Safe Opioid Prescribing

A Patient-Centered Approach to the FDA Blueprint

Part 1: ***Pain Management Fundamentals***

Charles E. Argoff, MD
Albany Medical College

Yvonne D'Arcy, CRNP, CNS
Suburban Hospital-Johns Hopkins Medicine

Bill H. McCarberg, MD
Kaiser Permanente San Diego

Wednesday, October 27, 2021
6:00–7:00 PM

Tension by Vicky Grant
Acrylics; London, UK

Introduction

Charles E. Argoff, MD
Professor of Neurology, Albany Medical College
Vice Chair, Department of Neurology
Director, Comprehensive Pain Center
Director, Pain Management Fellowship
Albany Medical Center
Albany, New York

Program and presenters

Topic	Presenter	Time
Introduction	Dr. Argoff	5 minutes
Assessment	Ms. D'Arcy	20 minutes
Treatment	Dr. McCarberg	20 minutes
Conclusion	Dr. Argoff	5 minutes
Live Q&A	Panel	10 minutes

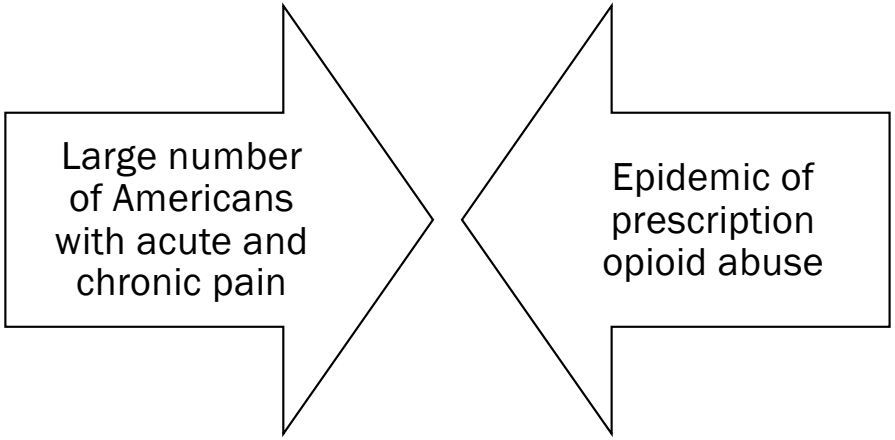
- **Learning objectives**
  - Explain the need for comprehensive pain education
  - Outline the fundamental concepts of pain management, including definitions and mechanisms of pain
  - Assess patients in pain, including identifying risk factors for opioid abuse and addiction
  - Discuss the range of therapeutic options for managing pain, including nonpharmacologic approaches and pharmacologic (non-opioid and opioid analgesics)

Disclosures

- Charles E. Argoff, MD: Consulting fees (eg, advisory boards): Amgen, BDSI, Collegium, Gruenenthal, Lilly, Lundbeck, Neumentum, Redhill Pharma, Teva, Vertex; contracted research (principal investigators must provide information, even if received by the institution): Abbvie, Amgen, Lilly, Teva; speakers' bureaus: AbbVie, Amgen, Biohaven, Gruenenthal, Lilly, Lundbeck, Red Hill Pharma, Teva
- Michael R. Clark, MD, MPH, MBA: Nothing to disclose
- Yvonne M. D'Arcy, CRNP, CNS: Nothing to disclose
- Bill H. McCarberg, MD, FABM: Consulting fees (eg, advisory boards): Averitas, Lilly, Silex; speakers' bureaus: Adapt, Silex; stock shareholder (individual stocks/stock options, diversified mutual funds do not need to be disclosed): Johnson and Johnson

What is the Opioid Analgesic REMS Blueprint?

- Developed with 2 competing US public health concerns in mind



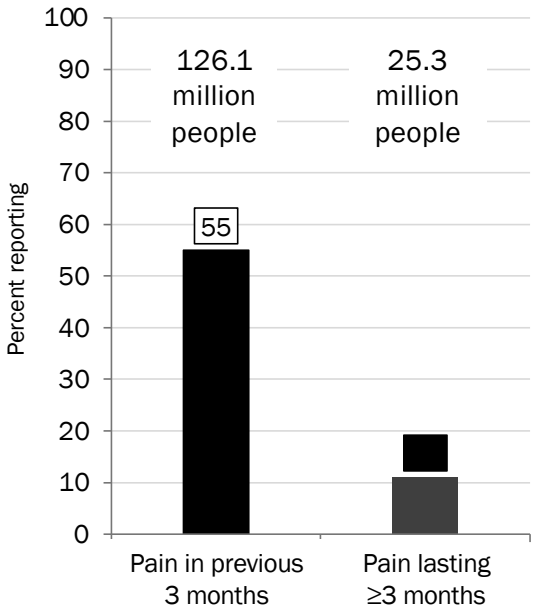
- Key areas for HCP education
  - Consideration of *all* pain management options
  - Opioid-specific risks
  - Use of opioids only when other options are inadequate and benefits > risks
  - Patient counseling and other strategies to reduce risk and contribute to alleviating both public health crises

HCP, health care provider.

Katz J, et al. *Can J Psychiatry*. 2015;60(4):160-167.

Pain is among the most common reasons for seeking medical care in the United States

Large number of Americans with acute and chronic pain



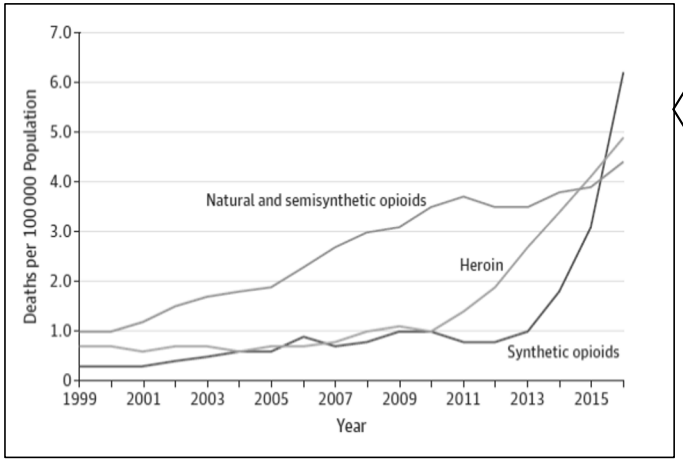
- Recent US estimates
  - National Health Interview Survey[1]
    - **55%** of respondents reported experiencing some amount of pain during the previous 3 months (N>100,000)
  - NHANES[2]
    - Acute pain: 26% to 34%
    - Chronic pain: 13% to 15%
  - Health and Retirement Study[3]
    - Acute pain: 27% to 33%
- Prevalence of moderate to severe chronic pain in developed countries: ~25%[4]

NHANES, National Health and Nutrition Examination Survey.

1. Nahin RL, et al. *J Pain*. 2015;16(8):769-780. **2.** Riskowski JL. *Pain Med*. 2014;15(9):1508-1521. **3.** Reyes-Gibby CC, et al. *J Pain*. 2007;8(1):75-84. **4.** Katz J, et al. *Can J Psychiatry*. 2015;60(4):160-167.

