

Mechanism-Based Treatment of Chronic Nonterminal Pain, and Responding to SB1446

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Conflict of Interest

- I have no financial relationships/conflicts of interest to disclose

Learning Objectives

- Identify primary mechanism(s) in a patient presenting with chronic nonterminal pain
- Provide evidence-based pain management targeting the mechanism of pain, including:
 - Non-pharmacologic treatment
 - Non-opiate pharmacologic treatment
 - Alternative/complementary therapy
- Determine when opiate therapy may be appropriate for a patient with chronic nonterminal pain
- Document opioid therapy in compliance with SB1446

Patient 1

- 62 year old male here for recheck chronic conditions
- DM2, HTN for 20 years (HgA1C 9.0%)
- Pain in bilateral feet: burning, “feels like I’m stepping on gravel”
- Tried and failed: ibuprofen; T#3 works “ok,” would like it refilled; tried nothing else
- Exam: decreased sensation to monofilament bilaterally



Patient 2

- 25 year old female, establish care visit
- Fibromyalgia, IBS, tension headaches
- Urgent care gave her Norco for recent “migraine” – requesting refill
- “nothing else works,” has “tried everything” (no records), and reports “a high pain tolerance”
- Also wants refill of benzodiazepine and zolpidem
- Exam: 12/18 tender points positive, diffuse abdominal tenderness with trigger points in rectus muscle, taut muscle bands in splenius capitis reproduce head pain



Patient 3

- 55 year old female
- Chronic low back pain without radiculopathy
- On disability from work as CNA due to back pain, divorced and has no family around for support
- Has SSI and Medicaid – limited PT benefit
- Requests prescription for muscle relaxer and pain medicine refills
- Has had no imaging or other intervention in years



For Each Patient:

- What type of pain does each have?
- What treatment modalities are most likely to be effective?
 - Non-pharmacologic
 - Non-opiate pharmacologic
 - Alternative/complementary
- Are opiates appropriate?



Mechanisms of Pain

- Nociceptive pain
- Inflammatory pain
- Neuropathic pain
- Functional pain
- Cognitive-affective pain

Sources: Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004 Mar 16; 140(6):441-51 and
Kumar SP, Saha S. Mechanism-based classification of pain for physical therapy management in palliative care: A clinical commentary. *Indian J Palliat Care* 2011;17:80-6



Mechanisms of Pain

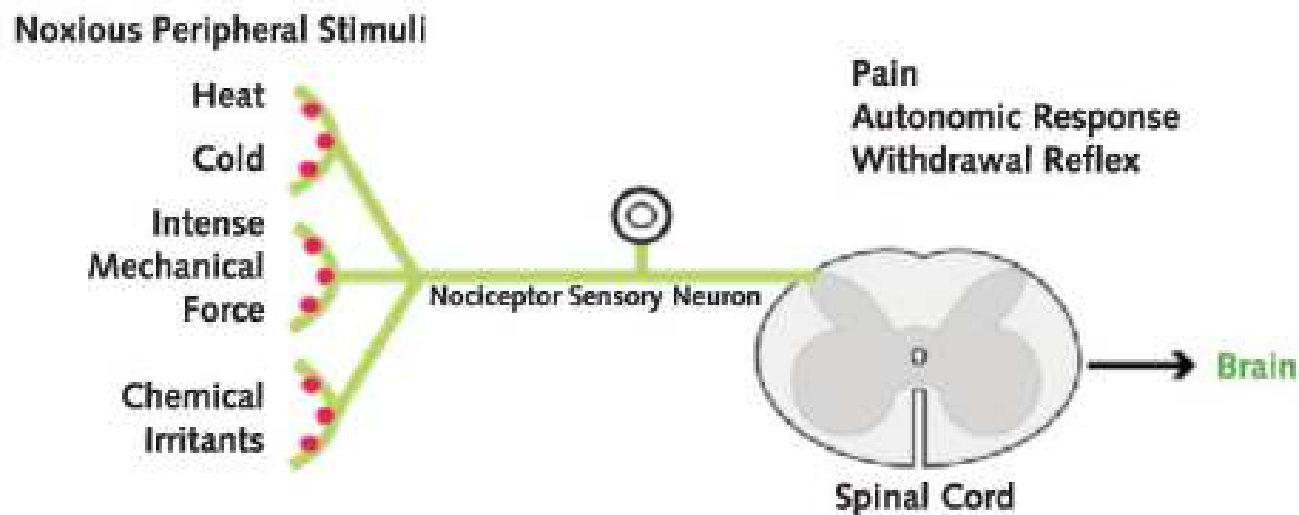
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Nociceptive Pain

