Clinical Advances in Optimal Approaches for the Management of Osteoarthritis and Low Back Pain

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Expert Panel

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Disclosures

Mark S. Wallace, MD has disclosed that he has served as an advisor or consultant for Pfizer, Insys, Jazz, Heron, Sorrento and has served as a speaker or a member of a speakers bureau for Jazz.

Lee Radosh, MD has no financial conflicts of interest relevant to this activity.

Theresa Barrett, PhD (Planner) has no financial conflicts of interest relevant to this activity.

Jessica Runyon (Reviewer) has no financial conflicts of interest relevant to this activity.

Conflicts have been resolved according to NJAFP policy.

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Support

This program is supported by an independent educational grant funded by Pfizer Inc., in partnership with Lilly USA, LLC.

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Learning Objectives

After participating in this session, the learner should be able to:

- Recognize the pathophysiologic mechanisms of chronic pain
- Describe the various clinical presentations of chronic pain
- Diagnose and manage chronic pain in osteoarthritis and low back pain
- Develop individualized, evidence-based treatment plans for chronic pain
- Discuss the latest clinical data on novel analgesic targets

Housekeeping

- Complete the pre-test questions now
- There is a space to record your answers for the case study
- Complete the post-test at the end of the session.
- Complete the evaluation form and claim your credit
- Return the form to a staff member or at the registration desk

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Pathophysiologic Mechanisms of Chronic Pain

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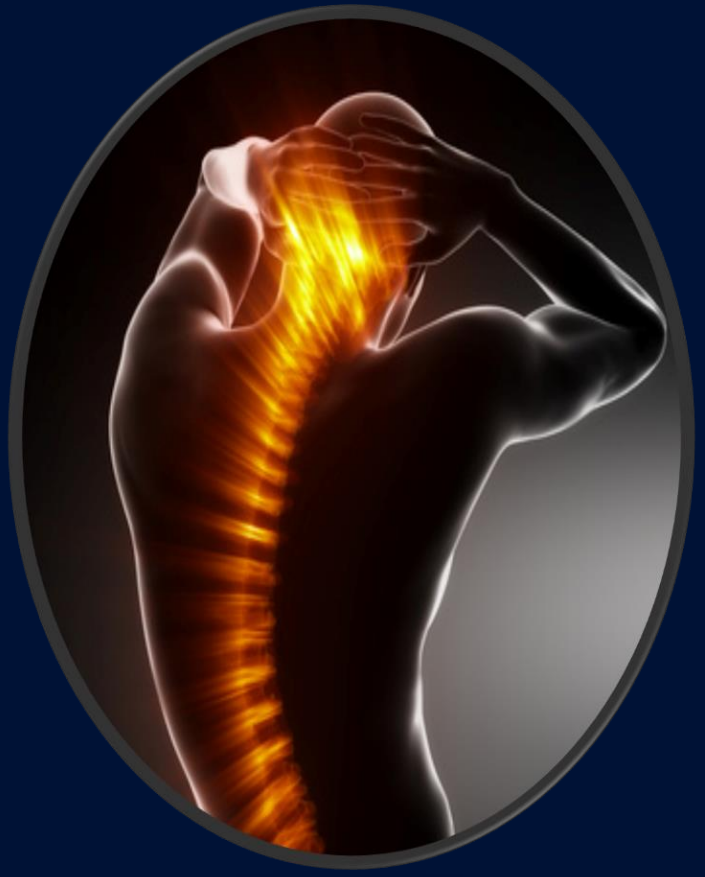
Chronic Pain in the United States

- Chronic pain affects more Americans than diabetes, heart disease, and cancer combined [1]
- Approximately 25 million (11%) US adults report suffering from chronic pain [2]
- It is well known that chronic pain is widely recognized and poorly managed [3]



Sources: 1 National Institute of Nursing Research. Fact Sheet--Pain Management. 2010 | 2 CDC. Health, Unites States, 2006 with Chartbook on Trends in the Health of Americans. 2006 http://www.cdc.gov/nchs/data/hus/hus06.pdf#chartbookontrends | 3 Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington D.C.: National Academies Press; 2011.

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Chronic Pain in the United States

- Rates of chronic pain (with associated suffering and disability) have never been higher in the US, yet we are spending more than ever to diagnose and treat the causes of chronic pain [1]
- The annual cost associated with untreated pain in the United States is reported to be $560 billion to $635 billion [2,3]

Sources: [1] Sullivan M. How Chronic Pain Treatment Falls Short of Patient-Centered Care. NEJM Catalyst. 5/18/17. | [2] National Institute of Nursing Research. *Fact Sheet--Pain Management*. 2010 | [3] Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington D.C.: National Academies Press; 2011.

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Defining Chronic Pain

- Persists longer than 6 months
  - CDC Guidelines state as pain that typically lasts >3 months
- Persists beyond the usual course of acute disease or a reasonable injury healing time
- Associated with chronic pathologic processes
  - Continuous or intermittent pain for months or years
  - May continue in presence /absence of demonstrable pathologies
- May not be amenable to routine pain control methods
- Healing may never occur

Manchikanti L, et al. *Pain Physician* 2012;15(3 Suppl):S1-S65.

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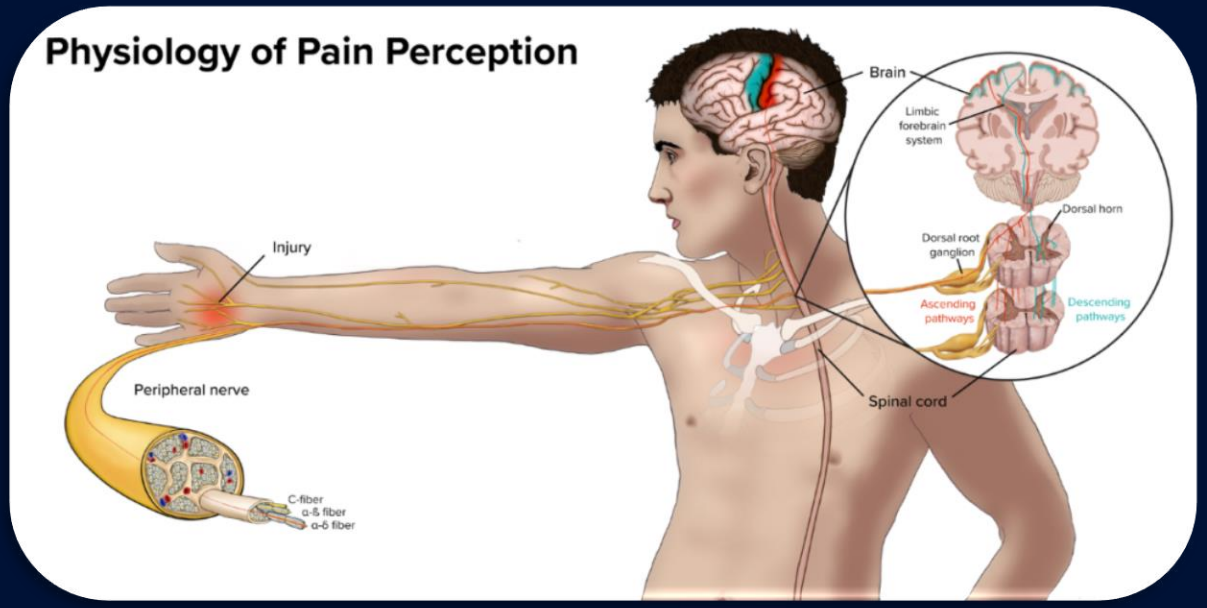
Physiology of Pain Perception

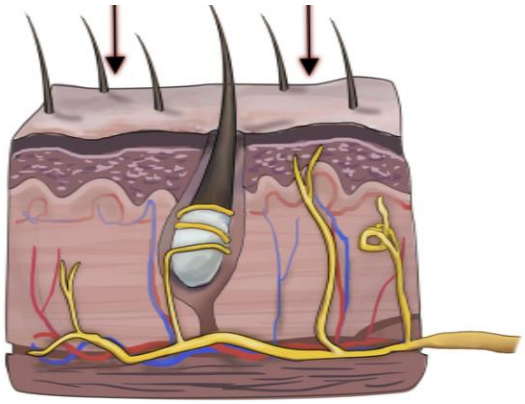
- Transduction
- Transmission
- Modulation
- Perception
- Interpretation
- Behavior