Trends in opioid misuse and deaths in the US

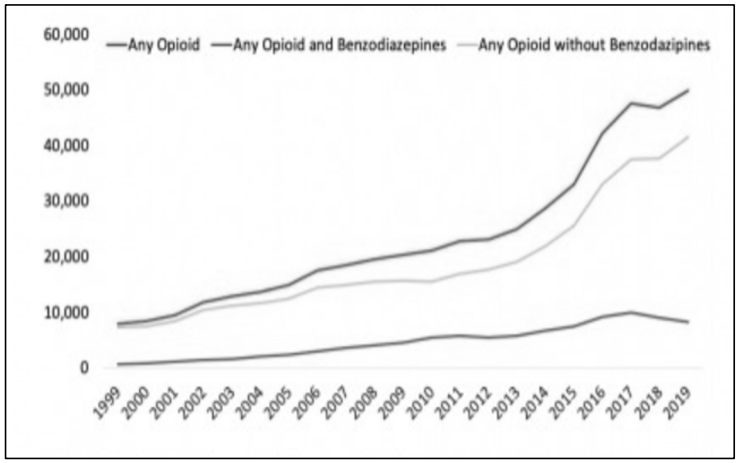
- Rapid increase in opioid prescribing for acute and chronic pain in the 1990
- Number of US opioid prescriptions increased from 76 to 207 million; highest in the world per capita[1]



Epidemic of prescription opioid abuse

Deaths from opioid misuse, 1999-2016[2]

- After 2012, decline in opioid prescribing due to concern about misuse and overdose
- Death toll continued to rise due to increased use of illicit fentanyl/heroin and use with benzodiazepines

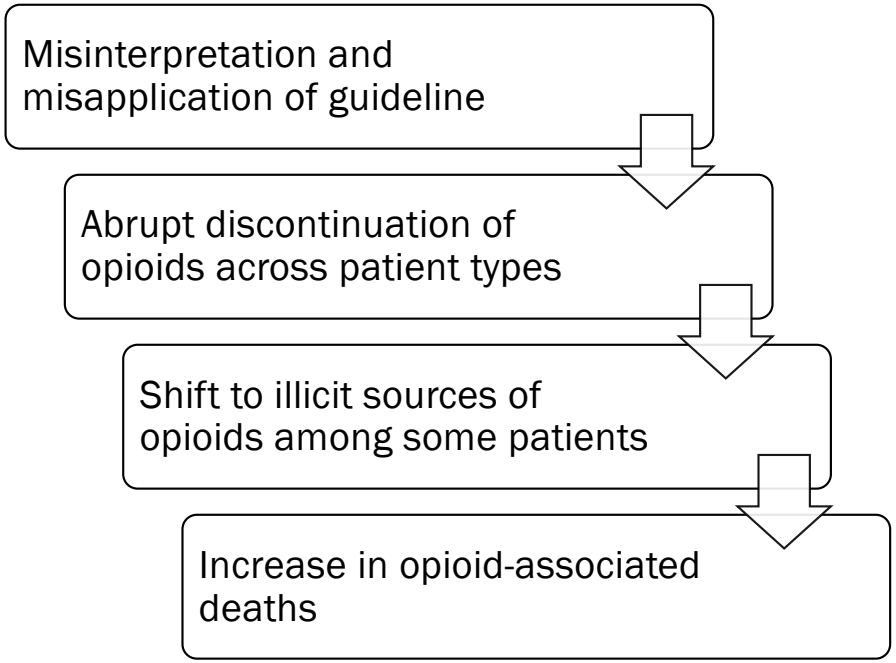


US drug overdose deaths involving opioids and benzodiazepines[3]

1. Stoicea N, et al. *Medicine (Baltimore).* 2018;98(20):e15425. **2.** Volkow ND, et al. *JAMA Psychiatry*, 2019;76(2):208-216.
3. National Institute on Drug Abuse. www.drugabuse.gov/drug-topics/opioids/benzodiazepines-opioids.

CDC guideline has good intention but difficult outcomes for some patients

- Highlights of 2016 guideline
  - No definitive evidence shows that opioids are beneficial beyond 12 weeks
  - Opioids are associated with tolerance, physical dependence, and OUD
  - ER/LA formulations pose specific risks
  - Inappropriate opioid therapy for acute pain may lead to chronic use or abuse
  - Opioids should not be used first-line except for cancer and end-of-life care
- Unintended consequence
  - Precipitous decline in opioid prescribing and increase in overdose deaths



ER/LA, extended-release/long-acting; **OUD,** opioid use disorder.

Dowell D, et al. *JAMA*. 2016;315(15):1624-1645.

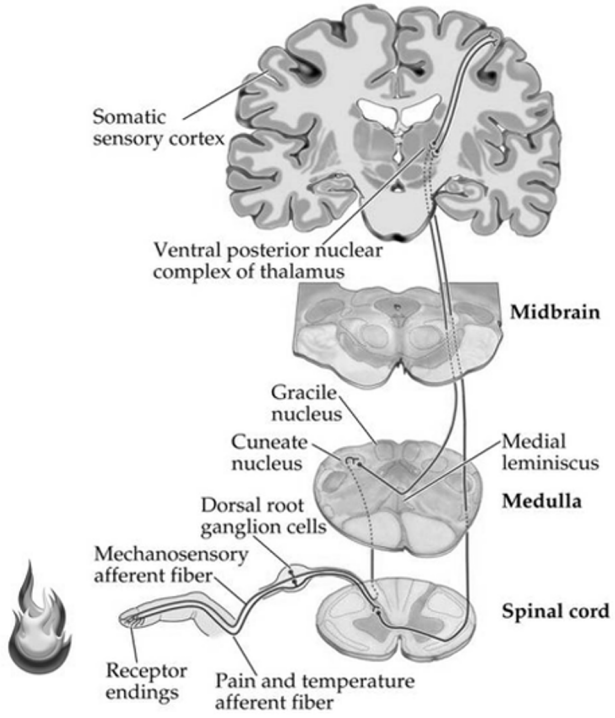
Definitions, Mechanisms, and Pain Assessment

Yvonne M. D'Arcy, CRNP, CNS

Pain Management and Palliative Care Nurse Practitioner
Suburban Hospital-Johns Hopkins Medicine
Bethesda, Maryland

What is pain?

- **Transduction:** Conversion of a noxious stimuli (chemical, mechanical, or thermal) into electrical energy
- **Transmission:** Electrical stimulus is sent to the dorsal horn of the spinal cord and synapse at the second-order neuron
- **Modulation:** Inhibition vs amplification of signal (facilitated by EAAs)
- **Perception:** Conscious awareness of pain as a culmination of previous processes in the context of the individual's experiences



EAA, excitatory amino acid.

What is pain?

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[1]

"A complex sensory and emotional experience that can vary widely between people and even within an individual depending on the context and meaning of the pain and the psychological state of the person."[2]

1. Merskey H, Bogduk N. www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698&navItemNumber=576#Pain.
2. Bushnell MC, et al. *Nat Rev Neurosci*. 2013;14(7):502-511.

Pain can be classified by *duration*

Acute

- Lasts <3 to 6 months
- Usually due to organic cause
- Treatment goal: cure

Chronic

- Persists for months to years
- Organic cause may be absent
- Treatment goals: ↑ function, 30%-50% ↓ in pain intensity

Katz J, et al. *Can J Psychiatry*. 2015;60(4):160-167; Watson JC. www.merckmanuals.com/professional/neurologic-disorders/pain/chronic-pain?query=pain.

Pain can be classified by *underlying pathophysiology*

Nociceptive

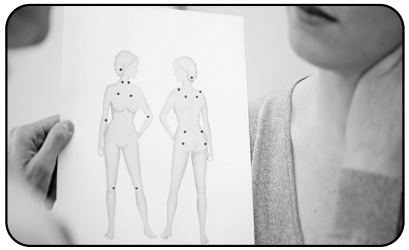
- Arises from damage to tissue in skin, muscle, and viscera; pain signal is relayed from nociceptors
- **Examples:** cuts, burns, fractures

Inflammatory

- Arises from activation or sensitization of inflammatory mediators due to injury, trauma, or surgery
- **Examples:** appendicitis, RA, IBD

Neuropathic

- Arises from damage to somatosensory peripheral and central nervous systems
- **Examples:** neuropathy, neuroma, phantom limb pain



Nociplastic

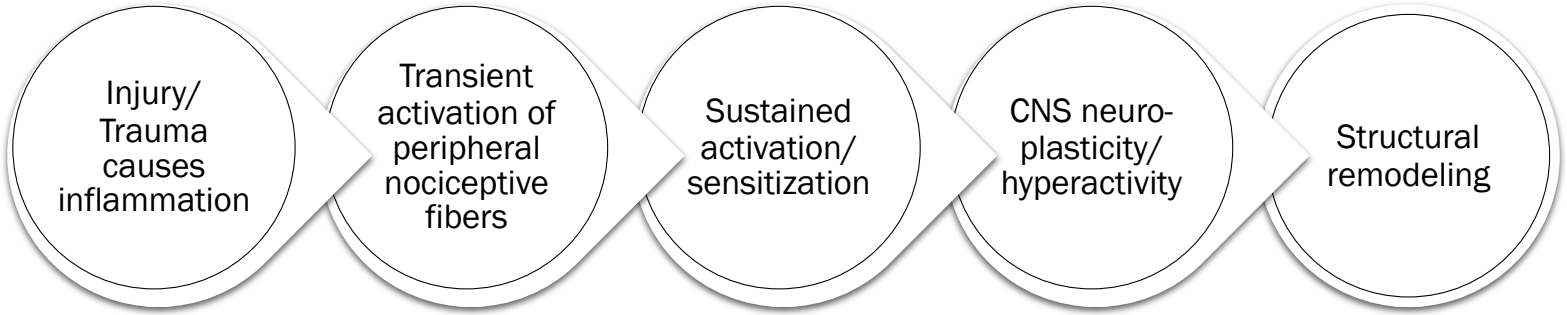
- Persistent neurochemical dysregulation without identifiable origin
- **Example:** fibromyalgia

IBD, inflammatory bowel disease; **RA,** rheumatoid arthritis.