Nociceptive Pain



Treatment: usually none (unless tissue damage has occurred, i.e. surgery, trauma)

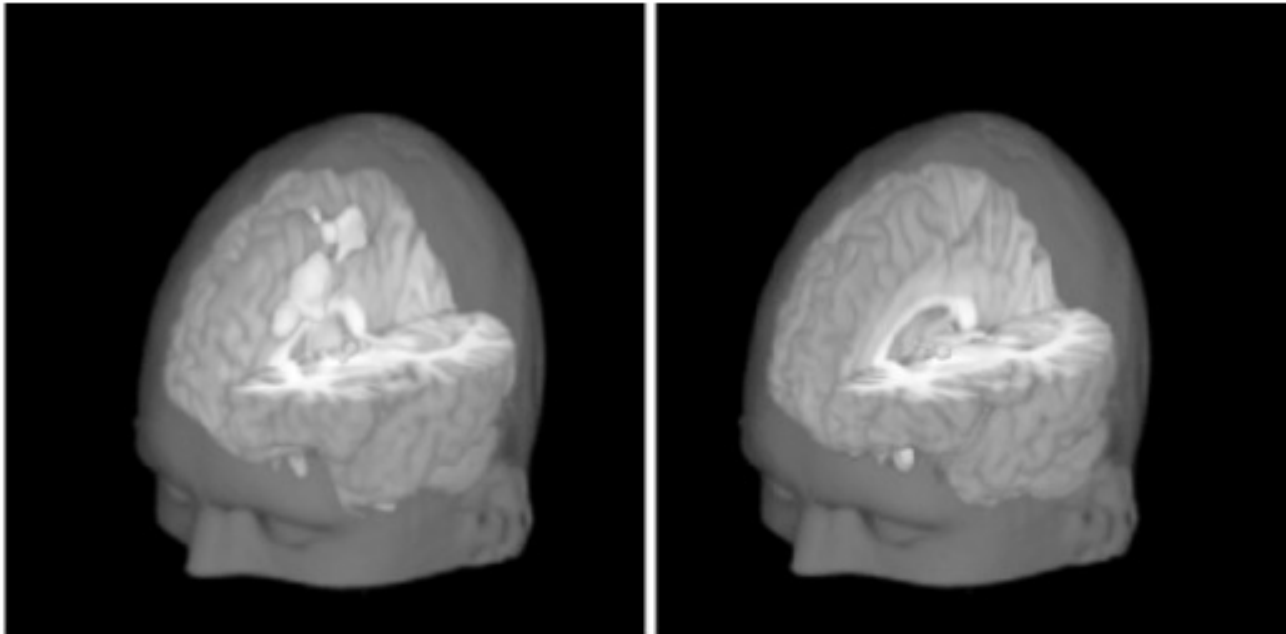
Goals of chronic pain therapy: DON'T DISABLE THIS

Should last only as long as the damage takes to heal

Source: Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004 Mar 16; 140(6):441-51



How Do People Experience Nociceptive Pain?

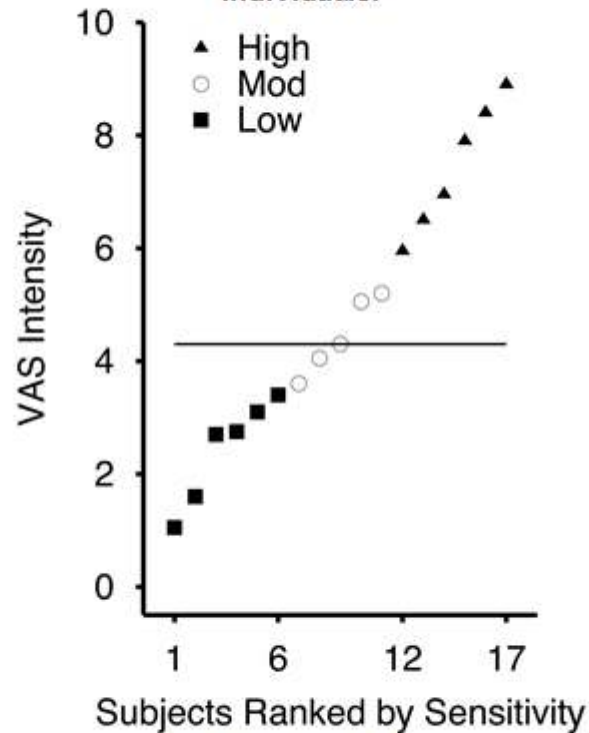


Coghill RC, McHaffie JG, Yen YF. Neural correlates of interindividual differences in the subjective experience of pain
PNAS 2003 100: 8538-8542



Some Suffer More than Others

The distribution of pain intensity ratings obtained during functional MRI scanning shows that the subjective experience of pain intensity evoked by a 49°C stimulus differed markedly across individuals.