Nociceptive Pain

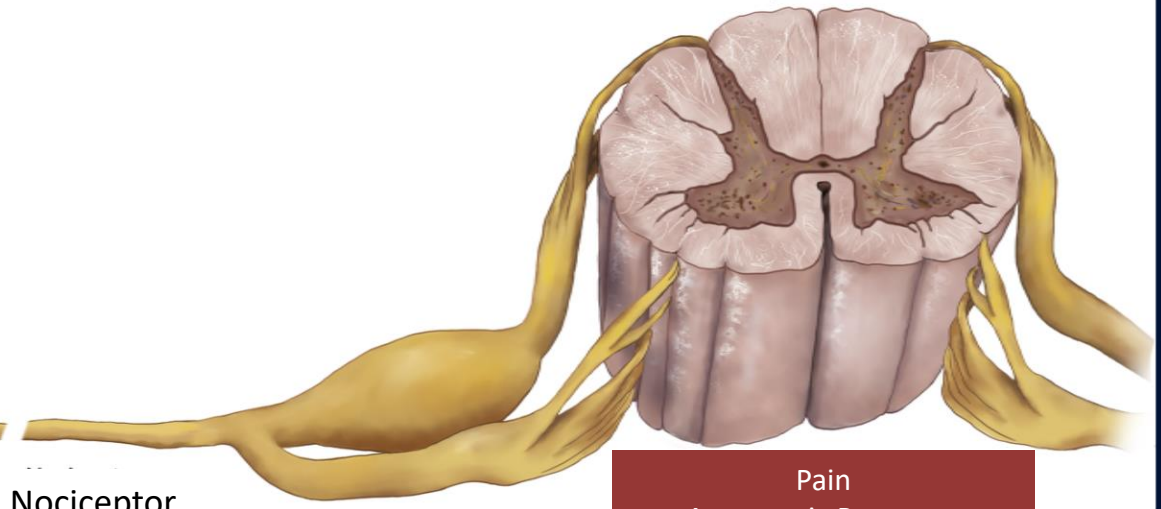
Noxious Peripheral Stimuli

Heat
Cold
Chemical Irritants
Intense Mechanical Force



Nociceptor
Sensory
Neuron

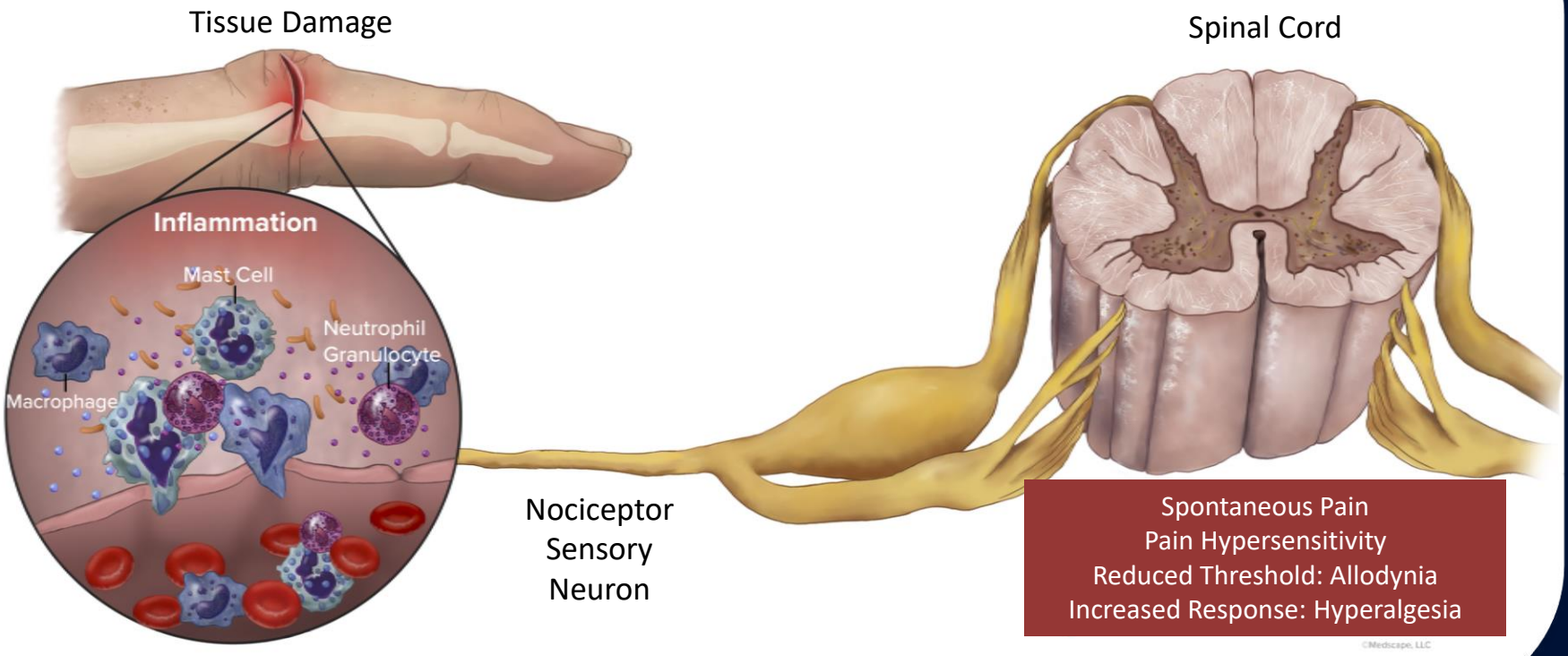
Spinal Cord



Pain
Autonomic Response
Withdrawal Reflex

Woolf CJ. *Ann Intern Med*. 2004;140:441-451

Inflammatory Pain



Woolf CJ. *Ann Intern Med*. 2004;140:441-451

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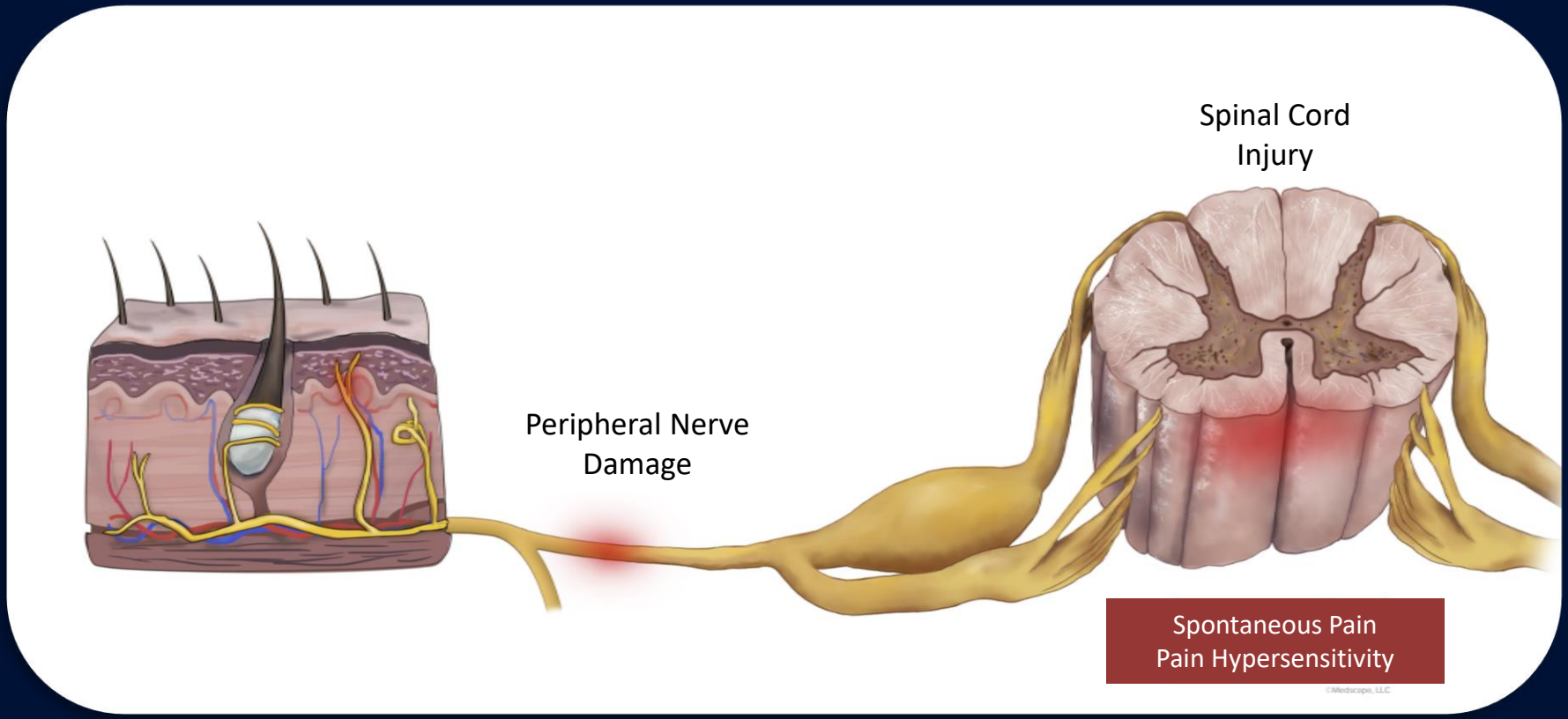
Neuropathic Pain



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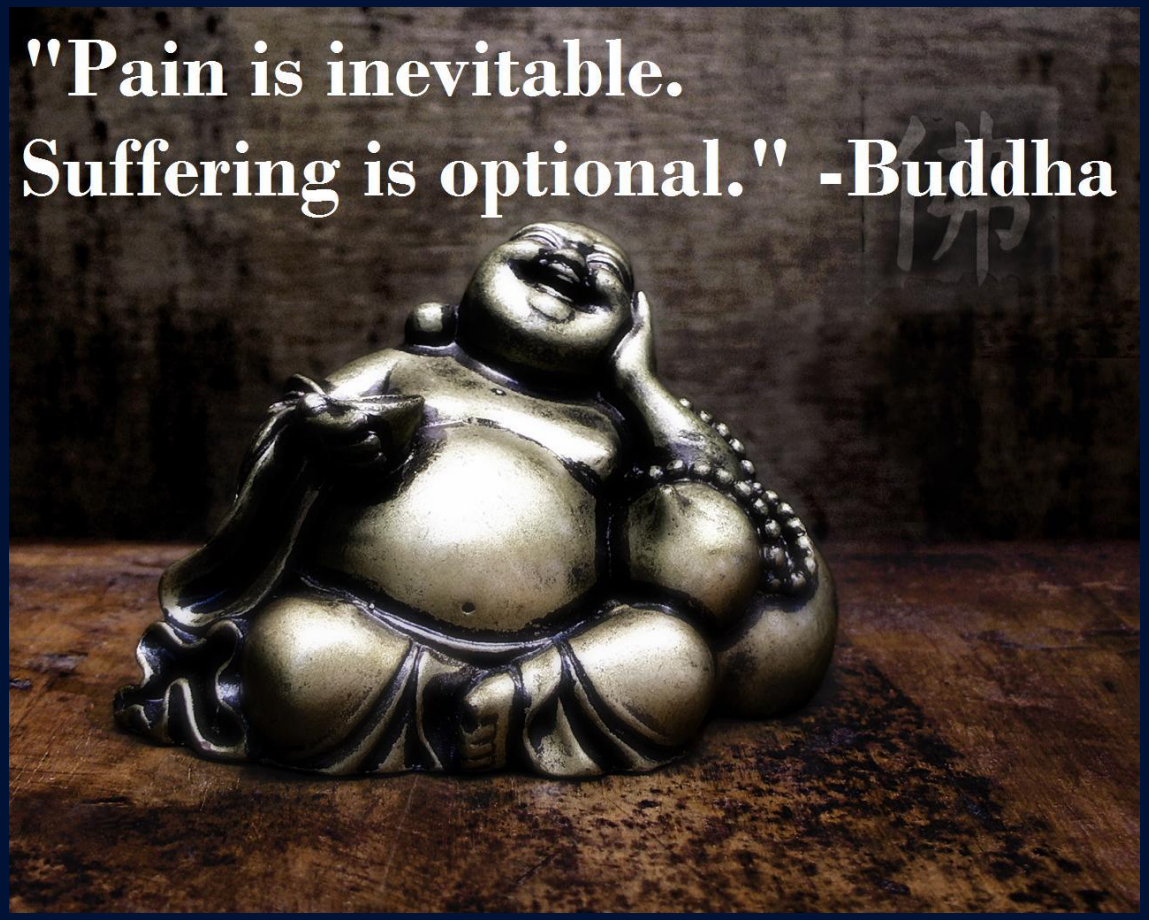
Pain vs. Suffering



http://ctcw.net/pain-vs-suffering/

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Clinical Presentations of Chronic Pain