Rathmell JP, et al. https://accessmedicine-mhmedical-com.proxy.cc.uic.edu/searchresults.aspx?q=pain&subonly=True.

Acute pain can become chronic pain

- Theorized to arise from maladaptive neuroplastic mechanisms involving peripheral/central sensitization and descending modulation



Acute pain

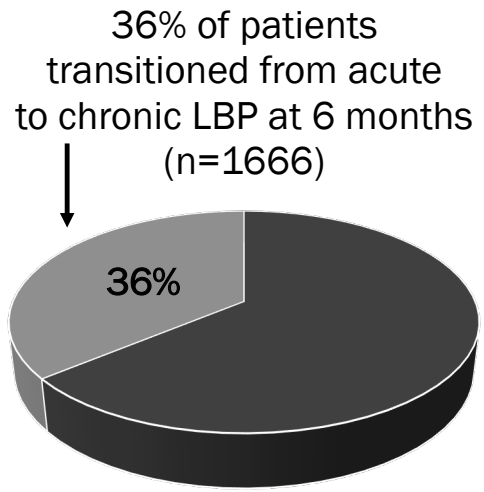
What can be done to prevent this?

Chronic pain

CNS, central nervous system.

Study finds high rate of transition from acute to chronic LBP

- N=5233 patients with acute LBP
- Characteristics associated with transition to chronic LBP
  - Obesity (aOR, 1.52; *P*<0.001)
  - Smoking (aOR, 1.56; *P*<0.001)
  - Severe/Very severe baseline disability (aOR, 1.82; *P*<0.001 and aOR, 2.08; *P*<0.001, respectively)
  - Diagnosed depression/anxiety (aOR, 1.66; *P*<0.001)
- Exposure to 1, 2, or 3 guideline-nonconcordant processes of care within the first 21 days makes the development of chronic LBP 1.39, 1.88, and 2.16 times more likely vs no exposure

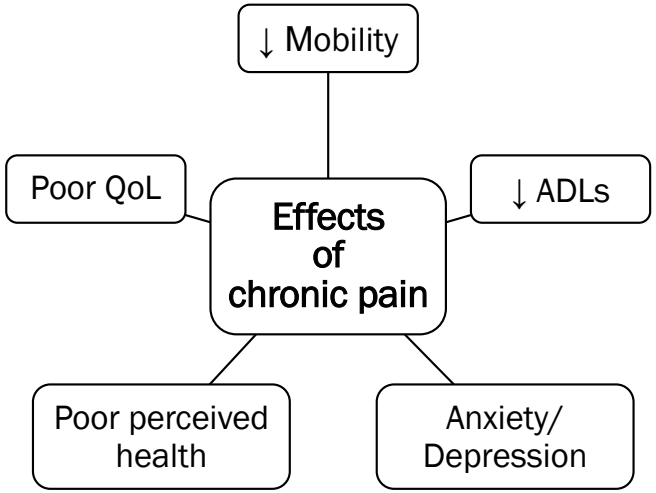


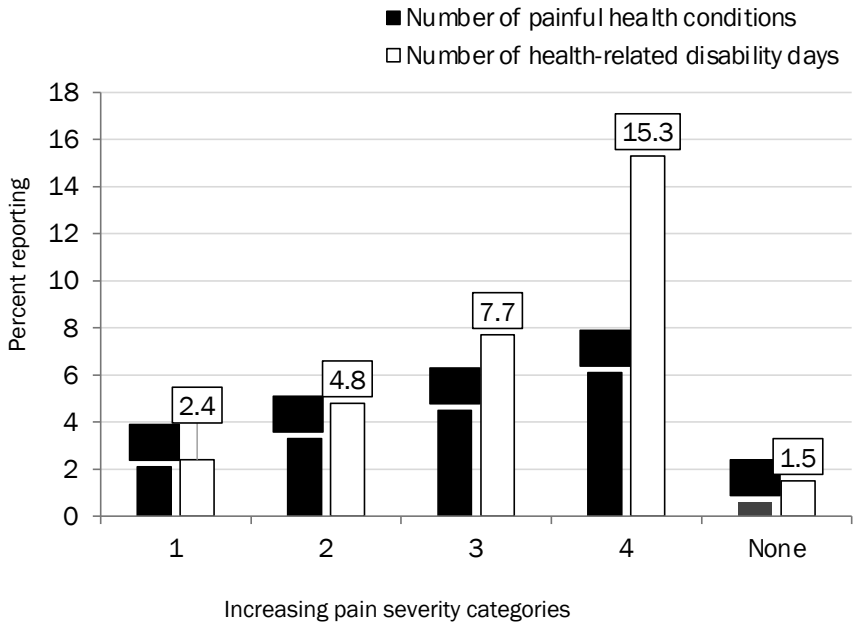
aOR, adjusted odds ratio; **LBP,** low back pain.

Stevans JM. *JAMA Netw Open*. 2021;4(2):e2037371.

Pain is associated with poorer health status and greater disability

- As the degree of pain increases, the number of health conditions, amount of disability, and use of health care resources increases



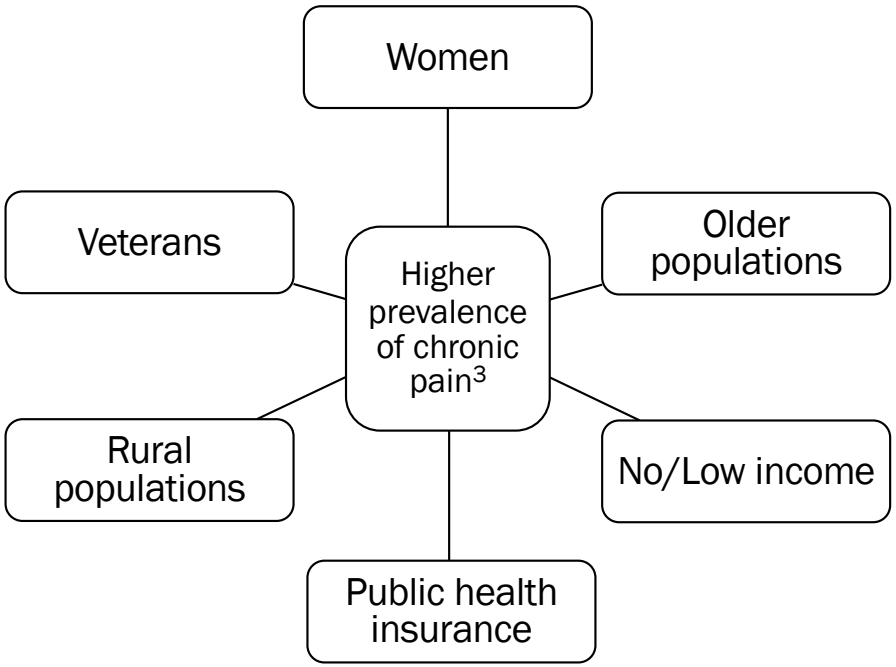


ADLs, activities of daily living; **QoL,** quality of life.

Nahin RL, et al. *J Pain*. 2015;16(8):769-780.