Robert C. Coghill et al. PNAS 2003;100:8538-8542

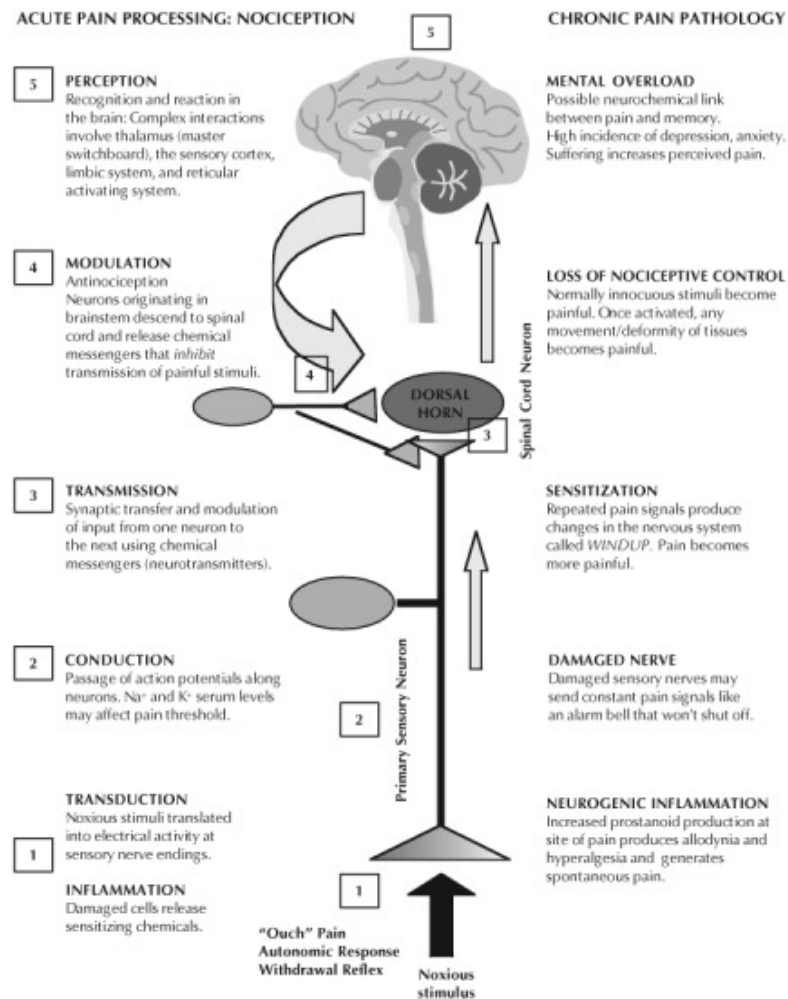
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PNAS

Coghill RC, McHaffie JG, Yen YF. Neural correlates of interindividual differences in the subjective experience of pain PNAS 2003 100: 8538-8542



Acute vs. Chronic Pain



Whitten CE, Donovan M, Cristobal K. Treating Chronic Pain: New Knowledge, More Choices. *The Permanente Journal*. 2005;9(4):9-18.



Maladaptive Pain

- Exists apart from stimulus or healing process
- Can be inflammatory, neuropathic or functional
- May have a cognitive-affective component
- Multiple causes
 - Damage to CNS (neuropathic pain)
 - Abnormal operation of CNS (functional pain)
- Is persistent or recurrent



Peripheral Sensitization

- Tissue injury/inflammation
- Activation of inflammatory mediators
- Increased sodium channel excitability
- More pain/pain in absence of apparent stimulus but *in anatomic distribution of injury*
- Example: painful shower after sunburn, trigger points in myofascial pain syndrome
- Treatments:
 - NSAIDS
 - Magnesium
 - TCA
 - Lidocaine
 - Opioids

Source: Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004 Mar 16; 140(6):441-51



Peripheral Sensitization: Trigger Points (TrP)

- Dysfunctional endplate:
 - Increased acetylcholine release from motor nerve terminal at rest
 - Enhanced by initiating traumatic event
- Results in:
 - Sustained depolarization of muscle fiber
 - Continuous release/decreased uptake of calcium at sarcoplasmic reticulum
 - Sustained shortening of sarcomeres with hypoxia
- Treatments:
 - PT: spray and stretch, pressure release
 - Local injection: disrupts endplate cycle, diffuses sensitizing substances
- Some experts recommend TrP release before treating FMS