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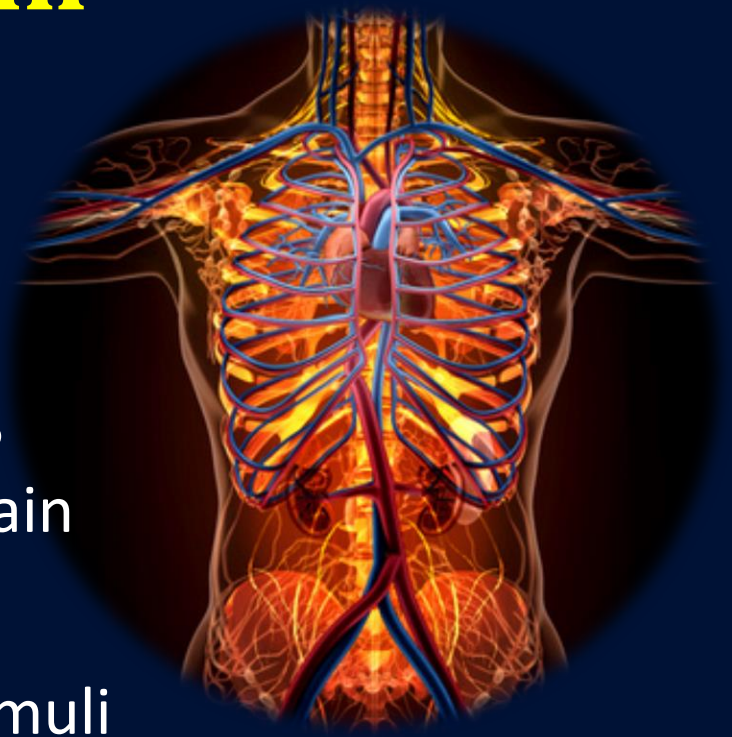
Chronic Pain

- May be associated with intermittent or chronic disease processes[1,2]
- Can significantly impair functional status[3]
- Influenced by physical and psychological factors[4]
- May persist in absence of acute injury or evidence of damage

[1]Sanders SH, et.al. *Pain Pract* 2005;5:303-15; [2]Chou R, et al. *J Pain* 2009;10:113-30; [3]Manchikanti L, et al. *Pain Physician* 2012;15(3 Suppl):S1-S65; [4]Jamison RN, Mao J. *Mayo Clin Proc* 2015;90:957-68; [5]Institute for Chronic Pain. Understanding chronic pain--central sensitization. 2016.

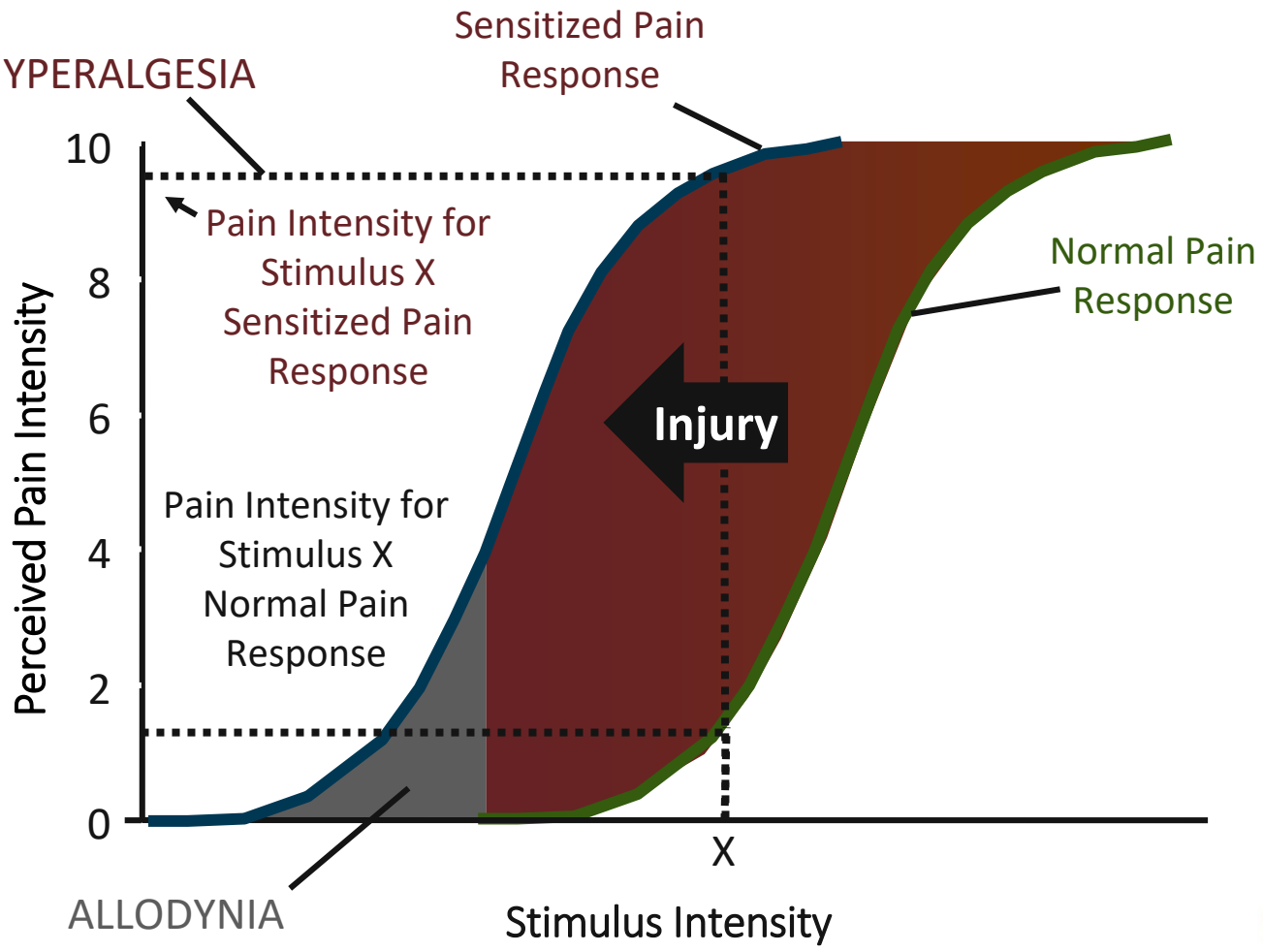
Chronic Pain



- May be associated with central sensitization[5]
  - A state of persistent, elevated CNS reactivity that helps to maintain pain after the initial injury has healed
  - Heightens sensitivity to painful stimuli (hyperalgesia)
  - Perception of otherwise non-painful stimuli as unpleasant or painful (allodynia)

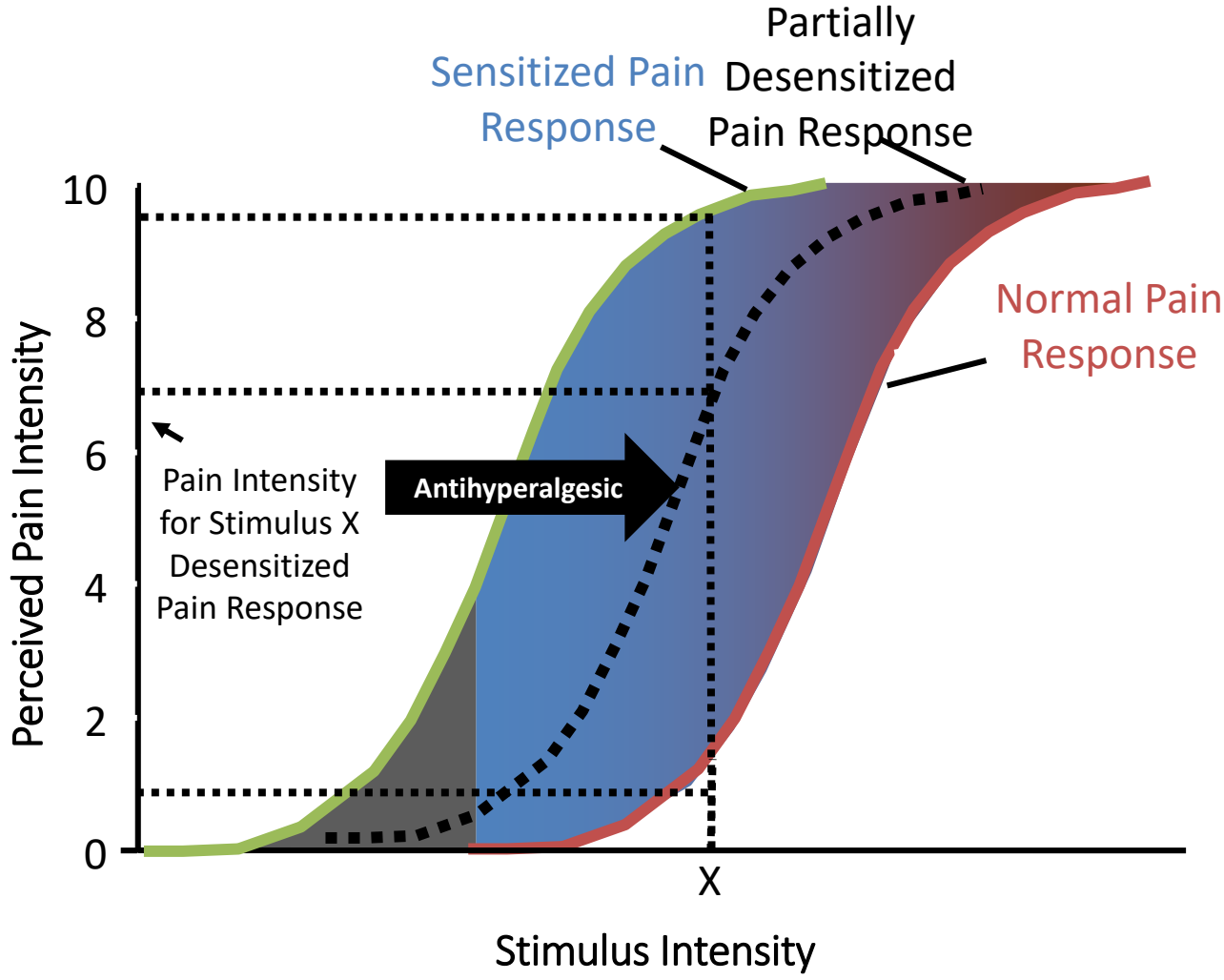
[1]Sanders SH, et.al. *Pain Pract* 2005;5:303-15; [2]Chou R, et al. *J Pain* 2009;10:113-30; [3]Manchikanti L, et al. *Pain Physician* 2012;15(3 Suppl):S1-S65; [4]Jamison RN, Mao J. *Mayo Clin Proc* 2015;90:957-68; [5]Institute for Chronic Pain. Understanding chronic pain--central sensitization. 2016.

Pain Sensitization



Gottschalk et al. *Am Fam Physician*. 2001;63:1979-1984.

Antihyperalgesic Therapy



Effects of Living With Chronic Pain

Physical Functioning

- Ability to perform activities of daily living
- Sleep disturbances

Social Consequences

- Relationships with family and friends
- Intimacy/sexual activity
- Social isolation

Psychological Morbidity

- Depression
- Anxiety
- Anger
- Loss of self-esteem
- Self-medication
  - Legal & illicit

Societal Consequences

- Healthcare costs
- Disability
- Lost workdays

[1]Reid MC, et al. *J Gen Intern Med* 2002;17:173-79; [2]Proctor SL, et.al. *J Addict Med* 2013;7:17-24.
[3] Galer et al. In: *A Clinical Guide to Neuropathic Pain*. 2000:15-19;
[4] Eisendrath. *Neurology*. 1995;45(suppl 9):S26-S34.

