NEW DEVELOPMENTS IN PAIN MANAGEMENT

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Topic Overview

This course provides insights into new developments in pain management, focusing on the current nonpharmacologic and pharmacologic approaches for acute and chronic pain conditions. Current challenges of pain management include misuse and dependence on opioids and challenges with patients needing long-term treatments. A newly approved drug Seglentis could mitigate these challenges and provide an alternative option to the existing armamentarium of analgesics. Future directions in pain management strategies are provided.

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Target Audience: This educational activity is for pharmacists.

How to Earn Credit: From November 11, 2022, through November 11, 2025, participants must:

1. Read the "learning objectives" and "author and planning team disclosures;"
2. Study the section entitled "educational activity;" and
3. Complete the Course Test and Evaluation form. The Course Test will be graded automatically. Following successful completion of the Course Test with a score of 70% or higher, a statement of participation will be made available immediately. No partial credit will be given.

Learning Objectives: Upon completion of this educational activity, participants should be able to:

1. **Provide** an overview of pain types and characteristics
2. **Describe** pain modulation, assessment, and diagnosis
3. **Describe** pharmacological and non-pharmacological approaches to pain management
4. **Discuss** current challenges in pain management
5. **Discuss** the new co-crystal (celecoxib and tramadol hydrochloride) drug for use in acute pain management

Disclosures

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Introduction

Pain is a universally understood sign of disease or injury, but it may also be considered a medical condition in its own right. The complexity associated with understanding or assessing pain makes its treatment challenging to the healthcare clinician. These difficulties can be serious when pain treatment gives rise to other health problems, such as medication tolerance or misuse. A newly approved oral drug, Seglentis, may offer an alternative pain management approach that addresses some of the challenges clinicians face when treating a patient's pain. Future directions in pain management include new target-directed small-molecule analgesics, gene therapy, ligand-gated ion channels, anti-inflammatory cytokines, pain-modulating neurotransmitters, and image-guided delivery of locoregional pain syndromes.

Defining Pain

Chronic pain is a commonly seen medical problem, and it is the main reason people seek medical attention. Pain is the leading cause of distress, disability, and disease in individuals worldwide.[1] Although pain is often caused by injury or disease, it is also understood to be "a separate condition in its own right."[1]

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[2] There are different types of pain, and each type tends to have a different presentation.

Types of Pain

Traditionally there were two major categories of pain: nociceptive and neuropathic. A third category may also be described as psychogenic pain.[3,4] Another type of pain proposed by Kosek, *et al.* (2016), known as nociplastic pain, has also found support among medical professionals.[5]

- Nociceptive pain is the normal physiologic response a person feels from mechanical, thermal, or chemical stimuli or changes. The nociceptors detect these changes, which are felt by the person as pain.[2-4] Nociceptors are involved in the perception of pain, and their sensitization is a major cause of hyperalgesia. The perception of pain is primarily regulated by the central nervous system, which integrates afferent input from peripheral nociceptors, creating the perception of pain and further amplifying the input from peripheral nociceptors.[6] Nociceptive pain may be divided into three subtypes:[3,4]

    1. *Superficial somatic pain* is caused when peripheral nociceptors on the skin or superficial tissues are activated.
    2. *Deep somatic pain* is caused when somatic nociceptors within deeper tissue are activated. Somatic pain is typically localized, but it may be referred to as radiating pain.
    3. *Visceral pain* is caused when visceral nociceptors located in bodily organs are activated. Visceral pain is generally difficult to localize, as it may be referred to as radiating pain.

- Neuropathic pain occurs when there is direct damage to the nerves or abnormalities within the somatosensory pathways.[2-4] For example, herpes zoster can cause neuropathic pain. It is believed that inflammation sensitizes nociceptors in the infected skin, "causing spontaneous burning pain and tactile allodynia."[7] Neuropathic pain is often difficult to treat. Standard pain medications may not provide the necessary relief. In such cases, multiple therapies are used. These therapies include psychotherapy, physical therapy, pharmacotherapy with antidepressants, anticonvulsants, and surgery.[3,4]

- Nociplastic pain is characterized as a mechanistic descriptor for chronic pain states not caused by activation of nociceptors or neuropathy but associated with altered nociceptive function.[5,8,9] This type of pain seldom occurs in isolation and is usually accompanied by central nervous system symptoms, such as fatigue, sleep disturbance, cognitive impairment, hypersensitivity to external stimuli, and mood disturbances which are

also present in neuropathic pain.[10] Because of this overlap with other pain types, nociplastic pain is not considered a distinct entity but is part of chronic pain conditions. It is particularly applicable to pain associated with fibromyalgia.[10]

Acute and Chronic Pain

Depending on the duration, pain can be classified into two types: acute or chronic.