Source: Giamberardino MA, Affaitati G, Fabrizio A, Constantini R. Effects of Treatment of Myofascial Trigger Points on the Pain of Fibromyalgia. *Curr Pain Headache Rep* (2011) 15:393-399



Central Sensitization

- Normal inputs = abnormal responses
 - Allodynia: pain to light touch
 - Hyperalgesia: pain out of proportion to stimulus
 - “*Non-anatomic*” pain (remember the fMRIs)
 - Contributes to inflammatory, neuropathic, and functional pain
- Examples:
 - Post-Herpetic neuralgia (neuropathic)
 - Complex Regional Pain Syndrome (neuropathic, ectopic excitability)
 - Fibromyalgia
 - Opiate-induced hyperalgesia

Source: Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004 Mar 16; 140(6):441-51



Mechanisms of Pain

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- **Inflammatory pain – spontaneous pain/hypersensitivity to pain in response to tissue damage and inflammation**
- Neuropathic pain
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Inflammatory Pain

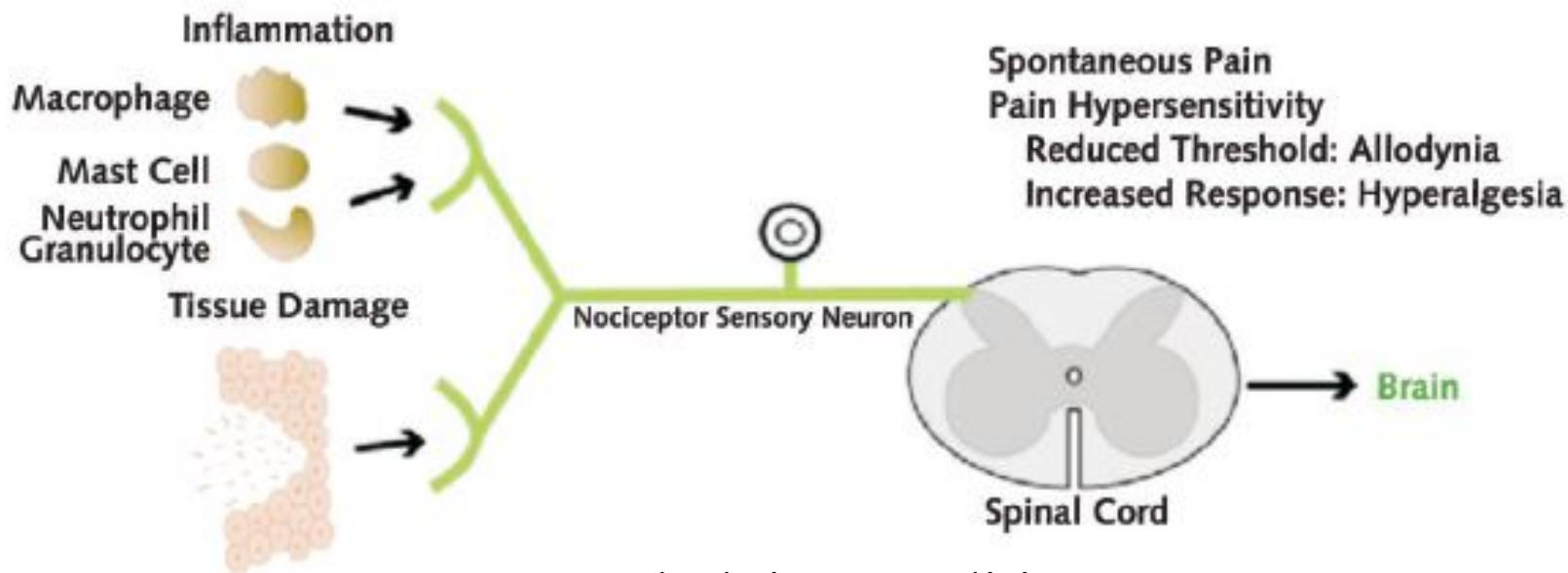
- When adaptive:
 - Allodynia (reduced pain threshold) limits use of an injured body part, prevents further injury (ex: burns)
 - Improves/resolves upon healing of injured part
- Problematic:
 - We can now survive more serious injury than we evolved to handle chronically (major trauma/surgery)
 - Our neurobiologic evolution hasn't kept pace