No 2 pain patients are alike

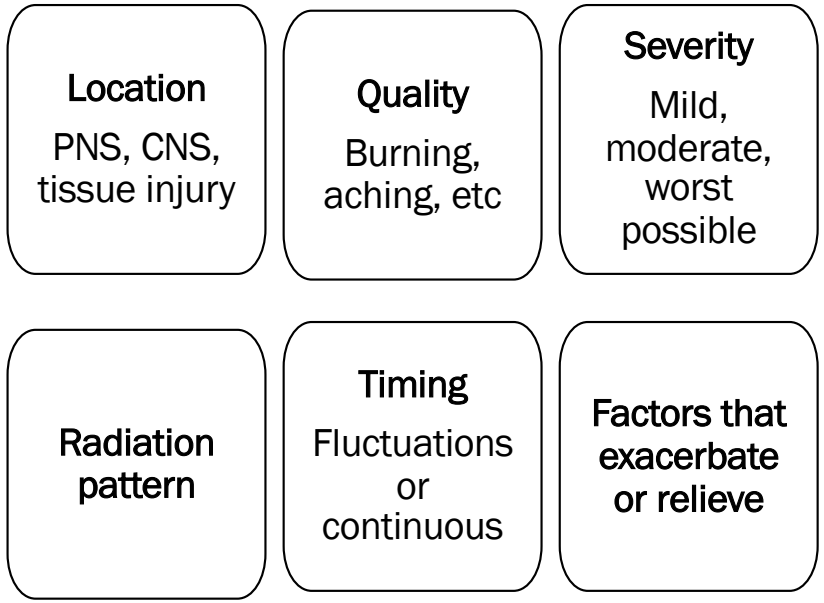
- Among US ethnic/racial groups[1]:
  - White patients are more likely to report pain
  - Asian patients are least likely to report pain
- Long-standing disparities in assessment and management of pain are acknowledged[2]
- Issues of access deepened during coronavirus pandemic[2]



1. Nahin RL, et al. *J Pain*. 2015;16(8):769-780. **2.** Green CR, et al. *Pract Pain Mgmt*. 2021;16(5). **3.** Dahlhamer J, et al. *MMWR Morb Mortal Wkly Rep*. 2018;67(36):1001-1006.

Elements of general pain assessment

- Patient history
- Physical examination, diagnostic studies
- Pain and functional assessment
  - Multifactorial
  - Screening tools
- Psychological and social evaluation
- Risk for transition from acute to chronic pain, where appropriate

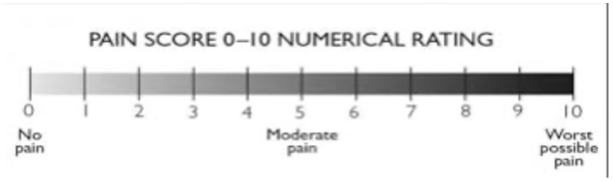


PNS, peripheral nervous system.

Validated assessment tools can complement clinical interviewing, provide documentation

Numerical Rating Score (NRS)

- Preferred for chronic noncancer pain in majority of patients across ages/cultures[1]
- Equally efficient as VAS for assessing cancer pain in literature reviews[1]



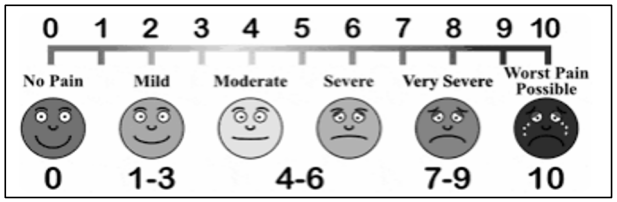
Verbal Rating Score (VRS)

- Preferred for less educated and elderly[1]
- Less sensitive to changes in pain intensity[2]

0 = No pain
1 = Mild pain
2 = Distressing pain
3 = Severe pain
4 = Horrible pain
5 = Excruciating pain

Visual Analog Score (VAS)

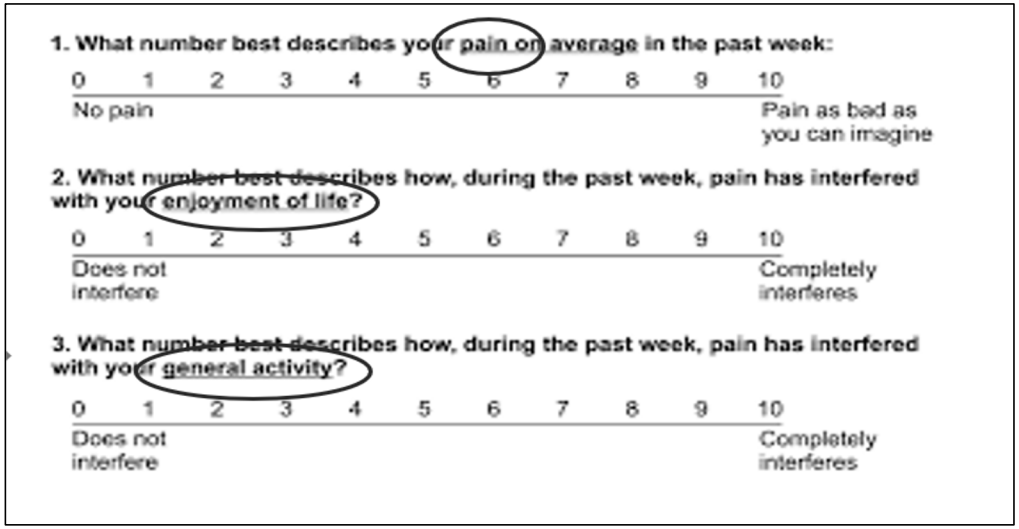
- Useful for patients with cancer pain, those with low literacy, and children[1]



1. Hjermstad MJ, et al. *J Pain Symptom Manage*. 2011;41(6):1073-1093. **2.** Breivika H. *Scand J Pain*. 2016;11:150-152.

Pain-related functionality may be more critical to patient QoL than pain intensity

- PEG is a popular multidimensional scale for chronic pain patients
  - Short, easy to administer
  - 0-10 rating for each parameter
  - Sensitive to changes in patient condition and differentiates between patients with and without pain improvement



P { • Pain intensity

E { • Enjoyment of life

G { • General activity

Krebs EE, et al. *J Gen Intern Med*. 2008;24(6):733-738.

Elements of pain assessment when considering opioid treatment

- Risk for OUD or abuse
  - Screening tools
- PDMP check for prescription-filling habits
  - CDC recommends checking every 3 months and before every opioid prescription
- UDT for ongoing monitoring

More on this in parts 2 and 3

Risks for OUD
• Male sex • Younger age • Lower educational level • Lower income • White, Black, or Native American race • History of anxiety disorders • History of SUD

Risks for opioid overdose

• Male sex
• Age 35-44 years
• History of:
  • SUD
  • Discontinuing treatment
  • Suicide attempt
  • Previous overdose
  • Severe chronic pain
• Use of opioids + other CNS depressants

CDC, Centers for Disease Control and Prevention; **PDMP,** prescription drug monitoring program; **SUD,** substance use disorder; **UDT,** urine drug testing.

Blanco C, Volkow ND. *Lancet*. 2019;393:1760-1772; CDC. www.cdc.gov/drugoverdose/pdf/pdmp_factsheet-a.pdf.

Social and economic risk factors for opioid abuse have been identified

- In a sample of 156,870 US adults from the National Survey on Drug Use and Health (2015-2018), US adults who are abusers of opioids were disproportionately:
  - White
  - Below the poverty line
  - Not highly educated
  - Uninsured
  - Disabled
  - Dealing with serious mental illness

Social characteristics		Opioid user, %[a]	Opioid + mAMP user, %[a]	% US adult population
Race/Ethnicity	White	70	84	60
	Black	13	2	12
	Hispanic	13	9	19
	Asian/ Other	4.2	5	9
Income below FPL		24	36	10.5
College graduate		14	10	37
Uninsured		21	25	11
Rate of disability		37	42	26
Serious mental illness		21	32	5

FPL, federal poverty level; **mAMP,** methamphetamine.

[a]*Opioid use* defined as misuse of prescription opioids 4 times in past month, or heroin use in past year.

Shearer RD, et al. *Drug Alcohol Depend*. 2020;214:108162.