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Diagnosing & Managing Chronic Pain

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Basic Principles

- Complete medical and psychological evaluation to establish diagnosis of chronic pain
- Attempt to establish etiology of pain
- Agree upon realistic treatment goals as full pain relief may not be feasible
- Tailor a multidisciplinary plan that may include pharmacologic and non-pharmacologic modalities
- Appropriately document treatment plan
- Carry out ongoing monitoring and follow-up

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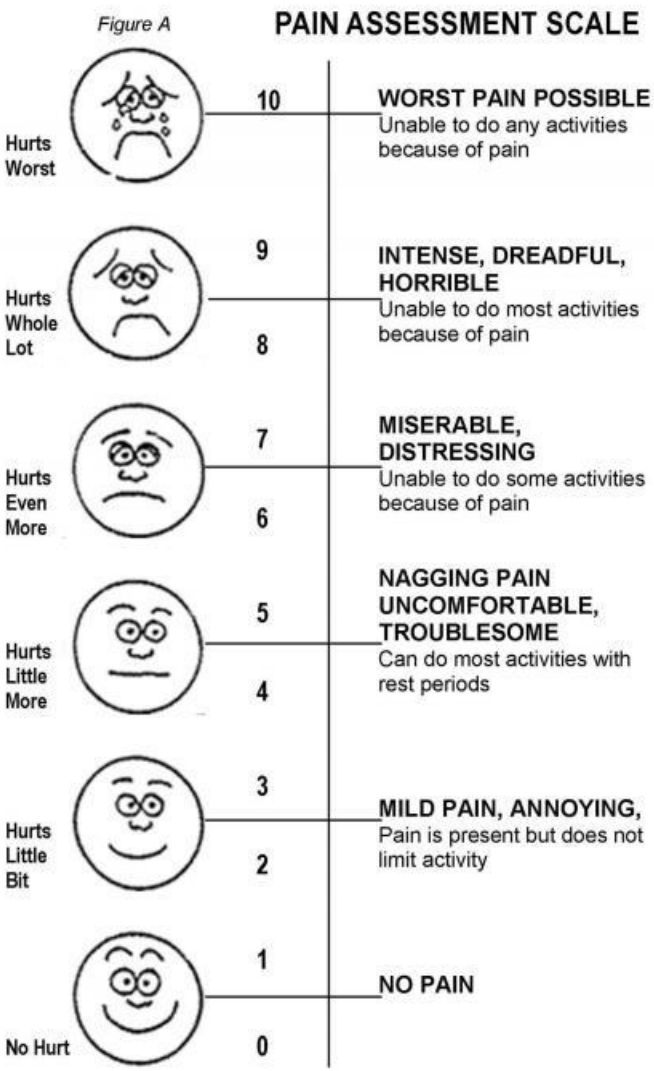
Establish a History

- General medical history
  - Surgeries, social history, family history, allergies, etc.
- Document symptoms
  - Onset
  - Intensity and location
  - Duration
- Sensory and affective components of pain
- Exacerbation of symptoms
- Relief of symptoms
- Document other symptoms
  - Autonomic, motor, and sensory changes
- Past diagnostic test and results
- Current therapies
- Impact of previous treatments

Practice Guidelines for Chronic Pain Management. Anesthesiology 2010;112(4):810-833. doi: 10.1097/ALN.0b013e3181c43103.

Assessing Pain Severity



- Assess the severity of patient's pain and impact on daily function
- Pain screening will be subjective and requires patient input
- Numerous validated tools can be used in primary care
- Screens can be simple or more comprehensive (anxiety, depression, medication use)

Example of a Pain Scale can be found in University of Washington's Pain Medicine Provider Toolkit at http://depts.washington.edu/anesth/education/forms/pain/PainTracker_PatientVersion.pdf

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Treatment Goals

- Reduce pain level
- Improve physical function
  - Range of motion, movement
- Improve functional status/daily activities
- Increase CNCP self-management
- Improve vocational ability/status
- Reduce healthcare utilization for CNCP
- Eliminate/minimize opioid use to treat CNCP

The complete elimination of pain is usually an unrealistic treatment goal for patients with chronic pain.

Sanders SH, et.al. *Pain Pract* 2005;5:303-15; Ablin JN, Buskila D. *Best Pract Res Clin Rheumatol* 2015;29:111-19.

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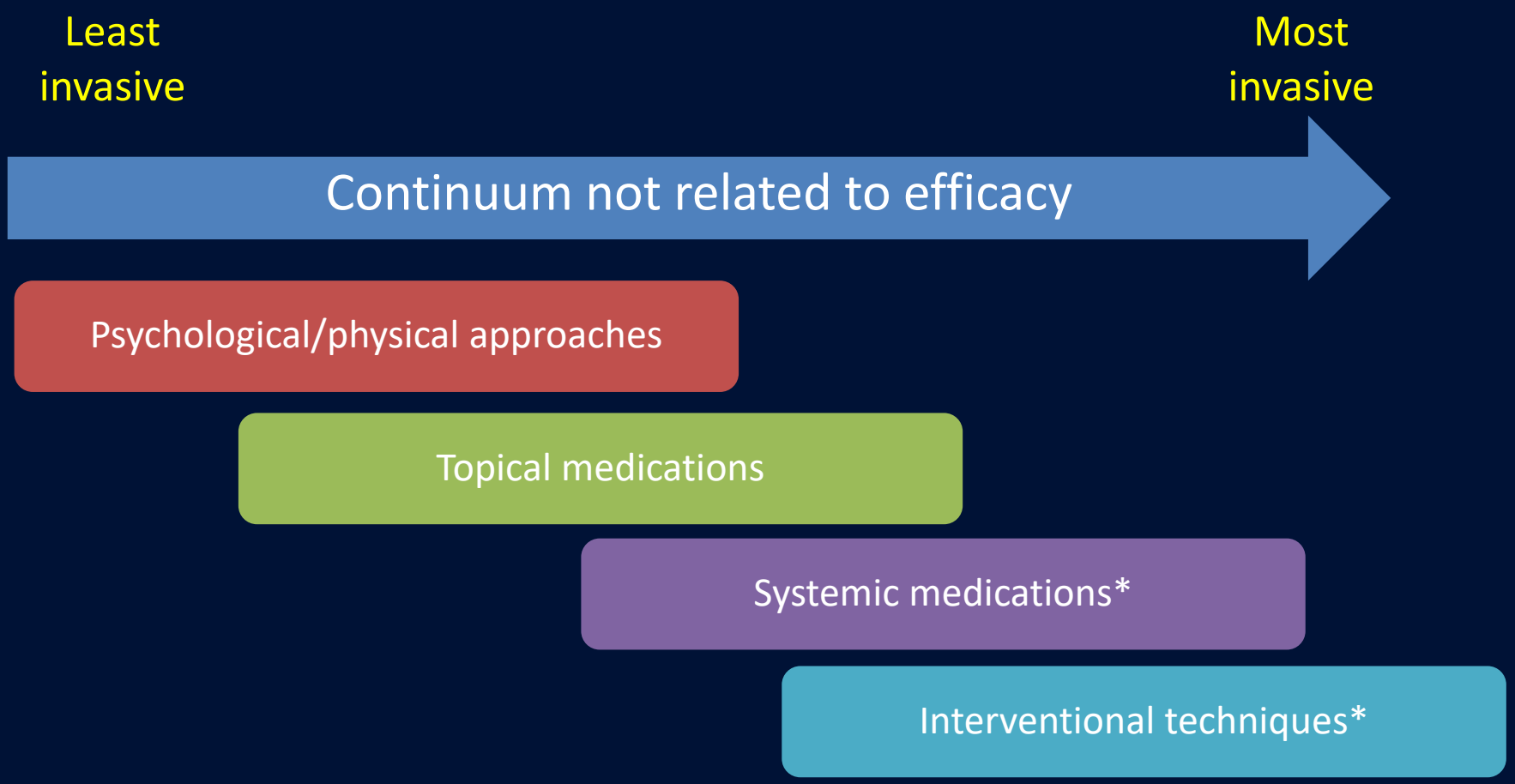
Pain Treatment Continuum



*Consider referral if previous treatments were unsuccessful.

1. Mackin GA. *J Hand Ther*. 1997;10:96-109; 2. Katz N. *Clin J Pain*. 2000;16:S41-S48; 3.Leland JY. *Geriatrics*. 1999;54:23-37.

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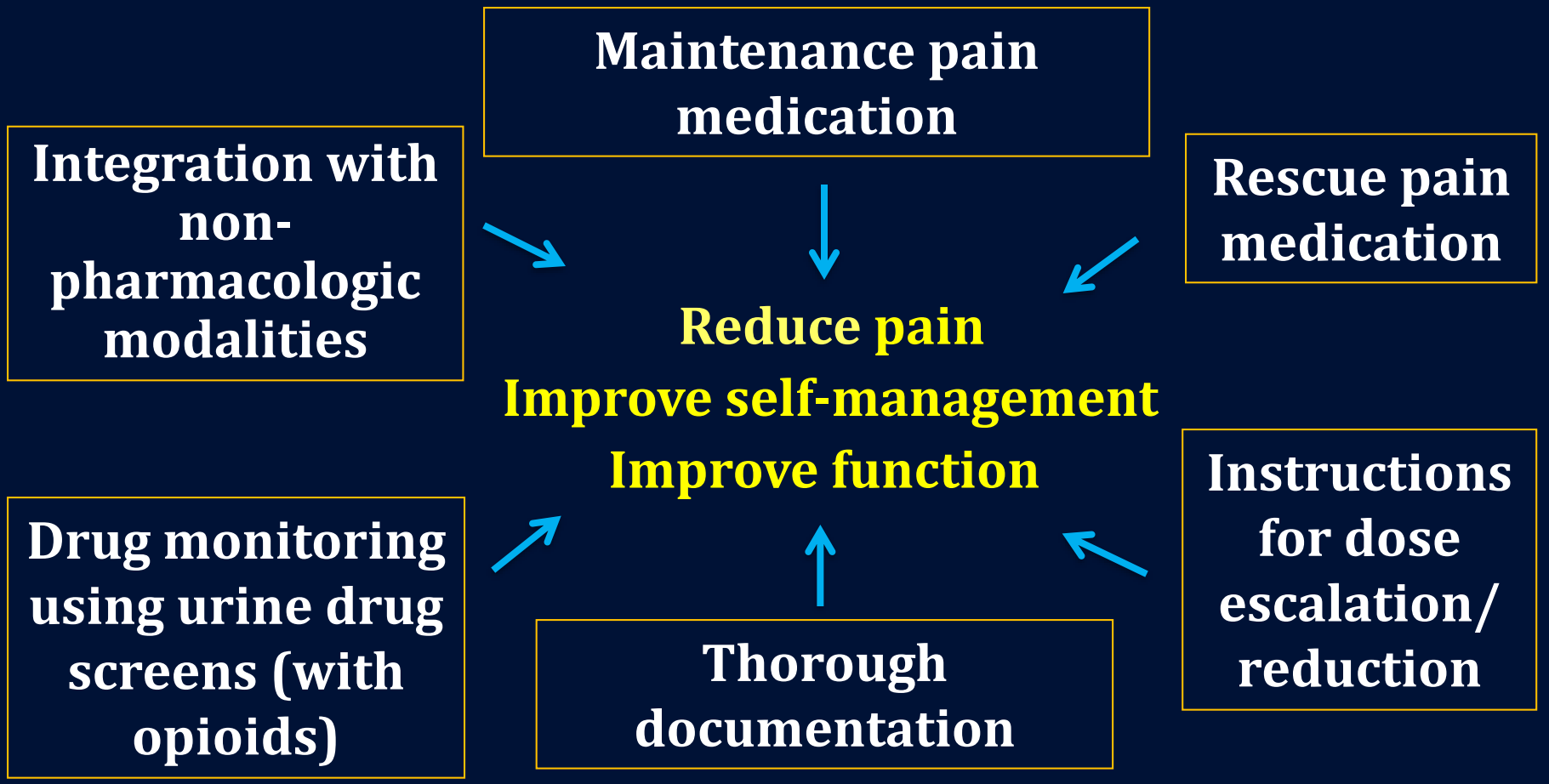
Pharmacologic Pain Management