Source: Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004 Mar 16; 140(6):441-51



The Treatment Plan – Inflammatory Pain

Inflammatory Pain



- Treat underlying condition
- NSAIDs/COX-2
- Identify/treat sensitization

Source: Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004 Mar 16; 140(6):441-51



The Treatment Plan – Inflammatory Pain/Rheumatoid Arthritis

- Follow inflammatory markers – treat inflammation if present (MTX, DMARD)
- If pain persists, consider maladaptation/sensitization as possible causes
- Non-pharmacologic options:
 - PT/OT
 - Massage
 - Compression garments
- Non-opiate pharmacologic option: NSAIDs



The Treatment Plan – Inflammatory Pain/Rheumatoid Arthritis

- CAM options:
 - Possibly effective:
 - Oils: fish oil, primrose oil, borage seed oil
 - Mind-body techniques: including hypnosis, guided imagery, meditation/prayer, tai chi
 - Uncertain efficacy:
 - Herbs: esp. valerian, ginger, curcumin
 - Ineffective:
 - Homeopathy
 - Magnets

Source: UptoDate Patient Information



Mechanisms of Pain

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- Inflammatory pain – spontaneous pain/hypersensitivity to pain in response to tissue damage and inflammation
- **Neuropathic pain – spontaneous pain/hypersensitivity to pain in association with damage to or a lesion of the nervous system**
- Functional pain
- Cognitive-affective pain

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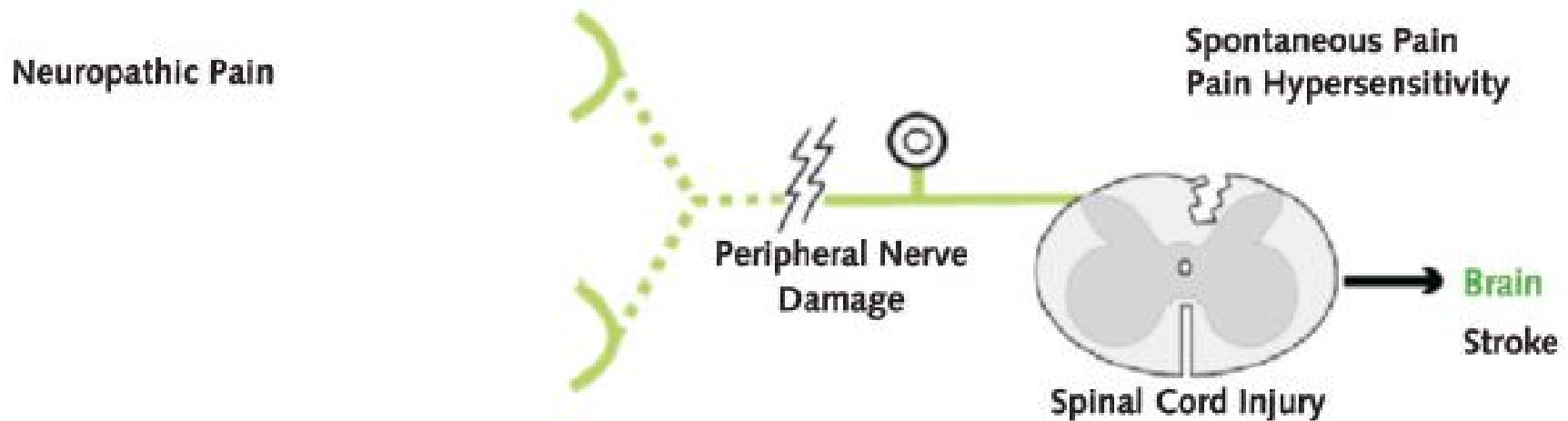


Neuropathic Pain

- Results from damage to nervous system
 - Peripheral:
 - Polyneuropathies (HIV/AIDS, diabetes, chemo)
 - Post-herpetic neuralgia
 - Lumbar radiculopathy
 - Central:
 - Spinal cord injury
 - Multiple sclerosis
 - Stroke



The Treatment Plan – Neuropathic Pain



- TCA
- Gabapentin/pregabalin/topiramate
- Opioids
- Alpha-lipoic acid, magnesium, vitamin D, B vitamins, others?