The ORT is validated to predict OUD

- Revised version recently validated
  - Demonstrated sensitivity, specificity, and predictive value
  - Successfully predicted OUD in a sample of patients with chronic pain on long-term opioid therapy
    - N=1178; OR, 1.624
  - Note: no questions about personal substance abuse or mental health
- Other tools
  - Screener and Opioid Assessment for Patients in Pain (SOAPP)
  - Diagnosis, Intractability, Risk, Efficacy Score

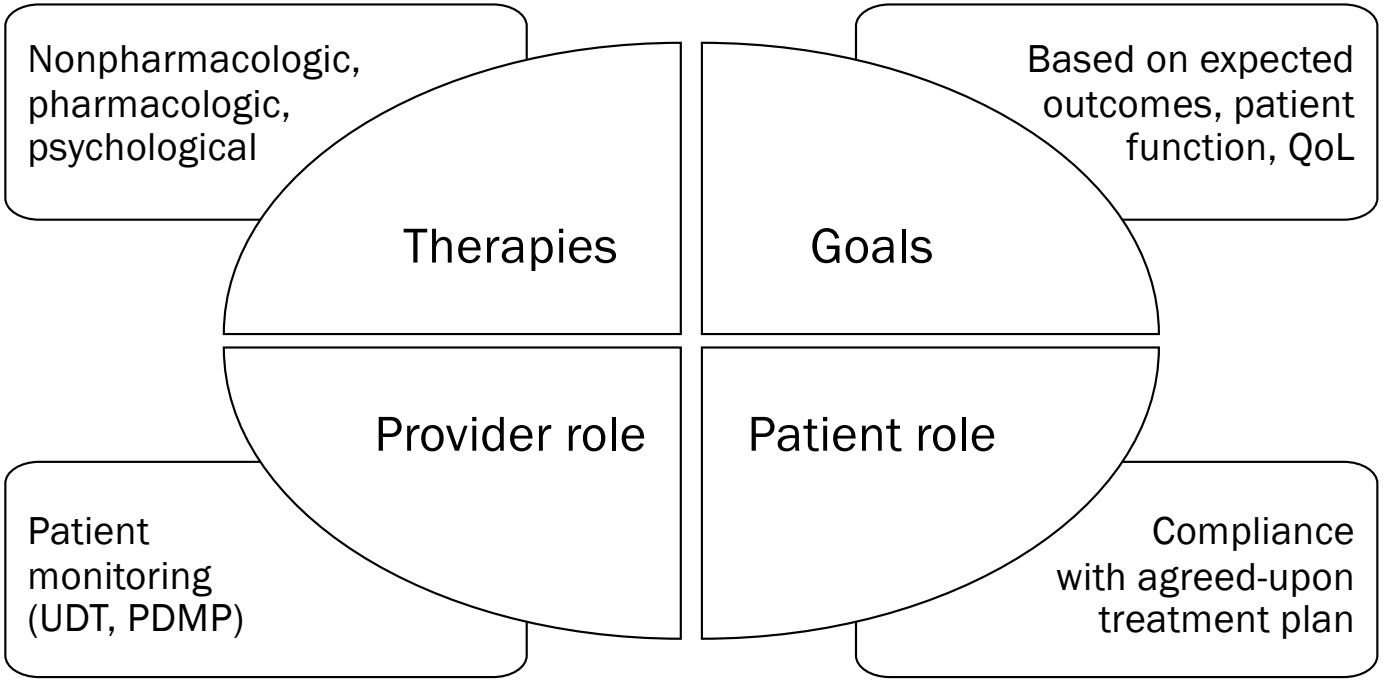
ORT domains

- Gender
- Marital status
- How many people live with you?
- Educational level
- Paid work
- Full- or part-time work
- Reason for non-employment
- Disabled with benefits
- Financial situation

ORT, Opioid Risk Tool.

Cheatle MD. *J Pain*. 2019;20(7):842-851.

A comprehensive, *documented* treatment plan should be developed to meet individual needs



Effective pain treatment requires a good patient–provider relationship

- Informed, involved patients are more likely to follow recommendations and undertake health-related behavior change
  - Understanding context of pain interference with ADLs
  - Mutual establishment and understanding of goals and expectations
  - Formulation of a tailored, meaningful treatment plan
  - Modification of plan based on reassessment and 2-way communication
  - Participatory decision making
  - Awareness of health care disparities and treatment barriers

Patients may assume physicians do not believe the severity of their pain or limitations in their function

Show empathy for the patient experience

Validate the belief that the pain is real

Zacharoff KL. www.painedu.org/patient-provider-relationship/.

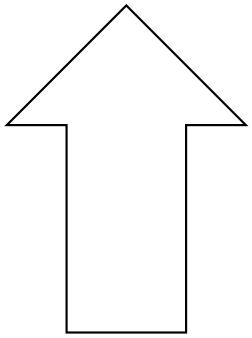
Overview of Pain Management Therapies

Bill H. McCarberg, MD, FABM

Kaiser Permanente San Diego (retired)
Adjunct Assistant Clinical Professor
University of California
San Diego, California

Nonpharmacologic interventions for pain have advantages and disadvantages

- Nonpharmacologic and nonopioid treatments are preferred as initial therapies
  - Exclusions: active cancer treatment, palliative/ end-of-life care[3]
- May be most useful as part of a multidisciplinary approach, particularly for musculoskeletal pain and chronic pain



Advantages

- Familiarity
- Ease of use
- Safety
- Accessibility
- Engagement

Disadvantages

- Limited evidence
- Few comparative studies
- Patient buy-in
- Patient commitment
- Insurance coverage

Tick H, et al. *Explore (NY).* 2018;14(3):177-211; US Department of Health and Human Services. www.hhs.gov/sites/default/files/pain-mgmt-best-practices-draft-final-report-05062019.pdf. Corp N, et al. *Eur J Pain*. 2021;25(2):275-295; Dowell D, et al. *JAMA*. 2016;315(15):1624-1645.

Several nonpharmacologic therapies should be considered for acute and chronic pain

Treatment category	Treatment options
Lifestyle	Exercise, weight loss, nutrition/diet, sleep hygiene
Physical rehabilitation	Thermal therapies, physical and occupational therapy, massage, yoga, tai chi, postural support
Mind–body	Cognitive–behavioral therapy, muscle relaxation, hypnosis, meditation, music/art therapy
Complementary and alternative medicine	Acupuncture/acupressure
Device- and procedure-based	Surgery, transcutaneous electrical nerve stimulation, laser therapy, electromyography, biofeedback

Pain Management Best Practices, Interagency Task Force Report, US Dept of Health and Human Services. May, 2019. https://www.hhs.gov/ash/advisory-committees/pain/reports/index.html.

Nonpharmacologic therapies have varying levels of evidence for efficacy in LBP treatment

- LBP is one of the most common reasons for visiting an HCP and causes of disability, and is associated with overprescribing of opioids
- Using data from 17 European clinical guidelines, nonpharmaceutical pain treatments were recommended based on strength of evidence

Intervention	Overall strength of recommendation
Manual therapy	Moderate FOR
Exercise therapy	Strong FOR
Psychological therapies, including behavioral and cognitive–behavioral	Strong FOR specific subgroups[a]
Psychological therapies + exercise	Moderate FOR
Work-based rehabilitation programs	Moderate FOR
Surgery	Strong FOR specific subgroups[b]
Thermotherapies	Mixed
Acupuncture	Mixed

[a]Mood problems; psychosocial risks; or complex, persistent pain problems. [b] Cases with signs of specific pathology.

Corp N, et al. *Eur J Pain*. 2021;25(2):275-295.

