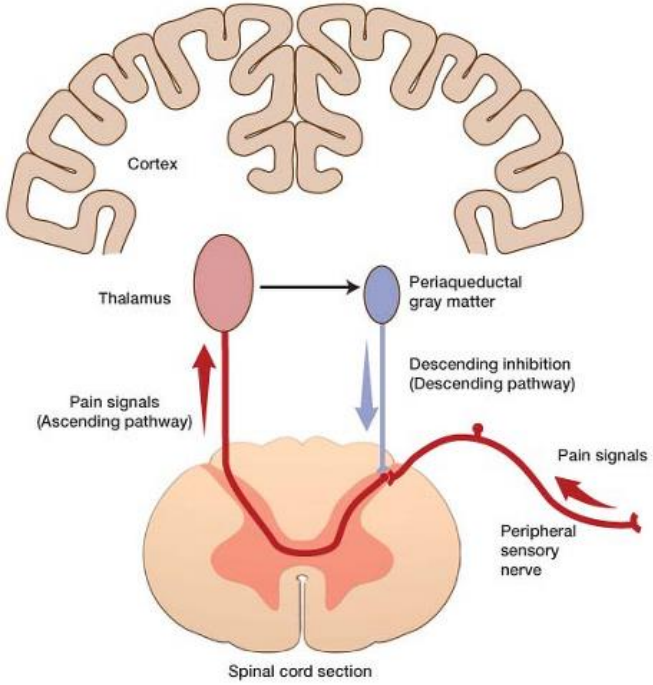
Jimenez, 2018;
Mücke et al, 2018.

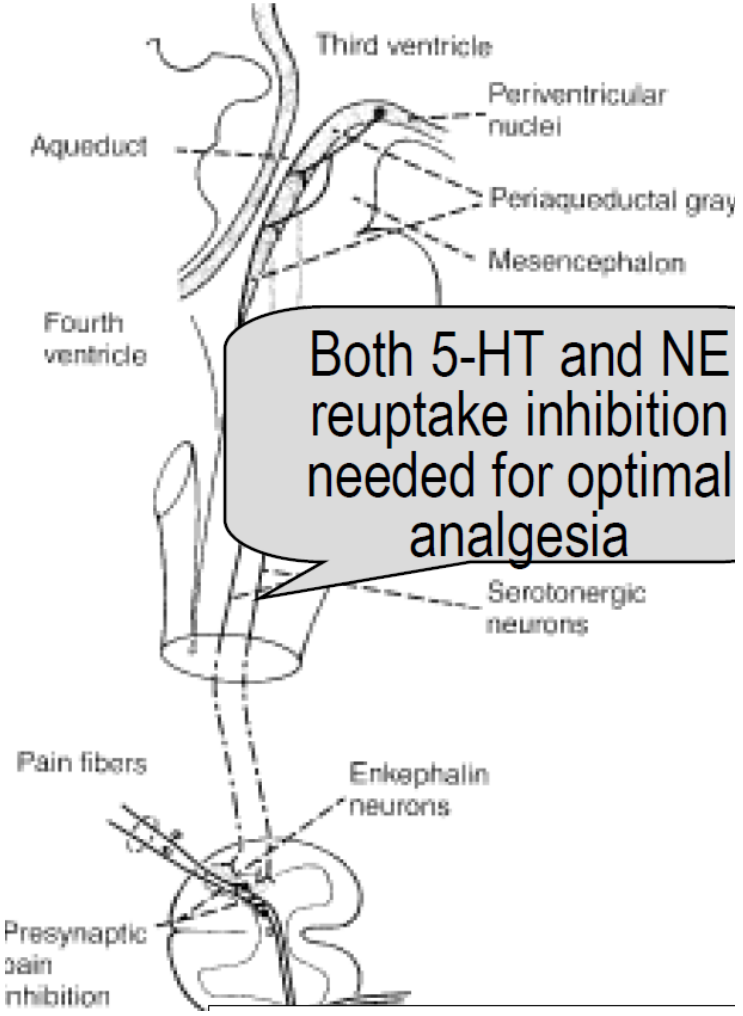
Chronic Pain Psychopharmacology



Antidepressant MOA: Descending Pain Inhibition

- Dorsolateral funiculus (contralateral corticospinal and spinothalamic tracts)
  - Electrical / opioid stimulation of DLF → analgesia
  - Analgesia antagonized by co-administered 5-HT and NE antagonists
- SSRIs thus mostly ineffective in pain mgmt.