Source: Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004 Mar 16; 140(6):441-51



The Treatment Plan – Neuropathic Pain

- Non-pharmacologic therapies
 - TENS/dorsal column stimulator – interrupts nociceptive pathway
 - Relaxation therapy/hypnosis – improves pain tolerance
- CAM therapies
 - Alpha lipoic acid: 300mg BID
 - Magnesium: 2000 mg/day decreased paroxysms but not pain score (2mg/kg/d worked in animals)
 - B-complex vitamins (B1, B6, B12) show promise in animal models

Pickering G, Morel V, Simen E, Cardot JM, Moustafa F, Delage N, Picard P, Eschalier S, Boulliau S, Dubray C. Oral magnesium treatment in patients with neuropathic pain: a randomized clinical trial. *Magnesium Research*. 2011;24(2):28-35. doi:10.1684/mrh.2011.0282



Mechanisms of Pain

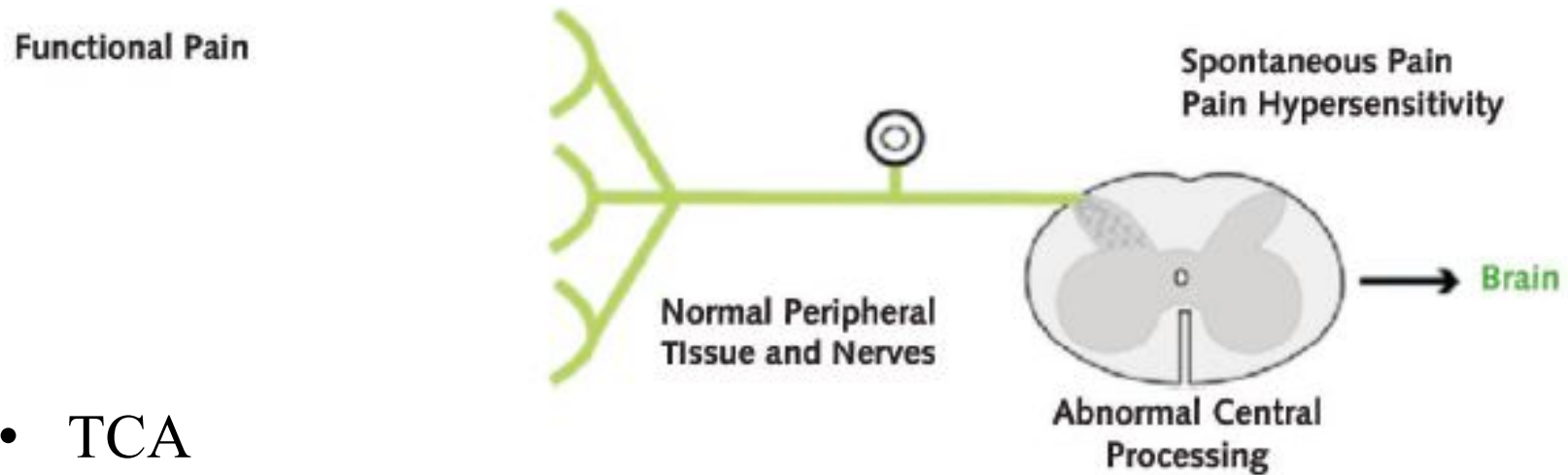
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- Inflammatory pain – spontaneous pain/hypersensitivity to pain in response to tissue damage and inflammation
- Neuropathic pain – spontaneous pain/hypersensitivity to pain in association with damage to or a lesion of the nervous system
- **Functional pain – hypersensitivity to pain resulting from abnormal central processing of normal input**
- Cognitive-affective pain

Sources: Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004 Mar 16; 140(6):441-51 and

Kumar SP, Saha S. Mechanism-based classification of pain for physical therapy management in palliative care: A clinical commentary. *Indian J Palliat Care* 2011;17:80-6



The Treatment Plan – Functional Pain



- TCA
- SSRI
- Pregabalin/topiramate
- Magnesium, vitamin D, B vitamins?
- Modalities: massage, stress reduction, yoga, local injection

Source: Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004 Mar 16; 140(6):441-51



The Treatment Plan – Functional Pain/Fibromyalgia

- CAM approaches:
 - Possibly effective:
 - Exercise: tai chi, qi gong, yoga
 - Massage: esp. manual lymph drainage therapy
 - Supplements: magnesium (500-1000mg BID), COQ10 (100mg BID), L-carnitine (500mg BID-TID)
 - Uncertain evidence:
 - Biofeedback
 - Acupuncture
 - Capsaicin
 - No evidence of benefit:
 - Reiki
 - Homeopathy

Sources: NIH NCCAM <https://nccih.nih.gov/health/pain/fibromyalgia.htm#science>

Rossini, M et al. Double-blind, multicenter trial comparing acetyl L-carnitine with placebo in the treatment of fibromyalgia Patients *Clin Exp Rheumatol* 2007 Mar-Apr; 25(2): 182-8