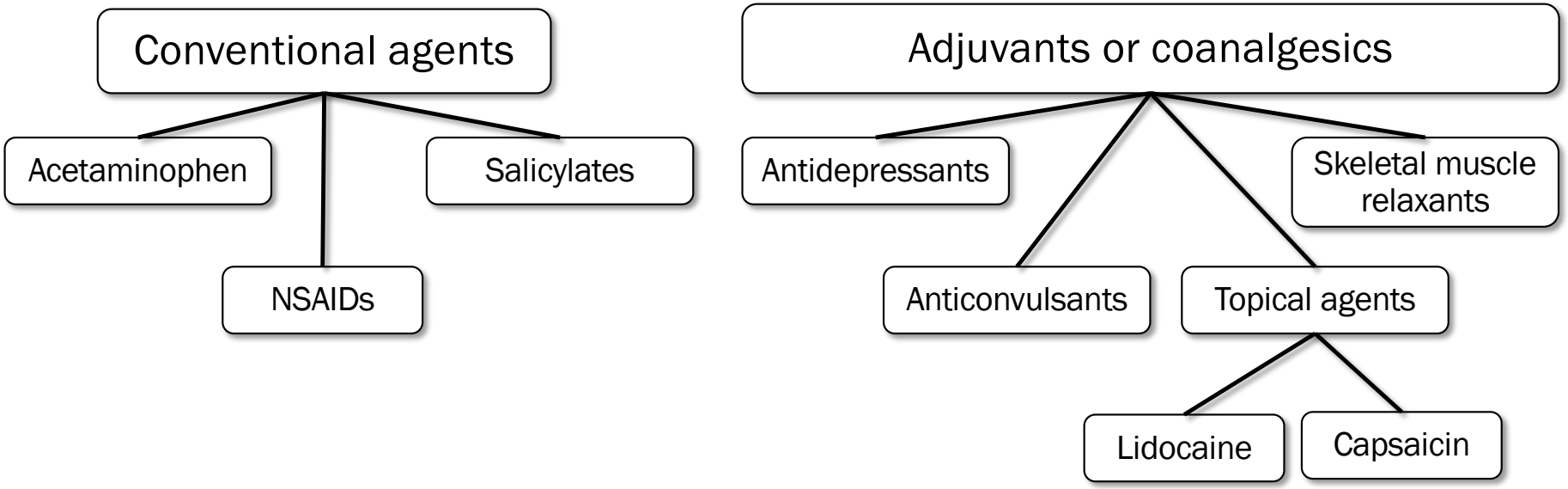
Acupuncture continues to gain momentum as a treatment for chronic pain

- Controversial due to origin outside Western biomedical science
- Growing body of evidence shows benefit in neck and shoulder pain, and pain and neuropathy in cancer survivors
- As of 2020, Medicare Part B covers acupuncture
  - LBP: ≤20 visits per year
  - Hospice/Palliative care?

- Recent evidence
  - Clinically relevant effect vs controls in a meta-analysis of 39 studies with ~21,000 patients[1]
  - Reduced chemotherapy-induced pain and neuropathy in 360 cancer survivors[2]

1. Vickers AJ, et al. *J Pain*. 2018;19(5):455-474. **2.** Mao JJ, et al. *JAMA Oncol*. 2021;7(5):720-727.

HCPs should be familiar with the range of available nonopioid analgesics



NSAID, nonsteroidal anti-inflammatory drug.

Finnerup NB. *N Engl J Med*. 2019;380(25):2440-2448. Munir MA, et al. *Med Clin N Am*. 2007;91(1):97-111.

Nonopioid agents have evidence for efficacy across several pain types

Nociceptive

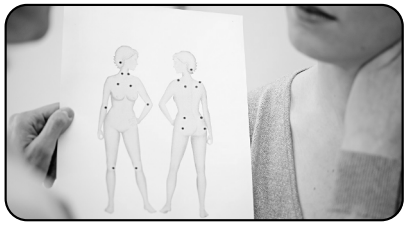
- Acetaminophen, NSAIDs, corticosteroids, muscle relaxants, anxiolytics, anticonvulsants, antidepressants[1]

Inflammatory

- NSAIDs (COX-1 and -2 inhibitors), corticosteroids for short-term use[1]

Neuropathic

- Nonpharmacologic treatments, then tricyclic and SNRI antidepressants, anticonvulsants[2]



Nociplastic

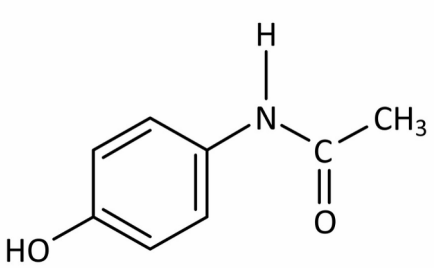
- Specific antidepressants, anticonvulsants, anxiolytics[3,4]

COX, cyclooxygenase; **SNRI,** serotonin-norepinephrine reuptake inhibitor.

1. Chou R, et al. *Ann Intern Med*. 2017;166(7):480-492. **2.** Szok D, et al. *Behav Neurol*. 2019:8685954.
3. Mills S, et al. *Curr Psychiatry Rep*. 2016;18(2):22. **4.** Sheng J, et al. *Neural Plast*. 2017;9724371.

Acetaminophen

- Available in PO, rectal, and IV formulations; IV primarily for in-hospital use
  - Usual adult PO dosage: 325-650 mg q4-6h or 1 g q6-8h
  - Maximum TDD, 4 g (3 g in elderly)



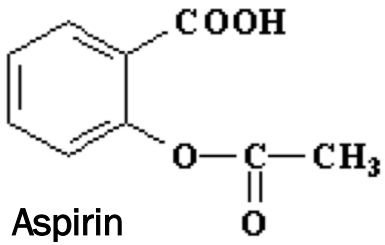
- FDA boxed warning: hepatotoxicity risk
  - Doses greater than maximum TDD should be avoided
  - Increased risk: elderly, hepatic disease, ≥3 alcoholic drinks per day: may need to limit TDD further
  - Avoid concurrent use of multiple acetaminophen-containing products
- Use during pregnancy: continue to weigh risks vs benefits
- Minimal drug interactions: warfarin may be of clinical significance

IV, intravenous; **PO,** oral; **TDD,** total daily dose.

US Food and Drug Administration. www.fda.gov/drugs/information-drug-class/acetaminophen-information; Facts & Comparisons. https://fco.factsandcomparisons.com/lco/action/home.

NSAIDs

- Routes of administration: PO, IV, IM
- Several chemical classes
- Usual adult dosage regimens vary
- Contraindications
  - History of asthma, urticaria, other allergic-type reactions
  - Perioperative period in patients undergoing CABG
- Boxed warning: CV and GI risks
- Other safety concerns: diabetes (note: ACEi/ARB), nephrotoxicity, hypertension, fluid retention and edema, anemia, numerous drug–drug interactions, bleeding

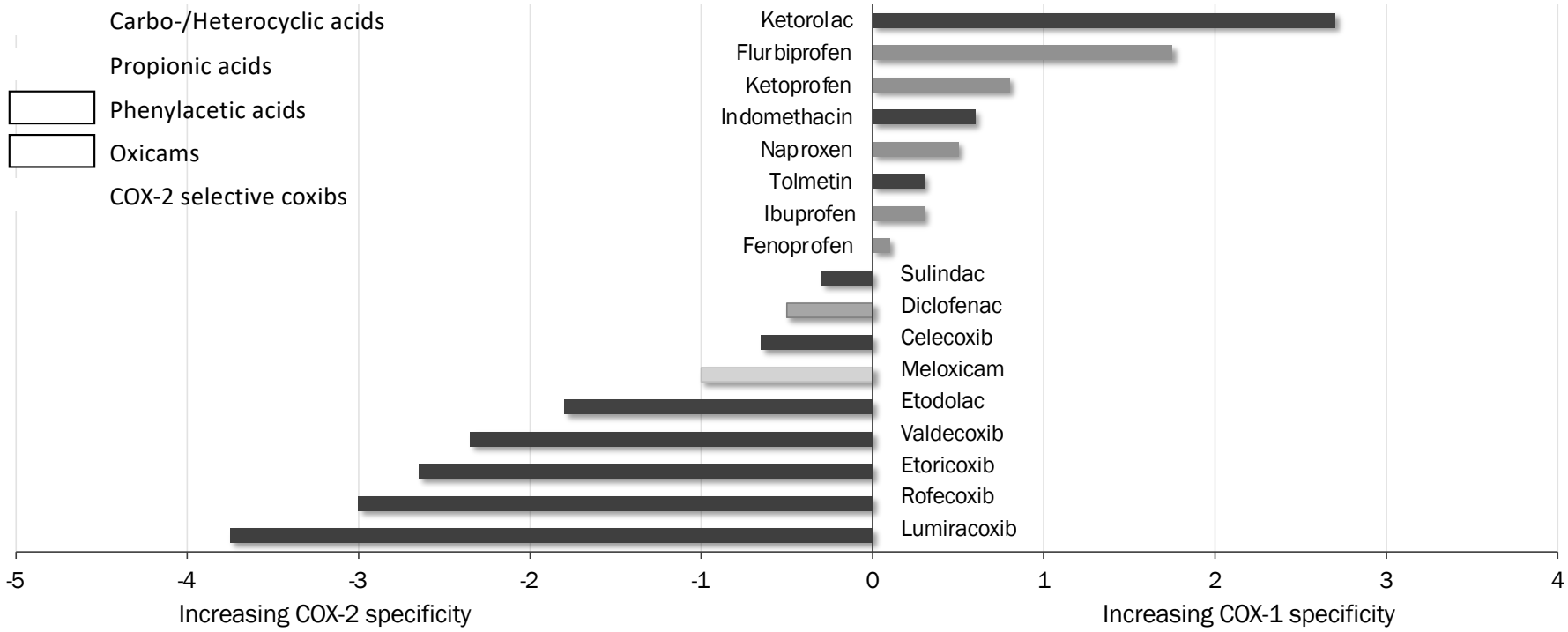


Aspirin

ACEi, angiotensin-converting enzyme inhibitor; **ARB,** angiotensin II receptor blocker; **CABG,** coronary artery bypass graft; **CV,** cardiovascular; **GI,** gastrointestinal; IM, intramuscular.