Hayashida K and Obata H, 2019.

Tricyclic Antidepressants

	REUPTAKE MECHANISM*	SEDATION	HYPO-TENSION	SEIZURES	WEIGHT	CARDIAC	INITIAL/MAX DOSING (for MDD)
Tertiary Amine TCAs							
Amitriptyline (Elavil)	5HT > NE	+++	+++	++	++	+++	25-75mg/ 200mg daily
Clomipramine (Anafranil)	5HT > NE	++	++	+++	+	++	25mg/ 250mg daily
Doxepin (Sinequan)	5HT = NE	++++	+	++	++	+	50-75mg/ 300mg nightly
Imipramine (Tofranil)	5HT = NE	++	+++	++	++	+++	50-100mg/ 200mg daily
Secondary Amine TCAs							
Despiramine (Norpramin)	NE > 5HT	+	+	+	+	++	100-200mg/ 300mg daily
Maprotiline (Ludiomil)	NE > 5HT	++	+	+	++	+	25mg-50mg/ 225mg nightly
Nortriptyline (Pamelor)	NE > 5HT	+	+	+	+	++	25-50mg/ 150mg daily

*Tertiary amine TCAs tend to preferentially inhibit serotonin reuptake (resulting in greater synaptic serotonin levels), whereas secondary amine TCAs tend to preferentially inhibit norepinephrine reuptake (resulting in greater synaptic norepinephrine levels). 5HT = serotonin; NE = norepinephrine; MDD = major depressive disorder.

Schneider, et al, 2019.

Indication	Medication(s)	Initial/Max Dosing	Dose Rate/Limits	Side Effect Management
Headache/ Migraine	Amitriptyline	10-25mg/100mg nightly	Individualized: 10-25mg increase every 5-14 days; assess for tolerability/ side effects Amitriptyline side effects (dry mouth, orthostasis) often limit dose escalation above 100mg; Nortriptyline vs Maprotiline may be considered (better tolerated at higher doses)	Dry mouth/ secretions: pilocarpine 5mg 2-3/day Constipation: stool softeners such as docusate sodium or senna glycoside Weight gain: consider augmenting with metformin 500-1000mg daily or topiramate 50-100mg/day Seizures, QT interval prolongation, active suicidal risk, and/or orthostasis/falls: **discontinue TCA**
Neuropathic Pain	Amitriptyline	25–50mg/150mg nightly (vs divided into twice daily doses if frequent pain/symptom flares)		
Chronic Low Back Pain	Amitriptyline, Maprotiline	25–50mg/150mg nightly		
Fibromyalgia/ Chronic Widespread Pain	Amitriptyline, Nortriptyline, Maprotiline	25–50mg/150mg nightly (vs divided into twice daily doses if frequent pain/symptom flares)		
Irritable Bowel Syndrome	Amitriptyline, Nortriptyline	10-25mg/100mg nightly		
Cyclic Vomiting Syndrome	Amitriptyline, Nortriptyline	25–50mg/100mg nightly		
Chronic Pelvic Pain/Interstitial Cystitis/Nocturia	Amitriptyline, Nortriptyline, Imipramine	10-25mg/100mg nightly		
Insomnia	Amitriptyline, Maprotiline, Doxepin	25–50mg/150mg nightly		

Schneider, et al, 2019.