- *Acute pain* usually results from tissue injury, inflammation, a surgical procedure, childbirth, or a brief disease process. It is sharp in quality, having a limited duration, with symptoms lasting hours, days, or weeks.[11] Causes of acute pain include:

    - Surgery
    - Broken bones
    - Dental work
    - Burns or cuts
    - Labor and childbirth
    - Acute inflammation

- *Chronic pain* is persistent and ongoing and usually lasts longer than six months. It can be continuous or recurrent, and it can continue even after the injury or illness that caused it has healed. Pain signals remain active in the nervous system for weeks, months, or years. Some patients suffer chronic pain even when there is no past injury or apparent body damage. Chronic pain is linked to conditions that include the following:[12]

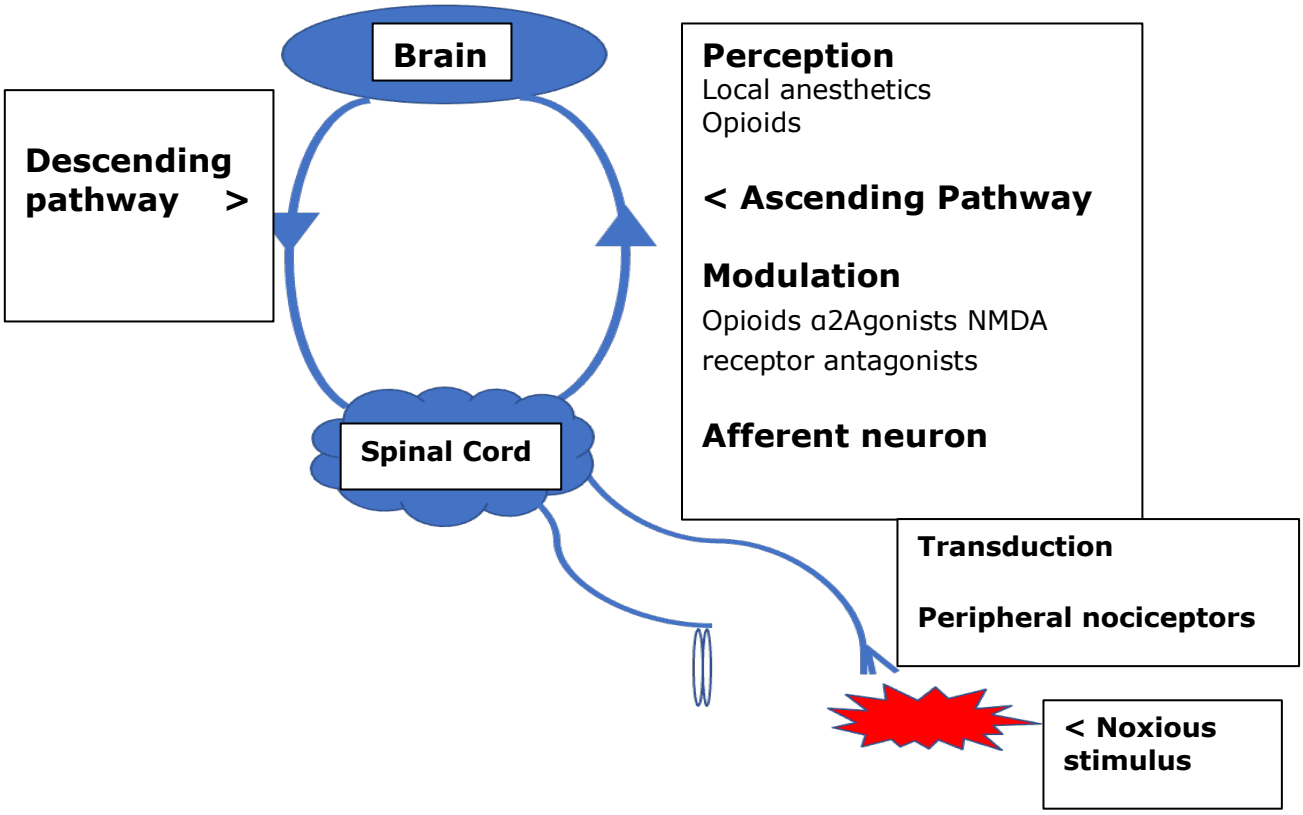
    - Arthritis
    - Cancer
    - Nerve pain
    - Back pain
    - Fibromyalgia