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Approaches to Pain Management

- **Non-pharmacologic**
  - CBT, relaxation therapy
  - Physical exercise programs
- **Topical medications**
  - Lidocaine patch 5%
  - Capsaicin
  - Custom-compounded topical agents
    - Unknown effectiveness
- **Oral medications**
  - Anticonvulsants (gabapentin)
  - Antidepressants (TCAs, SSRIs, and SNRIs)
  - Opioids
  - Miscellaneous agents (e.g., mexiletine, baclofen)
- **Injections**
  - Nerve blocks
  - Local infiltrations
  - Usually administered with local anesthetics and/or steroids[5]
- **Need specialist referral**
  - Spinal cord stimulation
  - Spinal analgesia
  - Brain stimulation
  - Various neurosurgical procedures

[1] Gatchel. *Spine J* 2008;8; [2] Williams. *Cochrane Database Syst Rev* 2012;(11); [3] Monticone. *Cochrane Database Syst Rev* 2015;(5}; [4] Colberg. *Diabetes Care* 2010;33; [5] Fransen. *Cochrane Database Syst Rev* 2014;(4); [6] Katz; *Clin J Pain*. 2000;16; [7] Belgrade. *Postgrad Med*. 1999; 106; [8] Mackin. *J Hand Ther*. 1997;10; [9] Wiffen. *Cochrane Database Syst Rev* 2013;(11); [10] Moore. *Cochrane Database Syst Rev* 2014;(4); [11] Moulin. *Pain Res Manag* 2014;19; [12] Johnson. *N Engl J Med* 2014;371; [13] Ables. *Am Fam Physician* 2003;67; [14] Artigas. *Psychopharmacol Bull* 2002;36 Suppl 2; [15] Galer. *Clin Guide to Neuropathic Pain*. 2000:97; [16] Gonzales. *Neurology*. 1995:45(suppl 9).

Peripheral Targets

- COX inhibitors
- Sodium channels
  - Nav 1.8
- Calcium channels
- TRPV1 receptors
- Neuropeptide receptors
- Peripheral α2 adrenoceptors
- Neurotrophic factors
  - TrkA
- Adenosine receptors
  - P2X3

Central Targets

- COX inhibitors
- Sodium and calcium channels
- Opiate receptors
- Serotonin/norepinephrine pathways
- NMDA receptor/modulation of glutamate release
- α2 adrenoceptors

Considerations: Low Back Pain

Non-Pharmacological Treatment

- *Moderate-quality evidence | Grade: strong recommendation*
  - Superficial heat
  - Exercise
  - Multidisciplinary rehabilitation
  - Mindfulness-based stress reduction
- *Low-quality evidence | Grade: strong recommendation*
  - Acupuncture
  - Massage, spinal manipulation
  - Yoga, Tai Chi
  - Progressive relaxation
  - Motor control exercise
  - Electromyography biofeedback
  - Low-level laser therapy
  - Operant therapy
  - Cognitive behavioral therapy

American Family Physician. https://www.aafp.org/afp/2017/0915/p407.html
Qaseem, et al. Ann Intern Med. 2017;166:514-530. doi:10.7326/M16-2367

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Considerations: Low Back Pain

Pharmacological Treatment

- *Moderate-quality evidence | Grade: strong recommendation*
  - First-line therapy
    - Nonsteroidal anti-inflammatories
    - Skeletal muscle relaxants
- *Moderate-quality evidence | Grade: weak recommendation*
  - Second-line
    - Tramadol or duloxetine
- *Moderate-quality evidence | Grade: weak recommendation*
  - Opioids
    - Only in patients who have failed the other treatments
    - Only if the potential benefits outweigh the risks for individual patients
    - Only after a discussion of known risks and realistic benefits

American Family Physician. https://www.aafp.org/afp/2017/0915/p407.html
Qaseem, et al. Ann Intern Med. 2017;166:514-530. doi:10.7326/M16-2367

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Considerations: Osteoarthritis

Non-Pharmacological Treatment

Moderate to strong recommendation

- Education and self-management
  - Regular patient contact to promote self-care
  - Evaluation to perform activities of daily living
  - Instruction in joint protection
- Psychosocial interventions
  - Creation of individualization treatment plans
  - Exercise and weight loss
- Psychosocial interventions
  - Low-impact aerobic exercise
    - Land and water-based exercises (knee/hip)
  - Range of motion/flexibility exercises
  - Quadriceps strengthening
  - Endurance/strengthening exercises
  - Weight loss - overweight persons with hip/knee OA

Nelson (2018). *Seminars in Arthritis and Rheumatism, 43(6),* 701-712.

Considerations: Osteoarthritis

Non-Pharmacological Treatment

Variable recommendations

- **Assistive devices, bracing, taping**
  - Generally recommended
    - Walking aids (canes, crutches, walkers)
  - Weak or low quality evidence
    - Patellar taping
    - Knee braces
    - Medial and lateral heel wedges
    - Appropriate footwear and/or insoles, and splints for trapeziometacarpal OA
- **Alternative & complementary modalities**
  - Recommended
    - Thermal modalities - hip, knee and hand OA
  - Not recommended
    - Therapeutic ultrasound
  - Insufficient evidence
    - Acupuncture
    - Tai Chi
    - TENS

Nelson (2018). *Seminars in Arthritis and Rheumatism, 43(6),* 701-712.

Considerations: Osteoarthritis

Pharmacological Treatment

- First-Line treatment
  - Acetaminophen
- Second-Line
  - Topical NSAIDs
  - Capsaicin
  - Oral NSAIDs
    - Gastroprotection (COX-2-specific med or PPI) for patients at high-risk for gastrointestinal AE (i.e., previous GI event, age, concomitant use of anticoagulants, corticosteroids, low-dose aspirin, high-dose NSAID therapy, chronic debilitating disorders, especially CVD)
  - Tramadol
- Controversial recommendations
  - Glucosamine and/or chondroitin
  - Intra-articular hyaluronic acid preparations
- Generally recommended for refractory pain
  - Intra-articular corticosteroids (hip and knee OA)
  - Opioids for hip and knee OA but not for hand OA
- Insufficient evidence
  - Intra-articular platelet-rich plasma
  - Growth factor injections

Nelson (2018). *Seminars in Arthritis and Rheumatism, 43(6),* 701-712.

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FDA-Approved Treatments for Neuropathic Pain

- Capsaicin patch 8%
  - Postherpetic neuralgia
- Duloxetine
  - Peripheral diabetic neuropathy
  - Fibromyalgia
- Gabapentin (1 short-acting and 2 extended-release)
  - Postherpetic neuralgia
- Lidocaine patch 5%
  - Postherpetic neuralgia
- Milnacipran
  - Fibromyalgia
- Pregabalin
  - Peripheral diabetic neuropathy
  - Postherpetic neuralgia
  - Fibromyalgia
  - Spinal cord injury
- Carbamazepine
  - Trigeminal neuralgia
- Tricyclic antidepressants
  - Chronic pain

www.ncbi.nlm.nih.gov/books/NBK279175/table/diab-neuropathies.medication/

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Creating Individualized Treatment Plans

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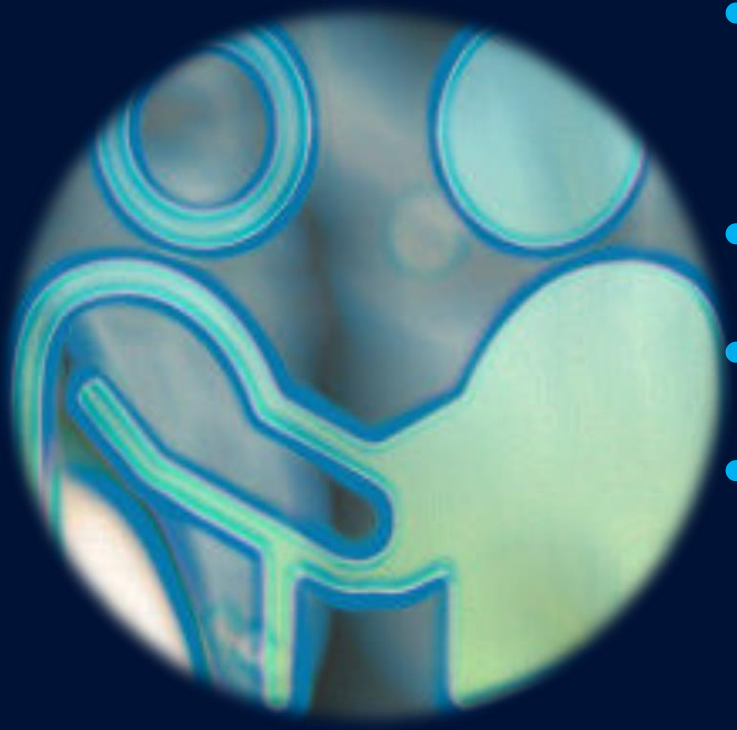
Shared Decision-Making in Pain Management



- Personalized management plan
- Self-management education
- Adherence to treatment
- Appropriate follow-up and monitoring

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Individualized Goals

Working with the patient, treatment should seek to:

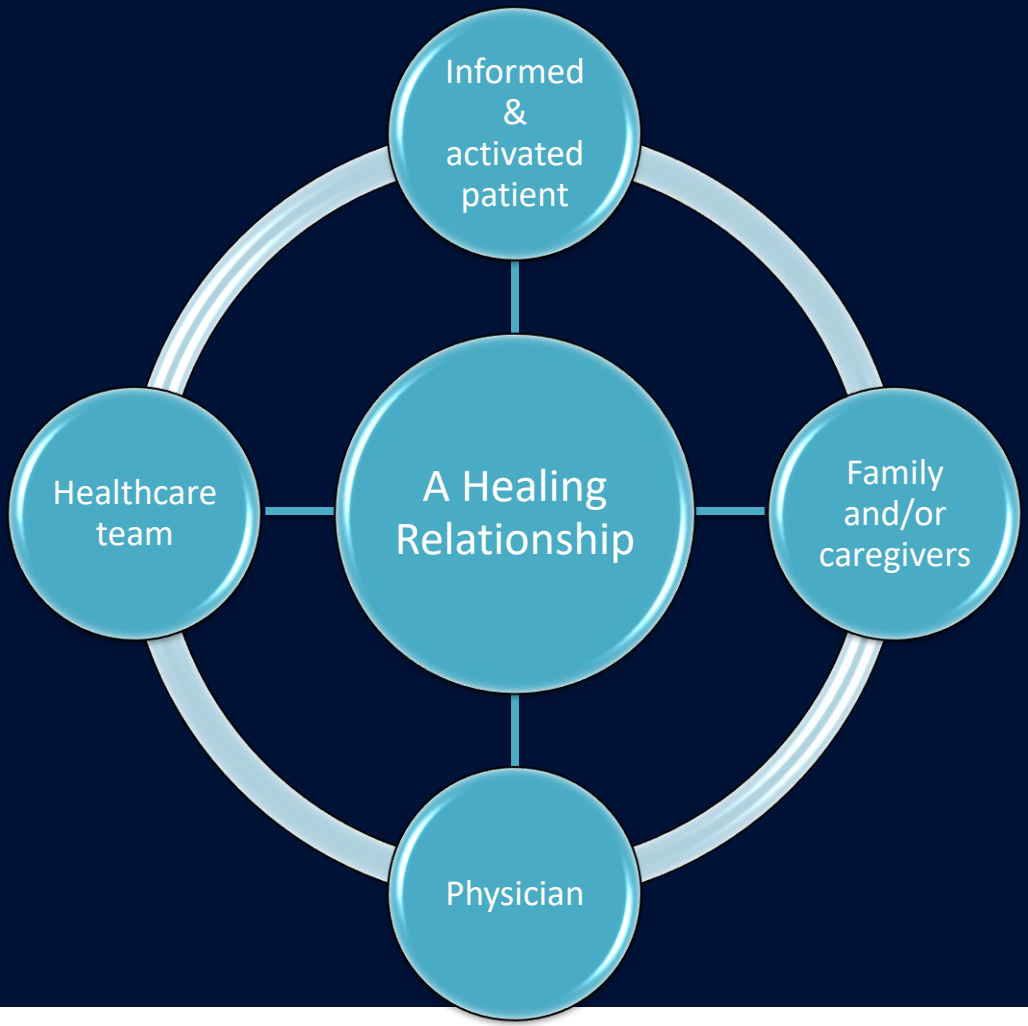
- Improve physical function
  - Range of motion, standing, walking
- Improve functional status, including activities of daily living, social/recreational activities, domestic activities
- Increase self-management of pain
- Reduce pain level
  - Reduce visual analog scale scores, verbal rating scores, verbal descriptor scores
- Improve vocational ability and status
  - Return to work, start job training, start classes
- Reduce healthcare utilization
  - Medical procedures, inpatient admissions, outpatient office visits
- Eliminate or minimize the use of opioids to treat chronic pain

1. Ablin et al. *Best Pract Res Clin Rheumatol* 2015;29:111-19.
2. Sanders et al. *Pain Pract* 2005;5:303-15.

Individualized Treatment

- Agree to realistic goals
- Develop a multidisciplinary treatment plan tailored to the patient's needs
  - Plan may consist of a combination of medications and non-pharmacologic modalities (e.g., physical therapy, occupational rehabilitation, behavioral therapy)
- Agree on timely and regular follow-up

Individualized Treatment



Emerging Pharmacotherapeutics and Novel Analgesic Targets

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Emerging Pharmacotherapeutics

Chronic Pain

- Nerve growth factor inhibitors
- New N-type calcium channel blockers
- Angiotensin II type 2 receptor antagonist
- Selective sodium channel blockers
- Cannabinoids
- Short interference RNA therapeutics
- C fiber toxins

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Nerve Growth Factor

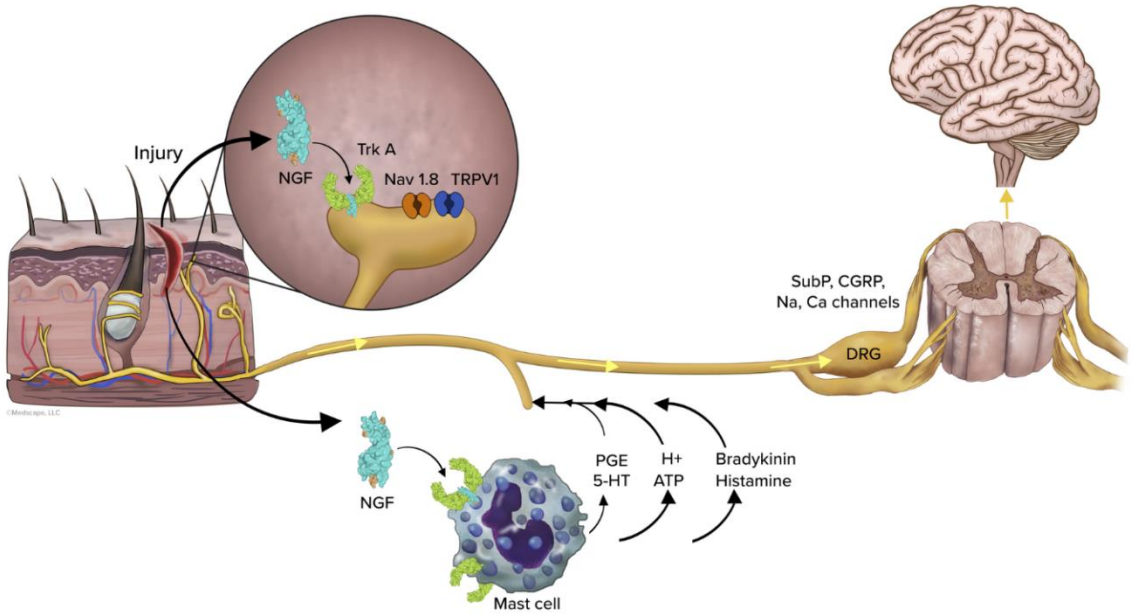
- Neurotrophin
- Upregulated in painful conditions
- Inhibition reverses pain in animal models
- Tanezumab, fasinumab, and fulranumab
  - Monoclonal antibody to NGF
  - Some abnormal peripheral sensations
  - Report of AVN (NSAID-dependent) leading to FDA hold that has now been lifted

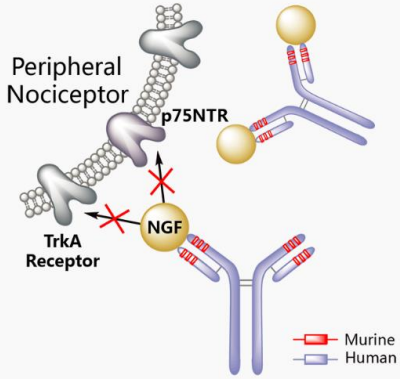
Nerve Growth Factor Studies

- Tanezumab
  - Positive in OA, CLBP, cancer
  - Negative in DPN, PHN, IC, pancreatitis
  - Phase 3 trials in cancer pain being conducted outside the Unites States
- Fasinumab
  - Strong evidence for efficacy in OA; long-term safety study needed
  - No benefit in single study for sciatic pain
  - Phase 3 trials in OA of the knee or hip and CLBP in patients with concomitant OA of the knee or hip
  - Halted the higher-dose arms of its phase 3 trials on the recommendation of data monitoring committee
- Fulranumab (discontinued phase 3 development in 2016)
  - Negative in LBP and OA

NGF Mechanism in Initiation and Maintenance of Pain

- Neurotropin
- Upregulated in painful conditions
- Inhibition reverses pain in animal models





- NGF monoclonal antibodies bind NGF with high selectivity and specificity
- Inhibit NGF binding to its receptors (high affinity R: TrkA, and low affinity R: p75)

Patel MK, et al. *J Anaesthesiol Clin Pharmacol*. 2018;34:111-116.

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Tanezumab - *Phase 3 OA Knee Pain*

- 32-week, randomized, double-blind, placebo-controlled trial (N = 690)
  - The patient criteria included diagnosis of OA; WOMAC Pain score ≥5 and Physical Function ≥4; PGA of osteoarthritis ≥3; and failure of nonopiate pain medications or candidacy for invasive interventions
- Patients received 3 IV doses of tanezumab (2.5, 5, or 10 mg) or placebo
- Coprimary efficacy endpoints were changes in WOMAC subscales and PGA at week 16
- The incidence of AEs was 55% to 60% for tanezumab-treated patients vs. 48% for placebo-treated patients
- Joint replacement was reported in 4 patients, 1 in each group

Brown MT, et al. *J Pain*. 2012;13:790-798.

Tanezumab - *Phase 3 OA Hip Pain*

- 32-week, randomized, double-blind, placebo-controlled trial (N = 621)
  - Patients with baseline WOMAC Pain score ≥ 5 and Physical Function ≥ 4, and patient's global assessment of OA as "fair," "poor," or "very poor" were treated at baseline and weeks 8 & 16
- Patients received 3 IV doses of tanezumab (2.5, 5, or 10 mg) or placebo
- Coprimary efficacy endpoints were changed from baseline to week 16 in WOMAC Pain and Physical Function subscales and PGA
- AE incidence ranged from 55% to 58% across tanezumab groups vs. 44% for placebo
- Safety findings were similar to those previously reported
- Total joint replacements were reported in 8 patients: 1 in the 10 mg, 2 in the 5 mg, 2 in the 2.5 mg, and 3 in the placebo group

Brown MT, et al. *Arthritis Rheum*. 2013;65:1795-1803.

Fasinumab - *Exploratory Study OA Knee Pain*

- 24-week, double-blind, placebo-controlled, parallel-group, repeat-dose, exploratory study
- Eligible patients (N = 217) 40 -75 years of age with a diagnosis of OA of the knee and moderate to severe pain were randomized 1:1:1:1 to IV fasinumab 0.03, 0.1, or 0.3 mg/kg or placebo and received study drug on day 1 and day 57
- Primary endpoint: safety and tolerability, assessed by the incidence of TEAEs
  - Incidence of TEAEs ranged from 66.1% to 75.0% in the fasinumab groups vs. 63.6% for placebo
  - The most common TEAEs included arthralgia, hyperesthesia, myalgia, peripheral edema, and joint swelling
  - Discontinuation for TEAEs occurred in 5.6% of fasinumab patients and 3.7% of placebo patients.
- Secondary endpoints: all 3 doses of fasinumab were associated with significant improvements vs. placebo in walking knee pain and WOMAC total and subscale scores. Fasinumab was generally well tolerated, and was associated with a significant reduction in walking knee pain and an improvement in function for up to 8 weeks.