Serotonin-Norepinephrine Reuptake Inhibitor

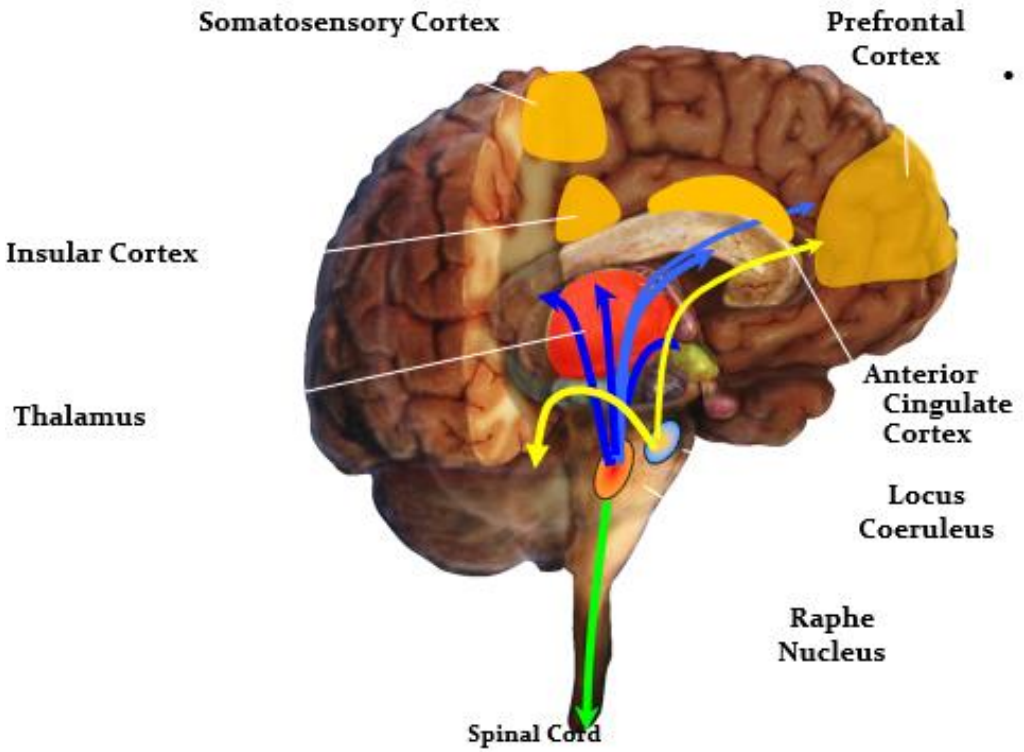
- High promise/potential
  - Combining efficacy of tricyclic antidepressants (older) for pain with safe side effect profile of SSRIs (newer)
  - Yet efficacy questionable...

AUTHORS' CONCLUSIONS: The update did not change the major findings of the previous review. Based on low- to very low-quality evidence, the SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in the frequency of pain relief of 50% or greater, but for patient's global impression to be much or very much improved and in the frequency of pain relief of 30% or greater there was a clinically relevant benefit. The SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in improving health-related quality of life and in reducing fatigue. Duloxetine and milnacipran did not significantly differ from placebo in reducing sleep problems. The dropout rates due to adverse events were higher for duloxetine and milnacipran than for placebo. On average, the potential benefits of duloxetine and milnacipran in fibromyalgia were outweighed by their potential harms. However, a minority of people with fibromyalgia might experience substantial symptom relief without clinically relevant adverse events with duloxetine or milnacipran.We did not find placebo-controlled studies with other SNRIs than desvenlafaxine, duloxetine and milnacipran.

Welsch P, et al. 2018.

A word on SNRIs…

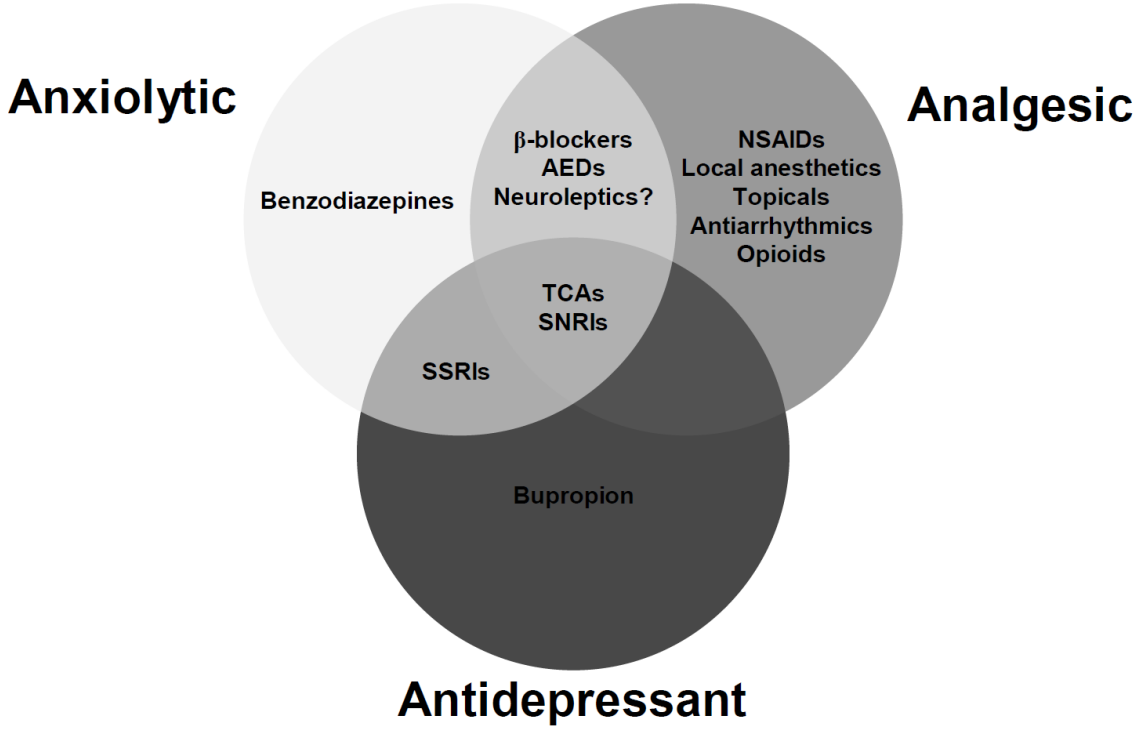
- Cymbalta: its in the water!
- Think more creatively, especially at an academic tertiary care hospital
- Cymbalta: OK for depression, mediocre for anxiety, OK for pain. Reasonable for depressed + mild-to-moderate pain cases
- NOT reasonable for other psychiatric concerns and/or severe pain cases
- Instead, look at the psychiatric priority !