Estimates of prevalence rates for acute and chronic pain in adults from epidemiological studies vary from 9–36% for severe acute pain[13] and from 11-40% for chronic pain.[14]

Pain Modulation

Pain modulation describes the manner in which a person's body "alters a pain signal as it is transmitted along the pain pathway."[15] This partly explains why pain is often subjective since people can respond differently to similar painful stimuli. Pain modulation also helps explain why pain neurons and sensory responses are not always in sync.[15] Descending signals from the frontal cortex and hypothalamus help modulate the ascending transmission of the pain signal by opiate receptors.[15,16] An understanding of these mechanisms of action can guide clinical analgesia and pain management.[15]

Diagram of Pain Signaling Pathways



Pain Assessment

Pain assessment must be reliable and systematic in order for a clinician to classify and diagnose it correctly.[17] As mentioned above, pain is subjective, so a patient's self-report is the "gold standard" for measuring pain.[17] A treatment plan can be developed from the assessment and diagnosis.[18] Single-dimensional (rating pain intensity only) and multidimensional scales are put in place. Examples of single-dimensional scales include the IASP Faces Pain Rating Scale and the Numeric Rating Scale.[2] Multidimensional scales (*e.g.*, McGill Pain Questionnaire, Brief Pain Inventory) measure the pain intensity, the nature and location of the pain, and the impact the pain is having on activity.[17] Pain outcomes are assessed by clinical effectiveness (*e.g.*, reduction in pain, pain relief, pain intensity scores) and adverse outcome measures (*e.g.*, harms, misuse).

Pain Diagnosis

Diagnostic tests can identify the root cause of a patient's pain as well as provide important information for therapeutic planning. These may include:

- Blood tests
- Imaging scans (x-ray, CT, MRI, nuclear scans, ultrasound)
- Dye-injection studies such as a diskogram to identify painful disks in the spine or myelogram to identify areas of spinal nerve compression
- Electromyography and nerve conduction studies to identify nerve abnormalities
- Muscle diagnostic modalities

For example, minimally invasive imaging-guided techniques are used by clinicians to evaluate and treat pain, *e.g.*, lower back pain.[19] Image-guided techniques, such as computed tomography (CT)–guided imaging, provide greater ease and success than "blind injections."[19] Injection therapies are also performed using fluoroscopically. Ultrasound-guided pararadicular injections

have been compared to CT-controlled interventions.[19] This procedure was shown to be a safe, effective alternative for treating lower back pain.[19,20]

Managing Pain

Acute and chronic pain conditions could be managed with either pharmacological or non-pharmacological approaches. Non-pharmacological approaches may include physical therapies, spinal cord stimulation (SCS), and transcutaneous electrical nerve stimulation (TENS). Chronic, refractory pain may be managed better using a multidisciplinary approach, *i.e.*, a combination of the above approaches.