The Treatment Plan – Functional Pain/Tension Headaches

- Non-pharmacologic approaches:
 - Possibly effective:
 - Acupuncture, PT
 - Supplements: magnesium (plus, for migraine: butterbur, feverfew, riboflavin, CoQ10)
 - Uncertain evidence:
 - Biofeedback
 - Massage, spinal manipulation, tai chi
- Non-opiate pharmacologic:
 - Trigger point injection
 - NSAIDs
 - TCA/SSRI

Source: NIH NCCAM <https://nccih.nih.gov/health/pain/fibromyalgia.htm#science>



Mechanisms of Pain

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- Neuropathic pain – spontaneous pain/hypersensitivity to pain in association with damage to or a lesion of the nervous system
- Functional pain – hypersensitivity to pain resulting from abnormal central processing of normal input
- **Cognitive-affective pain – symptom magnification due to maladaptive understanding of pain, “pain behavior” and emotions associated with the “pain experience”**

Sources: Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004 Mar 16; 140(6):441-51 and
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Cognitive-Affective “Pain:” Primary or Secondary Pain Condition?

- Primary presentation: symptom magnification/“suffering”
 - Related to “pain behaviors” (ie NOCEBO phenomenon)
 - Not the same as “malingering” (ie, not intentional)
- Comorbid mental health condition(s) often present
- Emerging evidence suggests an epigenetic stress to central nervous system as result of
 - Socioeconomic deprivation
 - Adverse childhood experiences
 - Child abuse

Sources: Davis, Debra et al. Are Reports of Childhood Abuse Related to the Experience of Chronic Pain in Adulthood?: A Meta-analytic Review of the Literature. *The Clin Jour Pain*. 21(5):398-405 Sept/Oct 2005

Imbierowicz, Katrin et al. Childhood adversities in patients with fibromyalgia and somatoform pain disorder. *Euro Jour Pain*. 2003, Vol7(2), 113-119

Morris, Gerwyn et al. Socioeconomic deprivation, adverse childhood experiences and medical disorders in adulthood: mechanisms and associations. *Molec Neurobio* 56(8):5866-5890 August 2019



Cognitive-Affective “Pain:” Management

- Requires extended (sometimes lifelong) multidisciplinary care
 - Emphasize empathic physician-patient relationship/motivational interviewing
 - Leverage behavioral health resources
 - Treat comorbid mental health conditions
- Opioids don’t help – and might hurt
 - Opioid-related central sensitization
 - Enhanced perception of side effects
- Prevention is more effective than a “cure” is

It is easier to build strong children
than to repair broken men.

Frederick Douglass



Factors that CLOSE the gate decrease pain	Factors that OPEN the gate increase pain
Physical <ul style="list-style-type: none"> • Comfortable furniture that fits (beds, chairs, car seats) • Heat/cold • Pacing activities • Adequate rest • Massage 	Physical <ul style="list-style-type: none"> • Inactivity/deconditioning • Poor or nonrestorative sleep
Chemical <ul style="list-style-type: none"> • Medications • Diet: eg, Mg⁺⁺, Ca⁺, vitamin B complex 	Chemical <ul style="list-style-type: none"> • Drug and alcohol dependence • Nicotine
Behavioral <ul style="list-style-type: none"> • Relaxation • Direct, rewarding communication • Humor • Pleasurable activities • Relaxation/meditation/prayer 	Behavioral <ul style="list-style-type: none"> • Trying to do too much too quickly • Difficult relationships • Social isolation • Stress • Persistent worry
Thoughts and emotions <ul style="list-style-type: none"> • Optimism/positive outlook • Setting realistic goals • Affirming of self 	Thoughts and emotions <ul style="list-style-type: none"> • Negative outlook/catastrophizing • Hopelessness/worry • Suppressing emotions • Anger • Depression/anxiety • Focusing on pain
Structural <ul style="list-style-type: none"> • Surgery (sometimes) 	Structural <ul style="list-style-type: none"> • Surgery (sometimes) • Trauma (eg, broken bones, inflammation, extensive dental work)

Whitten CE, Donovan M, Cristobal K. Treating Chronic Pain: New Knowledge, More Choices. *The Permanente Journal*. 2005;9(4):9-18.



Are Opioids Appropriate?