Facts & Comparisons https://fco.factsandcomparisons.com/lco/action/home; Tauben D. *Phys Med Rehabil Clin N Am*. 2015;26(2):219-248.

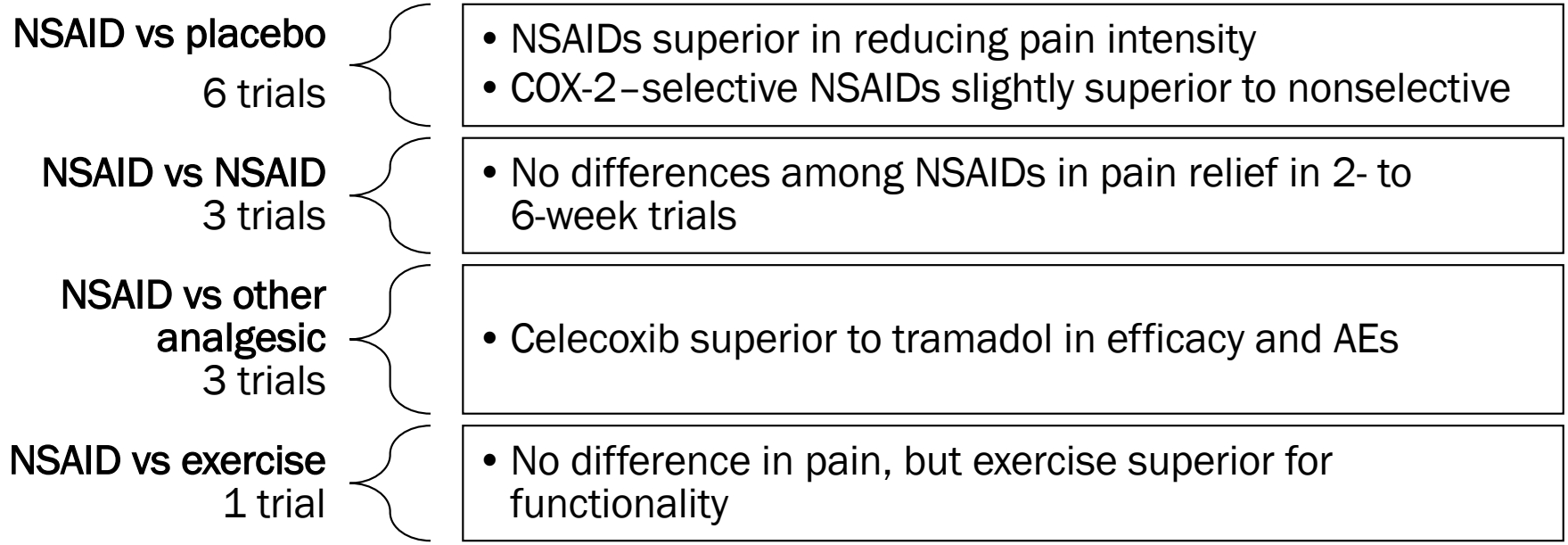
NSAIDs encompass numerous different agents



Adapted from http://paindr.com/wp-content/uploads/2015/12/Relative-Selectivity-of-NSAIDs-as-Inhibitors_edit.pdf.

NSAIDS > placebo in chronic LBP, but individual response varies greatly

Meta-analysis of 13 trials



AE, adverse event.

Enthoven WTM. *Cochrane Database Syst Rev*. 2016;2016(2):CD012087.

Adjuvant and coadjuvant agents can be useful

Class		Example	Pain type
Antidepressants	TCAs	Amitriptyline, nortriptyline, desipramine	Multipurpose
	SSRIs	Paroxetine, citalopram	
	SNRIs	Venlafaxine, duloxetine, milnacipran	
	Other	Bupropion	
Anticonvulsants		Gabapentin, pregabalin, carbamazepine, oxcarbazepine, lamotrigine, topiramate, tiagabine, levetiracetam, zonisamide, phenytoin, valproic acid	Multipurpose
Corticosteroids		Dexamethasone, prednisone	Multipurpose
α^2 adrenergic agonists		Clonidine, tizanidine	Multipurpose
NMDA receptor antagonists		Ketamine, dextromethorphan, memantine, amantadine	Neuropathic
GABA agonists		Baclofen	Musculoskeletal
Local anesthetics		Lidocaine, mexiletine	Neuropathic
Topical analgesics		Capsaicin, lidocaine, lidocaine/prilocaine (EMLA)	Neuropathic
Benzodiazepines		Diazepam, lorazepam, clonazepam	Musculoskeletal
Conotoxins		Ziconotide	Neuropathic
Muscle relaxants		Cyclobenzaprine, carisoprodol, methocarbamol, metaxalone, orphenadrine	Musculoskeletal
Bisphosphonates		Pamidronate, zoledronic acid, clodronate	Bone

EMLA, eutectic mixture of lidocaine; **GABA,** γ-aminobutyric acid; **NMDA,** N-methyl-*D*-aspartate; **SSRI,** selective serotonin reuptake inhibitor; **TCA,** tricyclic antidepressant.

Gupta N, Case AA. In: Smith HS, ed. *The art and science of palliative medicine*.
https://www.researchgate.net/publication/260284954_Adjuvant_Analgesics

Adjuvants are approved for pain but also carry risk

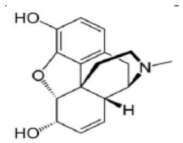
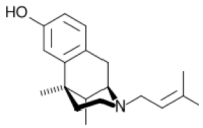
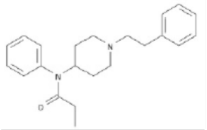
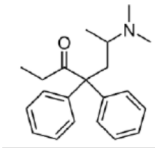
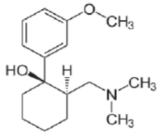
Analgesic	Indication
Duloxetine	Neuropathic pain associated with diabetic peripheral neuropathy; fibromyalgia
Milnacipran	Fibromyalgia
Gabapentin	Neuropathic pain associated with PHN
Pregabalin	Neuropathic pain associated with diabetic peripheral neuropathy and PHN; fibromyalgia
Carbamazepine	Neuropathic pain, trigeminal neuralgia, glossopharyngeal neuralgia
Bupivacaine liposome (inj. suspension)	Postoperative pain
Ropinirole	Pain associated with RLS
Pramipexole	Pain associated with RLS
Topiramate, divalproex	Migraine prophylaxis
Ziconotide	Severe chronic pain in patients intolerant or refractory to all other available treatment, including systemic analgesics, adjunctive therapies, intrathecal opiates

- Boxed warnings
  - TCAs and SNRIs: increased risk for suicidal thinking and behavior in children, adolescents, and young adults
  - Carbamazepine: serious skin reactions, aplastic anemia, agranulocytosis, HLA genotyping
  - Divalproex sodium/Valproate sodium: hepatotoxicity, fetal risk, pancreatitis
- FDA warning: risk for respiratory depression with gabapentin and pregabalin
  - Concomitant opioids
  - Other medications that depress respiration
  - Pulmonary disorders
  - Elderly; note Beers Criteria

HLA, human leukocyte antigen; **inj,** injectable; **PHN,** post-herpetic neuralgia; **RLS,** restless leg syndrome.

Gupta N, Case AA. In: Smith HS, ed. The Art and Science of Palliative Medicine. https://www.researchgate.net/publication/260284954_Adjuvant_Analgesics.