DEPRESSION
Spinal pain 2%-56%, Fibromyalgia 21%-83%, Pelvic pain 19%-22%
Abdominal pain 9%-54%, Arthritis 3%-39%
ANXIETY
Spinal pain 1%-26%, Neuropathic pain 5%-27%, Fibromyalgia 18%-60%
Pelvic pain 12-41%, Abdominal pain 21%-51%, Arthritis 1%-35%

…and another on SSRIs…

- Don’t forget them!
- High safety profile
- When dosed appropriately, excellent anxiolytics (better than Cymbalta!)
- If problem is predominantly anxiety/panic/PTSD/hypervigilance, do you even need analgesia?
  - Dose aggressively (e.g. Prozac/Paxil 20mg x 2 weeks, then up to 40mg x 4 weeks)
  - Avoid “ginger”/overly-cautious dosing
    - These are anxious patients – they need results!



Antiepileptic Agents = Mood Stabilizers

- Well-established in Pain Mgmt:
  - "Gabapentinoids" (**Gabapentin, Pregabalin**)
    - Evidence: Postherpetic neuralgia, diabetic neuropathy, migraine prophylaxis, spinal cord injury, Guillain Barre, lumbar canal stenosis, HIV neuropathy, fibromyalgia
    - Side effects/Monitoring: renal clearance, sedation, dependence/withdrawal
  - **Carbamazepine**
    - Evidence: trigeminal / glossopharyngeal neuralgia, Diabetic neuropathy, post-herpetic neuralgia, phantom limb pain, fibromyalgia
    - Side effects/Monitoring: myelosuppression, hepatic burden), drug-drug interactions
  - **Oxcarbamazepine**
    - Evidence: trigeminal neuralgia refractory to carbamazepine; other neuropathies
    - Side effects/Monitoring: hyponatremia, sedation

Dosenovic S, et al, 2017; Wiffen, 2014.

Other Mood Stabilizers – Less Established

Topiramate

- Indication: Migraine prophylaxis, chronic low back pain (other neuropathic pains?)
- Dose: 50mg/day to 300mg/day
- Side effects/Monitoring: Weight loss; renal calcifications; cognitive slowing; dizziness, somnolence

Lamotrigine

- Indication: traumatic/trigeminal neuralgia, HIV neuropathy, fibromyalgia, post-stroke central pain
- Dose: 200-400mg/day
- Side effects/Monitoring: Stevens-Johnson's rash/syndrome, requires slow titration, avoid other AEDs

Valproic Acid

- Indication: Migraine prophylaxis vs acute abortion; mixed neuropathic pain
- Dose: clinically dosed with trough serum level between 50 and 100
- Side effects/Monitoring: thrombocytopenia, hepatotoxicity, sedation

Lithium

- Indication: chronic cluster headaches
- Dose: clinically dose with trough serum level under 0.8
- Side effects/Monitoring: nephrogenic diabetes insipidus; hypothyroidism, toxicity/sedation/confusion

Dosenovic S, et al, 2017; Wiffen, 2013; Tfelt-Hansen and Jensen, 2012.

