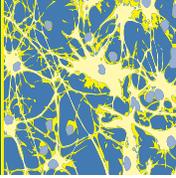


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Target Audience

Primary care clinicians, neurologists, anesthesiologists, physical medicine and rehabilitation specialists, nurses, and other healthcare professionals who treat patients suffering from common chronic pain conditions

Statement of Need

Chronic pain is a major public health problem in the United States, affecting at least 70 to 75 million Americans each year, with approximately 1 adult in 5 suffering from chronic pain. Some of the most common chronic pain conditions include daily headache, low back pain, osteoarthritis, cancer pain, postherpetic neuralgia (PHN), and diabetic neuropathy. Osteoarthritis affects approximately 20 million Americans, an estimated 5 million Americans suffer from low back pain, 40 million Americans are believed to suffer from chronic headaches, and up to 200,000 Americans are affected by PHN.

Back pain is the most common type of pain for which patients seek medical attention; it is the second most common cause of office visits and the third most common reason for hospital admissions. Other chronic pain conditions, such as diabetic neuropathy and cancer pain, also have a significant impact. Patients with chronic pain often experience decreased physical and psychosocial function, depression, loss of sleep, and, overall, diminished quality of life.

Chronic pain has a considerable economic impact stemming from increased healthcare costs, low productivity, and increased absenteeism. More than \$4 billion is spent each year on medications for the treatment of chronic pain. Chronic back pain alone accounts for nearly 3 times as many lost workdays and 3 times as much disability as other disease states and, in 1 year, accounts for an estimated \$16 billion in lost productivity, workers' compensation, and associated healthcare costs.

Poor pain assessment and diagnostic challenges are also significant barriers to appropriate treatment. Since pain is subjective, the best measure of its existence and severity is patient self-report, and there are many types of pain assessment scales available for clinicians to use. However, it is important not only to assess pain but also to evaluate the

impact of pain on the patient's quality of life and ability to function. Measures of functional status can be used to evaluate the effectiveness of pain management. Additionally, the diagnosis and classification of various chronic pain conditions can be challenging to the clinician. For example, the differential diagnosis of headache is complicated by the many presentations and types of headache. In addition, race, ethnicity, and cultural background may affect how patients perceive pain and need to be considered in patient assessment.

For some of the chronic pain conditions, guidelines exist. However, utilization of these guidelines in clinical practice is inconsistent. There are several evidence-based guidelines for the treatment of various chronic pain conditions, including neuropathic pain, osteoarthritis, and cancer pain. In an effort to improve patient care, clinicians should become familiar with these recommendations and apply them in their practice.

Educational Objectives

After participating in this program, participants should be able to:

- Summarize the epidemiology and public health impact of common chronic pain conditions, as well as current clinical practice guidelines and evidence regarding evaluation and treatment of patients with chronic pain
- Discuss the impact of ethnicity, gender, and age on the pathophysiology, assessment, drug metabolism, and management of various chronic pain conditions
- Explain the mechanisms of chronic pain
- Describe clinically useful methods to assess pain (eg, numeric rating scales, multidimensional assessment tools), barriers to pain assessment, and the use of assessment data to select pain management strategies and to evaluate patient outcomes
- Outline a stepwise approach for effective pain management based on the mechanisms of action, routes of analgesic administration, and comparative risks and benefits of commonly used therapies
- Describe recent advances in the management of chronic pain
- Differentiate between addiction, pseudoaddiction, physical dependence,

and tolerance and understand the clinical implications of each

- Outline best practices for the use of opioid analgesics with respect to patient selection, responsible prescribing, titration/rotation, adjunctive therapy, regulatory scrutiny, and risk/benefit evaluation
- Assess the efficacy of chronic pain treatment modalities in relation to their overall potential for adverse events
- Discuss the need to balance safety, tolerability, and efficacy when managing chronic pain in older patients
- Discuss the challenges surrounding pain management in the primary care setting, the impact of managed care, and the importance of patient education to improve outcomes

Breakthroughs and Challenges in the Management of Common Chronic Pain Conditions, as published in this CME slide kit, is based, in part, on the proceedings of a scientific roundtable held in Washington, DC.