Tiseo PJ, et al. *Pain*. 2014;155:1245-1252.

Tanezumab in CLBP
Safety and Analgesic Efficacy

Safety and analgesic efficacy of tanezumab in adults with CLBP

IV tanezumab 200 µg/kg plus oral placebo (n = 88)	IV placebo plus oral naproxen 500 mg twice a day (n = 88)	IV placebo plus oral placebo (n = 41)

- Primary outcome was average LBP intensity (aLBPI) at week 6
- Secondary outcomes were proportion of patients with ≥ 30% or ≥ 50% reduction in aLBPI, Roland-Morris Disability Questionnaire and Brief Pain Inventory-short form scores, Patients' Global Assessment of LBP, Patients' Global Evaluation of study medication, and rescue medication use

Katz N, et al. *Pain*. 2011;152:2248-2258.

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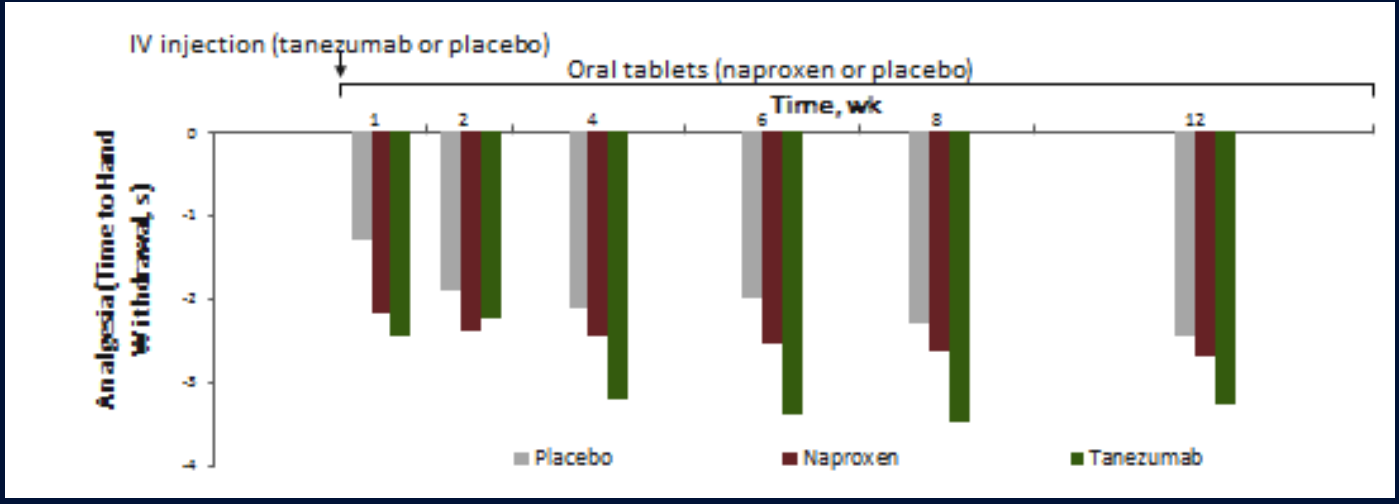
Tanezumab in CLBP
Analgesic Efficacy Results

- Greater proportions of patients reported ≥30% and ≥50% reductions in aLBPI with tanezumab vs. naproxen and placebo
- Greater improvements in Roland-Morris Disability Questionnaire
- Tanezumab was associated with AEs of abnormal peripheral sensation that were generally mild and resolved before study completion; there were no serious AEs
- 9 patients discontinued due to AEs



Katz N, et al. *Pain*. 2011;152:2248-2258.

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Tanezumab in CLBP

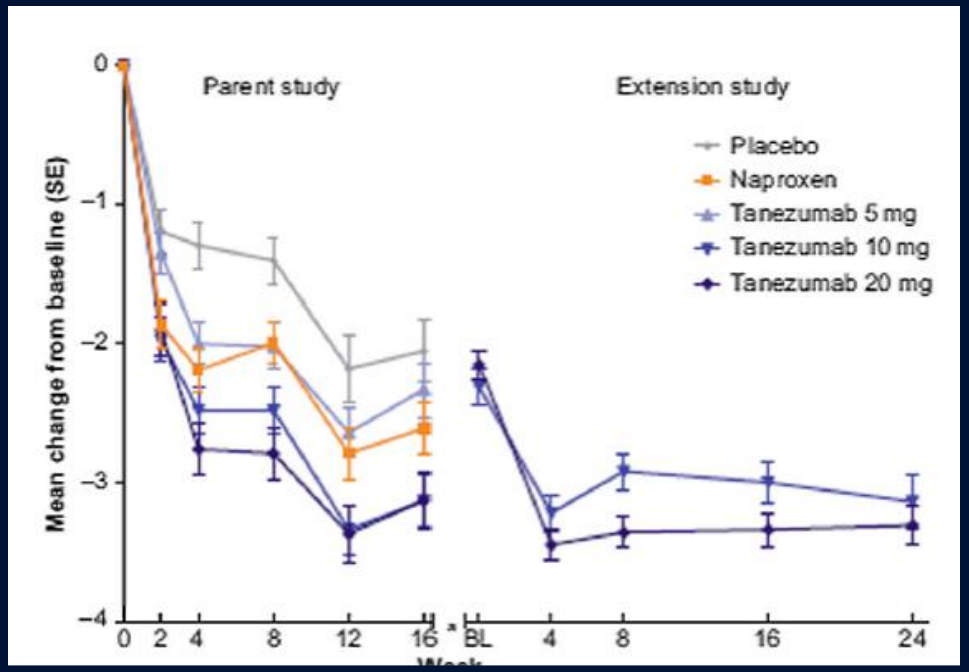
Long-Term Safety and Efficacy (Extension Study)

- Noncontrolled, randomized, multicenter study evaluating long-term safety and effectiveness of tanezumab in patients with CLBP (extension of analgesic study)
- Randomized to tanezumab 10 mg (n = 321) or 20 mg (n = 527) administered at 8-week intervals via 3 IV injections followed by 4 SC injections
- Mean treatment duration:
  - 194 days (10 mg) and 202 days (20 mg)

Gimbel JS, et al. *Pain*. 2014;155:1793-1801.

Tanezumab in CLBP - *Extension Study Results*

Brief Pain Inventory Short Form Score



Incidence of Adverse Events, n (%)		
	Tanezumab 10 mg n = 321	Tanezumab 20 mg n = 527
Patients with AEs	198 (61.7)	370 (70.2)
Patients with serious AEs	15 (4.7)	24 (4.6)
Patients discontinued due to AEs	20 (6.2)	39 (7.4)
AEs occurring in > 3% in any group*		
Arthralgia	41 (12.8)	77 (14.6)
Paresthesia	31 (9.7)	56 (10.6)
Hypoesthesia	23 (7.2)	41 (7.8)

*Other AEs include pain in extremity, peripheral edema, headache, upper respiratory tract infection, musculoskeletal pain, diarrhea, myalgia, infusion site reaction, back pain, muscle strain, joint swelling, osteoarthritis, and sinusitis.

Gimbel JS, et al. *Pain*. 2014;155:1793-1801.

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Selective Sodium Channel Blockers

- Nav 1.7, Nav 1.8, Nav 1.3
- Nonspecific sodium channel blockers (lidocaine, mexilitine, lamotrigine) have not been very successful clinically due to side effects
- Selective blockers better tolerated (not located in heart tissue or CNS)
- Central vs. peripheral effects unclear
- Two Na 1.7 channel inhibitors
  - BIIB095 in phase 1 trials
  - Vixotrigine to start phase 2 trials in small fiber peripheral neuropathy
- Na 1.8 channel inhibitor
- VX-150 currently in phase 2 for small fiber peripheral neuropathy

Voltage-Dependent Sodium Channels Subtypes and Associated Pain Syndromes

Neuropathic pain	Visceral pain	Inflammatory pain	Mechanical pain	Multiple sclerosis pain
Nav 1.3 Nav 1.6 Nav 1.7 Nav 1.8 Nav 1.9	Nav 1.8	Nav 1.7 Nav 1.8 Nav 1.9	Nav 1.7	Nav 1.2

Montero A, et al. *Rev Esp Anestesiol Reanim*. 2018;65:275-283.

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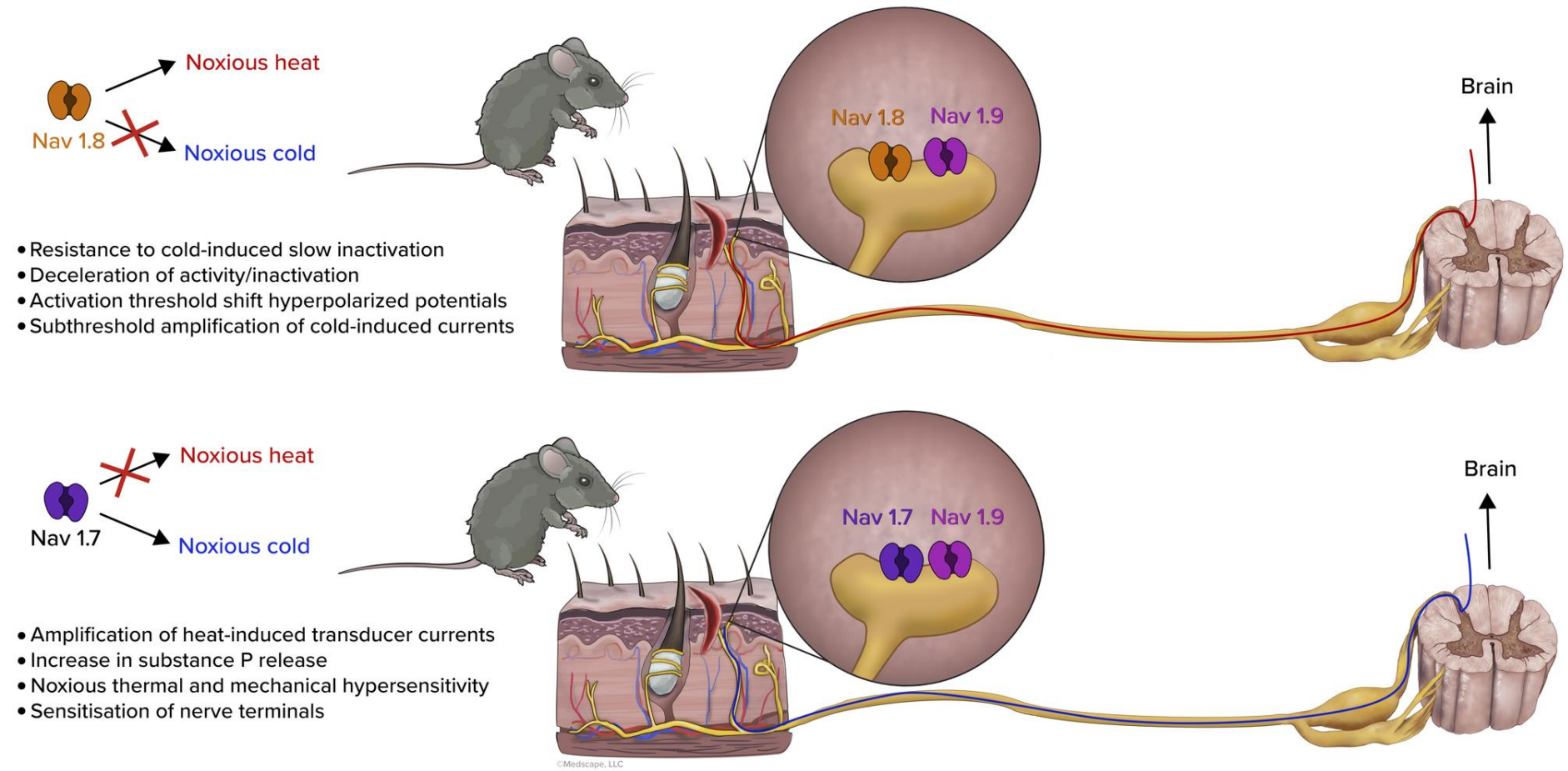
Modality-Specific Pain Pathways and Voltage-Gated Na+ Channels