Pharmacological Pain Treatments

Pharmacological management of pain includes acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) (ibuprofen and aspirin), and opioids such as morphine, and codeine.[21] Recommended pharmacotherapies for acute low back pain also include NSAIDs with or without a skeletal muscle relaxant.[22] Pharmacological options include several drugs, such as:[22-27]

- Non-narcotic analgesics, such as NSAIDs (*e.g.*, aspirin, ibuprofen, naproxen, indomethacin, ketorolac, celecoxib), acetaminophen, and corticosteroids
- Narcotics such as opioids (*e.g.*, codeine, oxycodone, morphine, hydromorphone, methadone, meperidine, fentanyl, tramadol) and antidepressants (*e.g.*, tertiary-amine TCAs)
- Cannabinoids (*e.g.*, THC, CBD, CBC, THCV)
- Antiepileptic drugs (*e.g.*, gabapentin and pregabalin)
- Muscle relaxants (*e.g.*, carisoprodol, carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, orphenadrine, baclofen, ozobax, tizanidine)
- Topical analgesic drugs (*e.g.*, diclofenac Emulgel, ketoprofen gel, piroxicam gel, diclofenac Flector plaster, Lidocane)
- Calcitonin and bisphosphonates for various cases of bone pain and as a second-line treatment for some neuropathic conditions

- Adjuvant drugs, such as tricyclic antidepressants, anticonvulsants, and other agents, alter neural membrane potentials, ion channels, cell surface receptor sites, synaptic neurotransmitter levels, and neuronal processes involved in pain signal processing

Chronic pain may require long-acting medications or other interventional modalities.[26] For mild to moderate pain, non-narcotic analgesics are used, whereas for moderate to severe pain, narcotic regimens are typically used.[27]

Non-pharmacologic Pain Treatments

Non-pharmacologic options are effective for the treatment of acute pain conditions.

Physical Therapies

Short-term pain relief may be found using a number of physical therapies, and superficial heat, massage therapy, acupuncture, and spinal manipulation may provide relief. Physical therapies used to treat pain also include cold packs, hydrotherapy, exercise, and laser treatments.

Psychological Therapies

Well-known psychological therapies include cognitive behavioral therapy, relaxation techniques, and meditation. Acupuncture blends psychological and physical therapies by combining mind and body techniques.

Spinal cord stimulation (SCS)

Spinal cord stimulation (SCS) is approved by the US Food and Drug Administration to relieve intractable pain.[28] Indications include failed back surgery syndrome, chronic painful peripheral neuropathy, complex regional pain syndromes, and intractable low back pain.[29,30] Spinal cord stimulation may also be considered for postherpetic neuralgia.[30] Experimental evidence

supports a beneficial SCS effect at the dorsal horn level, whereby the hyperexcitability of wide-dynamic-range neurons is suppressed.[29,31-33] Evidence also exists for increased levels of GABA, serotonin, substance P, and acetylcholine.[30]

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation is an adjuvant pain control device that is used to alleviate acute pain. It provides pulsatile low-voltage electric impulses[31,33] that reduce pain by presynaptic signal inhibition, endogenous pain control, direct inhibition of abnormally excited nerves, and restoration of afferent inputs.[32,33] Transcutaneous electrical nerve stimulation has been used for low back, arthritic, sympathetically mediated, neurogenic, visceral, and postoperative pain.[34,35]

Multidisciplinary Approach to Pain Management

Chronic, refractory pain is best managed with a multidisciplinary approach that includes psychology, occupational therapy, physical therapy, osteopathic manipulative treatment, vocational rehabilitation, and relaxation training. Patients with chronic pain frequently seek complementary and alternative medicine treatment options, including acupuncture, dietary supplements, and hypnosis. Opioids and cannabinoids are widely used for the management of pain related to cancer.[33] Combination regimens that contain opioids and nonnarcotic analgesics provide additive pain control; that is, combination regimens that contain opioids and nonnarcotic analgesics are beneficial and provide multimodal regimen for pain management. Adjuvant medications include tricyclic antidepressants, antihistamines, and anticholinergics.[32]

Challenges of Pain Management

Current challenges of pain management involve the failure of systemic analgesic drugs, such as opioids which is often due to their off-target toxicity, development of tolerance, misuse, and addiction potential.[21] Long-term care

challenges are associated with depression, anxiety, and other physical stresses that require nonpharmacologic and pharmacologic pain management approaches and guidelines.