CME Certification

AMA Category 1 Credit

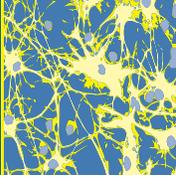
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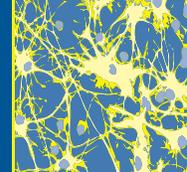
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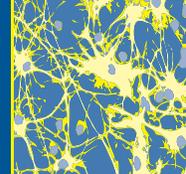
Generic Name	Approved Use (if any)	Off-Label/Investigational Use
Amantadine	<ul style="list-style-type: none"> • Infection due to influenza A virus • Parkinson's disease • Drug-induced extrapyramidal symptoms 	<ul style="list-style-type: none"> • Neuropathic pain
Amitriptyline	<ul style="list-style-type: none"> • Antidepressant 	<ul style="list-style-type: none"> • Back pain
Botulinum toxin	<ul style="list-style-type: none"> • Temporary improvement in appearance of glabellar lines associated with corrugator and/or procerus muscle activity in adults ≤65 years of age 	<ul style="list-style-type: none"> • Chronic low back pain • Migraine and tension headache
Bupivacaine	<ul style="list-style-type: none"> • Local anesthesia, nerve block 	<ul style="list-style-type: none"> • Neuropathic pain
Cannabinoid receptor agonist	<ul style="list-style-type: none"> • Not applicable 	<ul style="list-style-type: none"> • Cancer, neuropathic, and postoperative pain
Carbamazepine	<ul style="list-style-type: none"> • Seizure disorders • Trigeminal neuralgia • Pain in neck and throat 	<ul style="list-style-type: none"> • Postherpetic neuralgia • Painful diabetic neuropathy • Migraine prophylaxis • Central pain after stroke • Mono- and polyneuropathies
Conotoxin	<ul style="list-style-type: none"> • Experimental 	<ul style="list-style-type: none"> • Spontaneous pain • Hyperalgesia
Desipramine	<ul style="list-style-type: none"> • Antidepressant 	<ul style="list-style-type: none"> • Back pain
Fentanyl transdermal patch	<ul style="list-style-type: none"> • Persistent moderate to severe chronic pain 	<ul style="list-style-type: none"> • Low back pain
Fluoxetine	<ul style="list-style-type: none"> • Antidepressant 	<ul style="list-style-type: none"> • Low back pain
Gabapentin	<ul style="list-style-type: none"> • Management of postherpetic neuralgia in adults • Treatment of partial seizures 	<ul style="list-style-type: none"> • Low back pain • Neuropathic pain • Painful HIV-related neuropathy • Painful diabetic neuropathy • Pain related to multiple sclerosis • Disk herniation • Deafferentation neuropathy of the face • Sciatic-like pain in both legs
Hyaluronic acid	<ul style="list-style-type: none"> • Pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and to simple analgesics (eg, acetaminophen) 	<ul style="list-style-type: none"> • Intra-articular injection for osteoarthritis pain in joints other than the knee
Lamotrigine	<ul style="list-style-type: none"> • Epilepsy • Bipolar disorder 	<ul style="list-style-type: none"> • Painful neuropathy with HIV/AIDS
Levetiracetam	<ul style="list-style-type: none"> • Epileptic seizures in patients ≥4 years of age 	<ul style="list-style-type: none"> • Neuropathic pain conditions
Lidocaine	<ul style="list-style-type: none"> • Local or regional anesthesia • Postherpetic neuralgia 	<ul style="list-style-type: none"> • Low back pain add-on therapy • Neuropathic pain • Musculoskeletal pain • Osteoarthritis
Memantine	<ul style="list-style-type: none"> • Moderate to severe dementia of the Alzheimer's type 	<ul style="list-style-type: none"> • Neuropathic pain syndromes

HIV=human immunodeficiency virus; AIDS=acquired immune deficiency syndrome.

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Generic Name	Approved Use (if any)	Off-Label/Investigational Use
Mexiletine	<ul style="list-style-type: none"> • Ventricular arrhythmias 	<ul style="list-style-type: none"> • Osteoarthritis
Nerve growth factor	<ul style="list-style-type: none"> • Experimental 	<ul style="list-style-type: none"> • Neuropathic pain
Oxcarbazepine	<ul style="list-style-type: none"> • Partial seizures 	<ul style="list-style-type: none"> • Neuropathic pain
Pamidronate	<ul style="list-style-type: none"> • Hypercalcemia of malignancy • Paget's disease • Osteolytic bone metastases of breast cancer • Osteolytic lesions of multiple myeloma 	<ul style="list-style-type: none"> • Osteoporosis
Paroxetine	<ul style="list-style-type: none"> • Antidepressant 	<ul style="list-style-type: none"> • Low back pain
Tramadol	<ul style="list-style-type: none"> • Moderate to moderately severe pain • Painful diabetic neuropathy • Painful polyneuropathy • Osteoarthritis 	<ul style="list-style-type: none"> • Low back pain
Triptans: Frovatriptan Naratriptan Sumatriptan Zolmitriptan	<ul style="list-style-type: none"> • Acute migraine 	<ul style="list-style-type: none"> • Migraine prophylaxis
Ziconotide	<ul style="list-style-type: none"> • Severe chronic pain that does not respond to other analgesics 	<ul style="list-style-type: none"> • Chronic low back pain • Cancer, neuropathic, and postoperative pain