Opioids represent several chemical classes

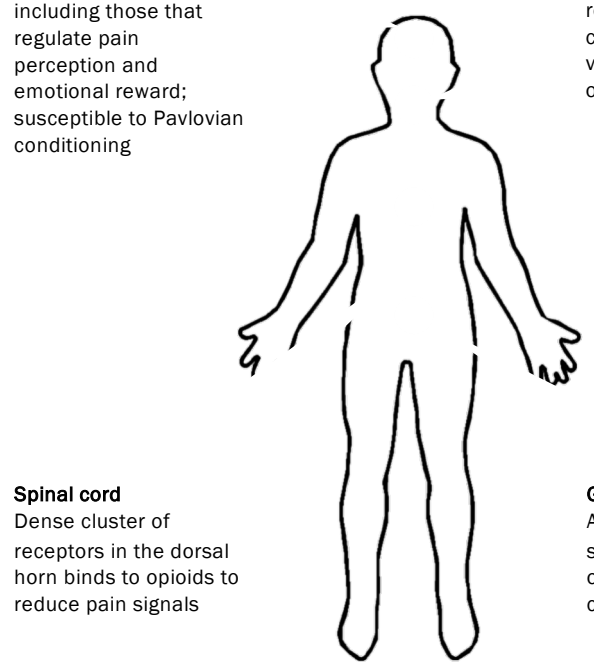
Phenanthrenes	Benzomorphans	Phenylpiperidines	Diphenylheptanes	Phenylpropyl amines
				
Morphine	Pentazocine	Fentanyl	Methadone	Tramadol
Buprenorphine,[a] butorphanol,[a] codeine, dextromethorphan,[a] dihydrocodeine, heroin, hydrocodone,[a] hydromorphone,[a] levorphanol,[a] methylnaltrexone,[b] morphine (opium), nalbuphine,[a] naloxone,[a] naloxegol,[a] naltrexone,[b] oxycodone,[a] oxymorphone[a]	Diphenoxylate	Alfentanil, fentanyl, meperidine, remifentanil, sufentanil	Methadone, propoxyphene	Tapentadol, tramadol
		Illicit fentanyl		
		Furanyl fentanyl, acetyl fentanyl, fluoro-fentanyl, carfentanil		
		Others		
		Pentazocine		
Cross-sensitivity risk				
Probable	Possible	Low risk	Low risk	Low risk

[a]Agents lacking the 6-OH group of morphine; possibly decreases cross-tolerability within the phenanthrene group.
[b]6-position is substituted with a ketone group; tolerability is similar to hydroxylation.

Fudin J. https://paindr.com/wp-content/uploads/2018/10/Opioid-Structural-Classes-Figure_-updated-2018Oct.pdf.

Opioid mechanisms produce analgesia and AEs

- Controlled substances that provide analgesia
- Several delivery modalities
  - Buccal, sublingual, spray, IV, IM, intrathecal, suppository, transdermal, lozenges
- MOA
  - Bind to mu receptors located in the brain, brainstem, spinal cord, and intestinal tract
  - Produces analgesia as well as AEs
  - Leads to release of dopamine
- Atypical opioids have additional MOAs
  - Tramadol, tapentadol
  - Buprenorphine (partial agonist)
- Use extreme caution with methadone



MOA, mechanism of action.

US Department of Health and Human Services. www.hhs.gov/sites/default/files/pmtf-final-report-2019-05-23.pdf; Stachnik JM. *Pract Pain Manag*. 2011;11(4).

Opioids can be classified as short- or long-acting

Short-acting opioids	Long-acting opioids
• Active in blood for 2-6 h • Use for initiation of opioid therapy • Indicated for moderate to severely moderate pain for which alternative treatments are inadequate	• Active in blood for 12-24 h • Some are safe only for opioid-tolerant patients: LA fentanyl, LA hydromorphone • Indicated for pain severe enough to require daily, ATC, long-term opioid treatment and for which alternative treatments are inadequate
○ Codeine ± acetaminophen ○ Hydrocodone ○ Hydromorphone ○ Morphine ○ Oxycodone ○ Oxycodone + acetaminophen ○ Tramadol ± acetaminophen ○ Tapentadol	○ Fentanyl transdermal patch ○ Hydrocodone ER ○ Hydromorphone ER ○ Morphine ○ Oxycodone CR ○ Methadone ○ Tramadol ER ○ Tapentadol ER

ATC, around-the-clock; **CR,** controlled-release.

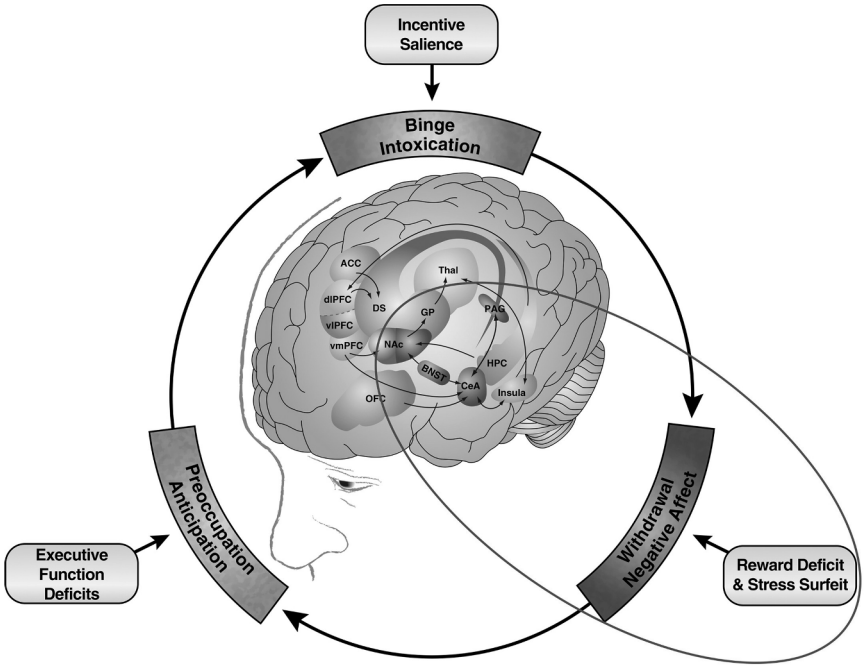
Opioids have many AEs and contraindications

Common AEs
• Nausea, vomiting • Constipation • CV effects • Sexual dysfunction, infertility • Rash/Pruritis

Contraindications
• Respiratory instability • Acute psychiatric instability • History of substance abuse • Life-limiting drug–drug interactions • Prolonged QTC interval (heart arrhythmia) • Active diversion of prescription opioids to street sales

Opioids and the development of addiction

- Even at prescribed doses, opioid analgesics carry risk for misuse, abuse, OUD, overdose, and death
- Clinical decision support tools should be used
  - PDMP
  - UDT
- Key concepts
  - *Tolerance:* diminished response over time
  - *Physiological dependence:* development of withdrawal when drug is discontinued
  - *Misuse:* taking more than prescribed for pain or giving to someone else in pain
  - *Abuse:* taking an opioid to get high
  - *OUD/Addiction:* unsuccessful reduction in use, even with functional decline



More on this in parts 2 and 3

Conclusion

Charles E. Argoff, MD
Professor of Neurology, Albany Medical College
Vice Chair, Department of Neurology
Director, Comprehensive Pain Center
Director, Pain Management Fellowship
Albany Medical Center
Albany, New York

Key takeaways

- Effective treatment for pain is an active, ongoing process requiring multiple skill sets and a good therapeutic relationship
- Poorly managed acute pain can transform into chronic pain
- Comprehensive assessment of patients in pain is multifactorial and includes identification of risk factors for opioid abuse and addiction
- Functional goals should be set, documented, and revisited

- Therapeutic options for managing pain are numerous and diverse
  - Nonpharmacologic approaches
  - Non-opioid analgesics
  - Adjuvants across a variety of classes
  - All treatments carry risk
- Opioid analgesics
  - MOA produces analgesia and AEs
  - Even at prescribed doses, these agents carry risk for misuse, abuse, OUD, overdose, and death

Coming in Part 2: All about opioids!

Saturday November 13, 2011 12 noon – 1:00 PM

- Formulations and routes of administration
- Abuse-deterrent products
- AEs, drug interactions, and warnings
- Key safety strategies
- Initiating treatment in acute and chronic pain
- Role in multi-modal analgesia
- Use in special populations

Q&A

Thank you