Antipsychotics/Neuroleptics

- Dopamine (D2) receptor antagonists
- “Atypical” (second generation/newer) have heterogeneous receptor action (5HT, histamine, Ach)
- Consider psych comorbidities (mood/anxiety/sleep disorder), central sensitization
- For pain: dosing much under that used in psychotic/bipolar disorders
  - Ex: **Olanzapine** 5-10mg daily (2.5 BID, or 2.5 AM and 5 HS); **Quetiapine** 25mg PO BID/TID
  - Side effects/Monitoring: weight gain/metabolic syndrome; QTc prolongation, sedation

REVIEW ARTICLE

A Systematic Review of Atypical Antipsychotics in Chronic Pain Management

Olanzapine Demonstrates Potential in Central Sensitization, Fibromyalgia, and Headache/Migraine

TABLE 3. Guidelines for Monitoring Adverse Effects From Atypical Antipsychotics

	Baseline AA Rx	Week 6	Week 12	Month 6	Month 9	Year 1
Weight	✓	✓	✓	✓	✓	
Height	✓					
BMI	✓					✓
Waist circumference	✓					
Fasting blood glucose	✓	✓	✓			✓
Total cholesterol	✓	✓	✓			✓
Total triglyceride	✓	✓	✓			✓
LDL-C	✓	✓	✓			✓
HDL-C	✓	✓	✓			✓
Hemoglobin A1C			✓	✓	✓	
Blood pressure	✓					✓
Heart rate	✓					
Electrocardiogram*	✓					✓

*Electrocardiogram should be assessed, any time an AA dose change is performed.

AA indicates atypical antipsychotic; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Adapted from Ventriglio et al.[71] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Jimenez et al, 2018

CHRONIC PAIN ASSESSMENT:

history (chronicity, features), physical exam (focal vs diffuse), comorbidities (medical, psychiatric), instruments/scales (PDI, CSI, PCS)

Neuropathic Pain?
(radiculopathy, neuropathy, etc)

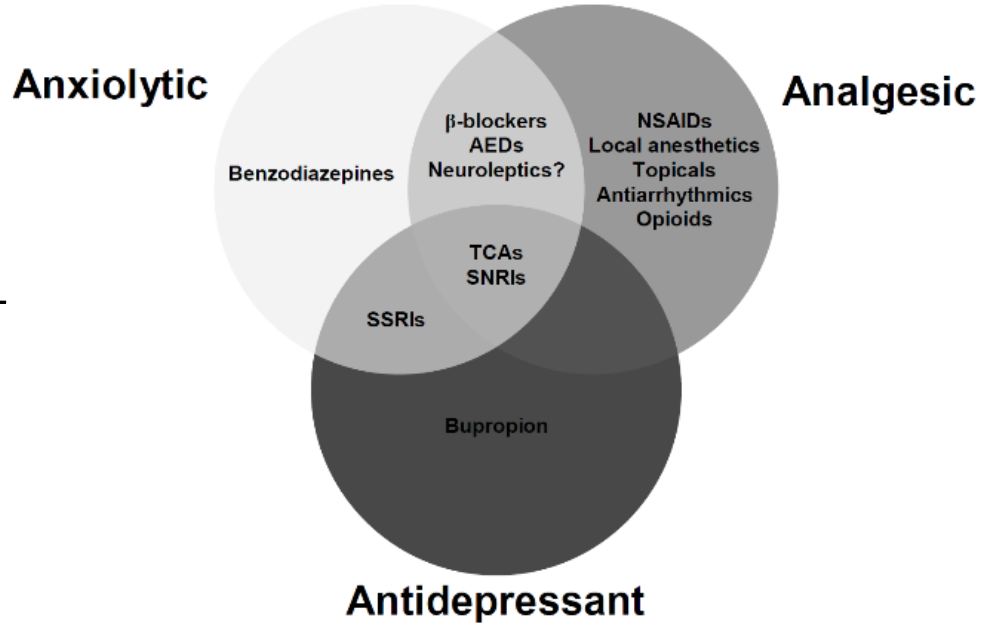
Medical: opioid detox; trials with gabapentinoids, TCAs, SNRIs
Physical: PT, OT

Central Sensitization Syndrome?
(migraine, fibromyalgia, IBS, TMJD, etc)

Medical: opioid detox; trials with gabapentinoids, TCAs, SNRIs
Physical: PT, OT
Psychological: CBT, biofeedback, MBSR

Psychiatric comorbidity?
(mood/anxiety/psychotic disorder)

Adjunct AA (olanzapine, others)
- low/slow dosing, PRN vs scheduled
- continuous safety monitoring (table 3)
- repeat exam/scales for effect



PDI = Pain Disability Index; CSI = Central Sensitization Inventory; PCS = Pain Catastrophizing Scale; IBS = Irritable Bowel Syndrome; TMJD = temporomandibular joint disorder; TCAs = tricyclic antidepressants; SNRIs = serotonin-norepinephrine reuptake inhibitors; PT = physical therapy; OT = occupational therapy; CBT = cognitive behavioral therapy; MBSR = mindfulness-based stress reduction; AA = atypical antipsychotic.