A newly approved oral drug, Seglentis, could provide an additional option for managing pain. It may help mitigate some of the challenges mentioned above by providing an alternative multimodal approach for acute pain for which other treatments are inadequate.[36] Seglentis was approved by the U.S. Food and Drug Administration on October 15, 2021.[36] Seglentis' uniqueness lies in its formulation. It is a combination of an anti-inflammatory analgesic Celebrex and the opioid tramadol hydrochloride.[36,37]

Misuse and Dependence on Opioids

Opioids are a class of drugs that includes prescription pain medicines and illegal drugs such as heroin. Though opioids can be prescribed to treat pain, their misuse may lead to a dependency or addiction (that is known in medicine as an "opioid use disorder"). Opioid use disorder is a medical condition defined by not being able to abstain from using opioids, and opioid use behaviors that interfere with daily life. Being physically dependent on an opioid can occur when someone has an opioid use disorder and is characterized by withdrawal symptoms such as cravings and sweating. However, people can misuse opioids and not have physical dependence. When a person has physical dependence, it can be particularly hard to stop taking opioids, and that dependence can interfere with daily routines, including personal relationships or finances.

Common signs of opioid addiction:[38]

- The inability to control opioid use
- Uncontrollable cravings
- Drowsiness
- Changes in sleep habits
- Weight loss
- Frequent flu-like symptoms

- Decreased libido
- Lack of hygiene
- Changes in exercise habits
- Isolation and withdrawal

Available treatments for opioid use disorders include medications such as:[38]

- Methadone
- Buprenorphine
- Naltrexone
- Naltrexone paired with support programs

Challenges of Pain Management in Long-Term Care

Untreated pain can impact long-term care (LTC) patients physically, mentally, and socially in many ways, including by interfering with their activities of daily living, sleep, and mobility. Pain can also lead to depression, anxiety, and other physical stresses.[39] Persistent pain is known to be common among patients residing in LTC facilities. It is most frequently associated with musculoskeletal disorders, such as degenerative spine conditions and arthritis.[40,41] It continues to go unrecognized and undertreated despite pain guidelines, such as those put forth by the American Medical Directors Association (AMDA), and the American Geriatrics Society (AGS).[42,43] These guidelines offer a wider range of pain assessment and management strategies, including non-pharmacologic pain management approaches, pharmacologic guidelines, as well as consideration of cognitively impaired patients.

Among the many barriers to effective pain management in LTC facilities are high staff turnover; government regulatory issues; lack of formal pain education for staff, including limited physician involvement; and cognitive impairment seen in many nursing home residents.[44,45]

Seglentis

Seglentis is a recently approved analgesic combination of Celecoxib and Tramadol. The formulation is a co-crystal tablet containing 1:1 molecular ratio of Celecoxib (56 mg) and Tramadol hydrochloride (44 mg) that provides a new treatment option for acute pain management in adults when other pain medicines have failed.[36,37]

Celecoxib is an NSAID that selectively inhibits cyclooxygenase-2 enzyme responsible for the formation of prostaglandin, prostacyclin, and thromboxane resulting in inflammation and pain.[46] Tramadol is an opioid that produces centrally mediated analgesia. It mimics endogenous opioid peptide and mediates its effect by binding to μ-opioid receptors and inhibiting the reuptake of norepinephrine and serotonin.[47-49]

Seglentis offers a new treatment option for acute pain aligned with the multimodal analgesia approach currently considered the standard of care.[50] Its novel co-crystal structure produces a unique pharmacokinetic profile of its active pharmaceutical ingredients (APIs) compared to their individual or combined administration.[51] Due to weak intermolecular interactions between two APIs within the crystalline structure, it has the potential for improved physicochemical properties compared with either constituent drug. The advantage may be apparent as enhanced solubility and dissolution characteristics, which in turn may improve pharmacokinetics and pharmacodynamics. This ultimately leads to a bimodal clinical benefit.[50,51]

Seglentis is used to relieve acute pain, which is usually severe enough to require an opioid drug for treatment. Opioids such as tramadol can be used successfully as a component of pain management; however, they carry risks of dependence and misuse. Misuse can lead to respiratory depression, overdose, and death. Seglentis may address some of these challenges. By using a combination of two drugs with different modes of action and non-overlapping toxicities, Seglentis provides additive pain relief superior to either drug alone. As a result, its therapeutic dose is less than the recommended dose of each drug component given individually. The lower dosage level of the

opioid in this combination drug may help reduce the side effects associated with a high-dose opioid given as a stand-alone therapy.[52]