Louloudis G. *Bioscience Horizons*. 2017;10.

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Mirogabalin

- N-type calcium channel modulator
- Specific to the α-2-delta type II subunit
- Fewer side effects that nonspecific modulators (i.e., pregabalin)
- Fewer side effects may result in ability for higher doses and improved efficacy

Angiotensin II Type 2 Receptor Antagonist (EMA-401)

- AT2 receptors expressed on small fibers and DRG
- Angiotensin I → (ACE) → angiotensin II
- Phase 2 study in PHN
  - N = 183
  - Primary outcome positive: pain intensity
  - Secondary outcomes positive: onset, 30% and 50% responder rate, McGill, PGI of change
  - Safe and well tolerated
- Phase 3 trial in PHN soon to start

Rice ASC, et al. *Lancet* 2014;383:1637-1647.

Online Resources

Organization	URL
American Society of Interventional Pain Physicians	asipp.org
Centers for Disease Control and Prevention	www.cdc.gov
American Academy of Pain Medicine	www.painmed.org
American Chronic Pain Association	theacpa.org
University of Washington—Pain Medicine	depts.washington.edu/anesth/education/pain

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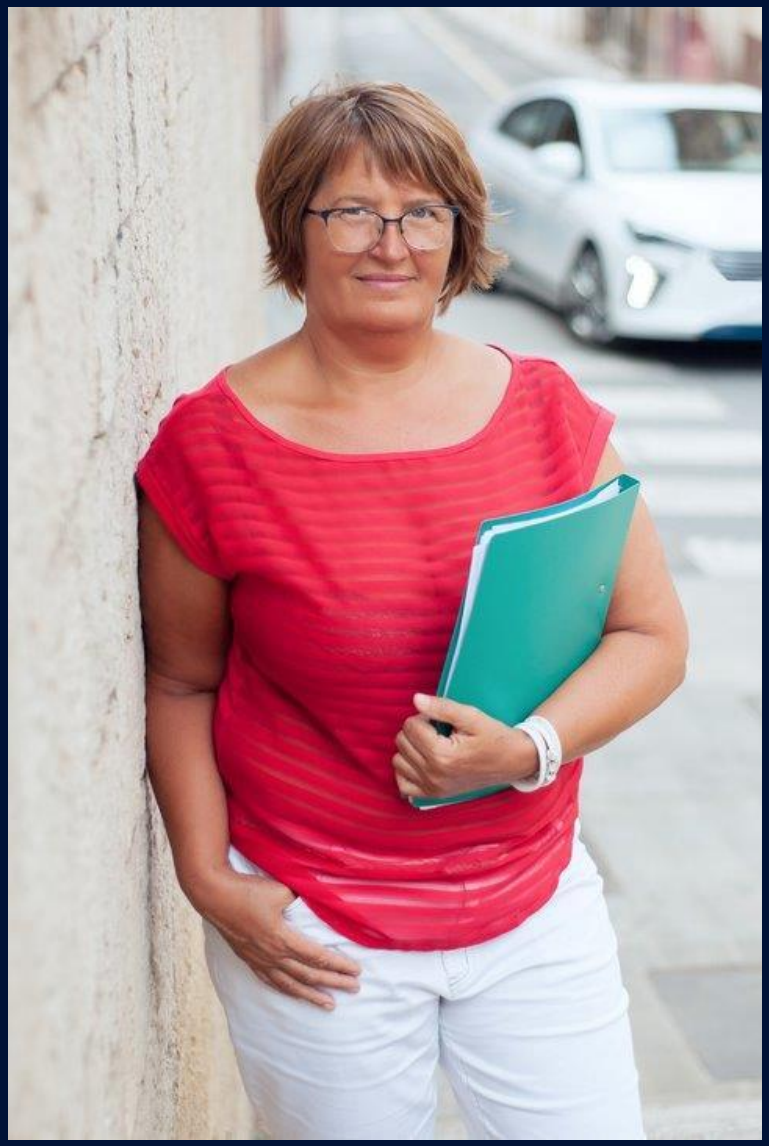

Case Study

ANNA

Anna is a simulation case study

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Case Study: Anna

- 43 year old female - BMI 36
- Uncontrolled left knee pain with acetaminophen
- No history of recent injury
- 2 previous left knee surgeries in teens due to athletics
- Unsuccessful attempts at weight loss
- Current medications: fluticasone, statin
- Started OTC analgesics ~ 1 year
  - Increasing frequency and doses last 6-8 months

Case Study: Anna

- Physical Exam
  - She is slightly uncomfortable with ambulation but in no distress
  - The left knee may be slightly swollen
  - No erythema and no focal tenderness
  - Full range of motion (ROM) and her ligaments seem intact
  - Good distal pulses and intact neurovascular status

Case Study: Anna

Given the patient's medical history and physical examination, which of the following options would be the least appropriate?

A. Encourage exercise
B. Consider referral for bariatric surgery
C. Recommend hamstring stretches with a trial of over-the-counter capsaicin cream
D. Obtain a left knee MRI, given the duration of symptoms

Case Study: Anna

- Anna's benign exam accompanied by an unremarkable history reassures you that the diagnosis is probably OA.
- Anna begins an exercise regimen and changes her diet with the goal of losing weight.
- She still has some pain in the evening, and she wants a medication to help in addition to using capsaicin cream.

Case Study: Anna

Which of the following medications would be the next best option given evidence and guidelines available?

A. Oxycodone 5 mg every 8 hours as needed
B. Naproxen 250 to 500 mg every 12 hours as needed
C. Acetaminophen (up to 4000 mg daily)
D. Chondroitin 800 mg/day

Case Study: Anna

- Committed to a high-protein diet
- Used naproxen as needed
- Reduced BMI to 32
- Knee pain slightly improved
- Gained weight back over 3 years
- Bariatric surgery
- Knee pain eventually improved

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Case Study
BILL

Bill is a simulation case study

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Case Study: Bill

- 56 year old male
- Lower back pain
- 1 year ago after hiking
- Mild intermittent sciatica – right leg
- No bowel or bladder issues
- HTN (controlled with ACE)
- ½ pack cigarettes per day
- Recreational marijuana several times per week

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Case Study: Bill

Which of the following would be the most appropriate next steps?

A. Try to obtain previous records to determine what treatments have been tried and see the patient back in 1-2 weeks; in the interim, basic interventions would be based on initial history and physical examination
B. Order a lumbar MRI
C. Order nerve conduction studies
D. Orthopedic referral

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Case Study: Bill

- Documented HTN & preventive care
- No formal back pain evaluation
- L4-5 changes consistent with OA
- No follow-up from PT (lumbar strain/back exercises)
- Medications tried:
  - Naproxen 500 mg
  - Meloxicam 7.5 mg orally once daily
  - Tramadol 50 mg every 6 hrs as needed

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Case Study: Bill

Considering Bill's presentation and limited prior treatments, according to guidelines, which of the following options would be the least appropriate choice for pain management at this time?

A. Acetaminophen
B. NSAIDs
C. Nonpharmacologic approaches
D. Oxycodone/acetaminophen

Case Study: Bill

- Referred to physical therapy
- 2x per week/3 weeks
- Ergonomic adjustments at work
- Returns in 6 weeks with only minimal improvement

Case Study: Bill

Which would be the most appropriate next medication for this patient?

A. Acetaminophen
B. An NSAID
C. Oxycodone/acetaminophen
D. A tricyclic antidepressant

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Case Study: Bill

- Persistent LBP after 2 weeks oral naproxen 500mg
- Radicular symptoms have actually slightly worsened
- Requests MRI and “something stronger for pain”
- Screen for depression
- PHQ-9 score of 13

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Case Study: Bill

What would be the most appropriate next medication for this patient?

A. Tramadol
B. Duloxetine
C. Oxycodone/acetaminophen
D. Morphine, hydromorphone, or oxymorphone

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Case Study: Bill

- MRI - slight disc bulging at L4-5 with some nerve impingement on the right - referred to pain specialist
- CBT for depression and chronic pain
- Continue pharmacologic/non-pharmacologic interventions
- Initiated duloxetine 20mg bid
  - Monitored for Serotonin Syndrome
- Delay to see pain specialist allowed duloxetine & CBT to help Bill feel a little better
  - More energy
  - Could exercise
- Received epidural injection
- Gradual improvement with relief

Park et al. J of Pharmacy Practice; 27(1): 71-78

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Conclusions

- Chronic pain may result from multiple underlying mechanisms
- More than one mechanism can operate in a single patient, and these may change over time
- Chronic pain may present as nociceptive, inflammatory, or neuropathic
- Management of chronic pain in OA or LBP requires an integrated strategy that includes pharmacologic and non-pharmacologic modalities
- Clinicians and patients must set realistic treatment expectations, such as improved functionality and reduced pain level, with the understanding that the complete elimination of pain is unlikely
- Various classes of agents, including OTC medications, antidepressants, anti-epileptics, and opioid analgesics may be appropriate to treat various pain syndromes
- Nerve Growth Factor studies show promise in reducing LBP and OA Pain
- There are many therapeutic analgesic alternatives in the pipeline with the potential to have a significant impact on reducing pain in the United States

Questions

To learn more about chronic pain management and earn additional CME credit, visit *https://www.njafp.org/courses*

Don't forgot to complete your evaluation and claim credit. Return the completed form to a staff member.

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