Jimenez et al, 2018

Sympathetic Modulators

- Adrenergic system implicated in many pain syndromes (e.g. CRPS/RSD) as well as comorbidities (PTSD/anxiety/panic)
- Heightened sympathetic nervous system results in increased attention/vigilance to pain, poor sleep (unrefreshed to deal with pain), and kinesiophobia (avoidance of movement 2/2 fear).
- Consider Propranolol, Clonidine, etc.
  - Clonidine PO vs patch; good for anxiety/cravings/insomnia
- Prazosin for nightmares – good in PTSD; FDA approved (1-10mg QHS, assess response, slowly titrate as needed) – watch for hypotension, orthostasis/falls

Ketamine

- Good evidence base of its use in CRPS, diffuse body pain
- Pain anesthesia: anesthetic doses
- Psychiatry (eg TRD): subanesthetic doses (eg 0.5mg/kg/hour infusion)
- Of 7 studies w/ subanesth ketamine for CP and depression…
  - 3 reduction in pain AND depression
  - 3 reduction in pain OR depression
  - 1 reduction in neither

Efficacy of ketamine for comorbid depression and acute or chronic pain: A systematic review

Aksharra Balachandran[1†], Vanessa K. Tassone[1†], Fathima Adamsahib[2], Anne-Marie Di Passa[2], Sarah Kuburi[2], Ilya Demchenko[1], Karim S. Ladha[2,3] and Venkat Bhat[1,4,5,6,7*]

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Balachandran et al, 2022

Suboxone (buprenorphine-naloxone)?

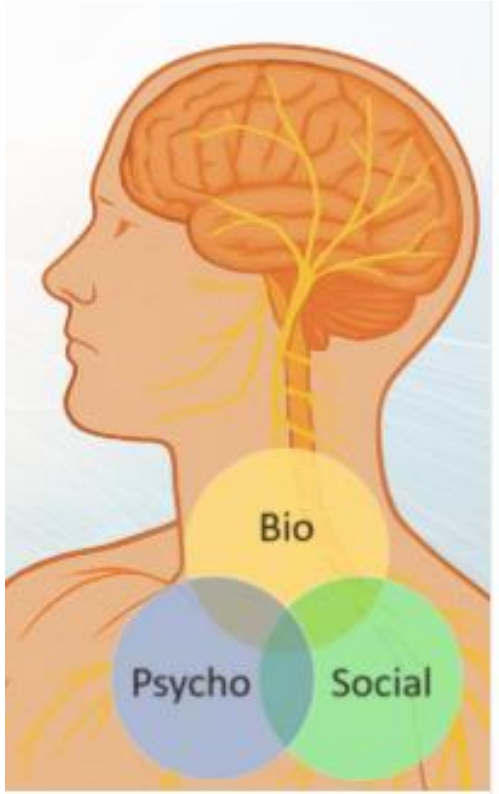
- 1 (small) study showing promise

Reference	Year	Patient Population	Study Duration	N	Route and Dose	Comparator	Scale	Mean/Median Pain Score	Outcome and Results
Neumann et al[9]	2013	Chronic nonmalignant pain related to the spine or a large joint	6 mo	54	Average daily sublingual dose of buprenorphine/naloxone was 14.93 mg/3.73 mg	Oral methadone (20–60 mg, divided 3–4 times daily)	NRS	5.5 ± 1.9 after 6 mo compared to initial visit (6.3 ± 1.2)	There was significant difference in pain relief for both buprenorphine and methadone treatment groups (P = .043)

- Are we just treating a variant of opioid use disorder?

Aiyer, 2018

Conclusions/Summary



- Understand/embrace complexity of pain!
  - Chronic Pain ≠ Acute Pain…
- Consider biopsychosocial dimensions of chronic pain
  - Central sensitization? Pain psychology?
- Educate patients and expand their view
  - Medically validate: transition from peripheral → integrative view
- Explore pain psychopharmacological options with creativity and confidence: be practical and helpful!
- Pair medical interventions with physical and psychological rehabilitative efforts.

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