Future Trends

Treatment for chronic, locoregional pain ranks among the most prevalent, unmet medical needs. Currently, available analgesic drugs exert their effect through very few categories of molecular targets.[53,54] Recent advances in the neurobiology of nociception identified a variety of candidate therapeutic targets located in the peripheral nervous system that are not targeted by current analgesic drugs. Important examples include ion channels expressed by primary sensory neurons,[55] proinflammatory cytokines that play a critical role in the pathogenesis of neuropathic pain,[56] and inhibitory and excitatory neurotransmitters that modulate nociceptive signaling.[57]

Regional analgesia with therapeutic injections can provide excellent relief for patients with localized pain and inflammation. Depending on the clinical scenario, nerve blocks may be used for therapeutic, sympathetic, diagnostic, prognostic, or prophylactic purposes and provide new directions for pain management.[58] Transdermal patches provide controlled drug delivery with a lower potential for misuse that is present with oral analgesics,[59] as well as a lower risk of adverse effects and reduction in dosing frequency.[60]

Interventional pain procedures provide target specificity but lack pharmacologically selective agents with long-term efficacy. Gene therapy with vectors and gene editing are new tools for the development of molecularly selective pain therapies.[61,62] Advances in image-guided delivery and gene therapy may lead to a new class of dual-selective analgesic treatments integrating the molecular selectivity of analgesic genes with the anatomic selectivity of interventional delivery techniques.

Summary

Management strategies for acute and chronic pain include non-pharmacologic and pharmacological approaches. Non-pharmacologic options

are best suited for acute pain conditions and produce short-term relief. Chronic pain is best managed with multidisciplinary pharmacological and non-pharmacologic long-lasting treatment options. Challenges of pain management include dependence on opioid analgesics with their potential side effects, such as the development of tolerance, misuse, addiction, and abuse potential. Challenges of pain management in LTC are associated with persistent pain and its inadequate treatment with several adverse outcomes. New development in pain management resulted in a recent approval of a multimodal analgesic Seglentis that could mitigate these challenges. Future directions in pain management may involve gene therapy, gene editing, anti-inflammatory cytokines, and selective interventional delivery techniques as new tools for molecularly selective pain therapies.

Course Test

1. Pain modulation describes the manner in which a person's body

a. muscles relax.
b. generates a psychogenic response to a pain stimulus.
c. suppression of the hyperexcitability of neurons.
d. alters a pain signal as it is transmitted along the pain pathway.

2. What are key pain management strategies?

a. Pain medicines
b. Physical therapies
c. Psychological therapies
d. All of the above

3. Which of the following is not an opioid?

a. Morphine
b. Tramadol
c. Celecoxib
d. Fentanyl

4. Which of the following is an NSAID?

a. THC
b. Tramadol
c. Ibuprofen
d. Cyclobenzaprine

5. Which of the following is a common sign of opioid addiction?

a. Isolation and withdrawal
b. Weight gain
c. An overly outgoing personality
d. The person is too optimistic

6. What is the available treatment for opioid addiction?

a. Fentanyl
b. Seglentis
c. *Naltrexone
d. Tramadol

7. Persistent pain is known to be common among patients residing in long-term care facilities and is most frequently associated with

a. cancer pain.
b. musculoskeletal disorders.
c. psychogenic pain.
d. post-operative pain.

8. Seglentis is an approved drug that contains a combination of

a. tramadol and acetaminophen.
b. tramadol and celecoxib.
c. tramadol and naltroxene.
d. tramadol and ibuprophen.

9. What are the potential advantages of Seglentis?

a. May alleviate adverse effects associated with opioid use
b. Provides additive pain relief
c. The co-crystal structure provides a unique pharmacokinetic profile
d. All of the above

10. Future trends in injectables might include

a. gene therapy and gene editing.
b. pain-modulating neurotransmitters.
c. anti-inflammatory cytokines.
d. All of the above

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