- Maybe, after other therapies exhausted:
 - Neuropathic Pain
 - Inflammatory Pain
 - Peripheral/Central Sensitization (controversial)
- **NO:**
 - Functional pain syndromes: fibromyalgia, chronic headache, chronic low back pain
 - Cognitive-affective pain: insomnia, anxiety, depression, “suffering”
- Starting an opiate does not mean stopping other therapies, especially PT/behavioral health treatments



Opioid-Induced Hyperalgesia: Central Sensitization?

- Suspect if:
 - Patient gets worse on/despite opiates
 - Pain moves to another area without new injury
- If present, consider:
 - Pain management referral
 - Reducing opiate dose
 - Weaning patient from opiates
 - Rotating opiates
 - Adding NMDA receptor modulators (controversial)
 - COX-2 inhibitors
 - Magnesium (animal studies used 2mg/kg)
 - N-acetyl-cysteine (animal studies)
 - D-serine (animal studies)

Sources: Mao J. Opioid-induced hyperalgesia. *Pain Clinical Updates*. 2008;16:1-4.

Lee M et al. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 2011; 14:145-161



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- Has SSI and Medicaid – no PT benefit
- Requests prescription for muscle relaxer and pain medicine refills
- Has had no imaging or other intervention in years



Mechanism-Based Pain Management - Summary

- Chronic, maladaptive pain can be classified into one or more mechanisms
- Choose MULTIMODAL therapy based upon mechanism
 - Inflammatory: treat underlying cause, use NSAIDs, address sensitization if present
 - Neuropathic: consider TENS or stimulator, anticonvulsants, TCA/SSRI, alpha-lipoic acid, B vitamins, magnesium
 - Functional: TCA/SSRI, magnesium, vitamin D, anticonvulsants
 - Opiate therapy is a “trial” for appropriate mechanisms of pain
- PT/OT, massage, and behavioral health referrals are appropriate for most patients – find resources for those who lack them (AAOS handouts, support groups)
- CAM therapies have shown some efficacy, especially in Neuropathic and Functional pain syndromes



SB 1446

Regulation of Opioid Drugs

- Requires that all licensees receive at least one hour of education in pain management OR one hour of education on use of opioids or addiction annually to renew license.
- Defines terms such as
 - Acute pain
 - Chronic pain
 - “Initial Prescription”



Initial Prescription

- A prescription issued to a patient who:
 - has never previously been issued a prescription for the drug or its pharmaceutical equivalent in the past year, or
 - requires a prescription for the drug or its pharmaceutical equivalent due to a surgical procedure or new acute event and has previously had a prescription for the drug or its pharmaceutical equivalent within the past year.
- In order to determine if the patient was previously issued a prescription for a drug or its equivalent, the provider will consult with the patient and review the medical record and prescription monitoring information of the patient.



SB 1446

Regulation of Opioid Drugs

- Lays out the details that must be documented in a “Patient-provider agreement” (a contract for chronic pain treatment) – one in development for OU Medicine Enterprise

“The provider shall be held harmless from civil litigation for failure to treat pain if the event occurs because of nonadherence by the patient with any of the provisions of the patient-provider agreement.”



Patient-Provider Agreement

- Explain possible risk of dependence and addiction
- Document understanding of provider and patient regarding the pain-management plan
- Establish rights of the patient in association with treatments and obligation of the patient to responsible use, discontinuation, and storage
- Identify specific medications and other modes of treatment
- Specify the measure the provider may employ to monitor compliance
- Explain process for terminating the agreement



Patient-Provider Agreement

- Pregnant patients and patients under age 18 must have a documented patient-provider agreement upon initial prescription



Requirements for Chronic Pain

- For any Schedule II continuously prescribed for three months or more (elsewhere also mentions “opiates”)
 - Review and document every three months in the chart the course of treatment, new info about the pain etiology, and progress towards treatment objectives
 - Must assess the patient before every renewal to see if they are having any problems and must document the assessment
 - Periodically make reasonable efforts and document measures taken to stop drugs unless contraindicated
 - Review the PMP and document date and findings in EMR at least every 180 days.
 - Monitor compliance with the Patient-provider agreement

***Excludes patients with cancer, hospice care, palliative care, or LTCF patients, or drugs used to treat addiction.



Documenting SB1446 Compliance

- Office Visits – new and return
- Refills



Marijuana and Chronic Pain:

- Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. Whiting, P. et al, JAMA, June 2015
 - There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity
- Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems- A Clinical Review. Hill, K. JAMA, June 2015
 - Use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence



Resources:

- FDA REMS Strategy (free CME)
 - www.scopeofpain.com
- CDC guideline for prescribing opioids for chronic pain
 - <http://www.cdc.gov/drugoverdose/prescribing/guideline.html>



Thank You!