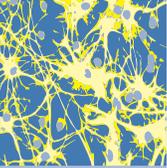


Slide 1



**Breakthroughs
and Challenges in
the Management of
Common Chronic
Pain Conditions**

Slide 1



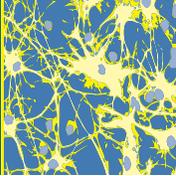
**A World of Pain:
The Undertreatment
of Chronic Pain**

Slide 2



“We all must die. But if I can save him from days of torture, that is what I feel is my great and ever new privilege. Pain is a more terrible lord of mankind than even death himself.”

Albert Schweitzer



Slide 3

Scope of the Problem

- One third of Americans experience severe chronic pain

Americans with severe chronic pain

- It is the most common cause of long-term disability

Brookoff D. Hosp Pract. 2000;35:45-52,59.

- Severe chronic pain partially or totally disables as many as 50 million Americans during their lifetimes¹
- Despite this, chronic pain is often not viewed as a physical condition that warrants treatment¹

Slide 4

Prevalence of Pain Associated With Medical Conditions

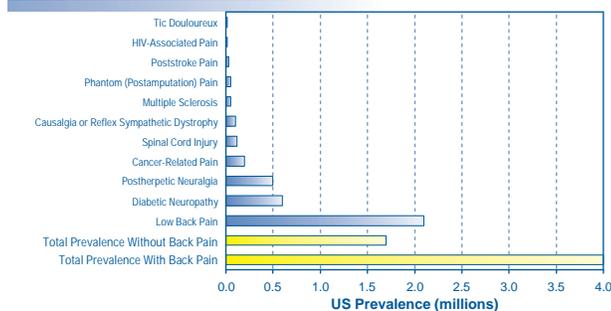
	HRS (1996) ¹ Age 54-64 y N=6837	AHEAD (1993) ² Age ≥70 y N=5807
Overall prevalence (%)	27	33
Condition (%)		
Lung disease	50	44
Stroke	44	41
Heart disease	41	41
Arthritis	40	60
Diabetes	39	39
Cancer	35	34
Hypertension	33	37

HRS=Health and Retirement Study; AHEAD=Asset and Health Dynamics Study Among the Oldest Old.
1. Data from HRS. Analyses courtesy of C. Reyes-Gibby, MD, Houston, Texas, 2005. 2. Reyes-Gibby CC et al. Pain. 2002;95:75-82.

- Prevalence of pain in the United States is significant
- Results from the Health and Retirement Study showed that in patients 54 to 64 years of age²:
 - 27% of people reported having pain often
 - 40% had pain from arthritis
 - 35% had pain associated with cancer
 - 39% had pain associated with diabetes
- In patients aged ≥70 years, the Asset and Health Dynamics Study Among the Oldest Old reported³:
 - 33% of patients reported having pain often
 - 60% of patients had pain from arthritis
- Data show that, as people age, they report having more pain
 - Especially with certain medical conditions, such as arthritis
 - Pain prevalence compared to that with other chronic medical conditions, such as cancer and diabetes, is comparable³

Slide 5

Estimated Prevalence of Neuropathic Pain

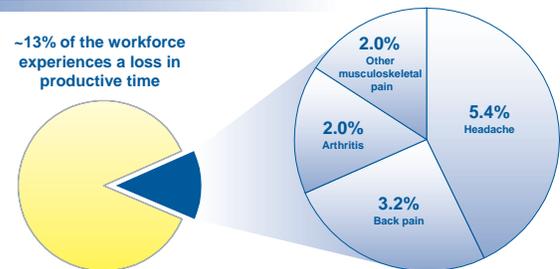


N=270 million; HIV=human immunodeficiency virus.
Adapted with permission from Bennett GJ. *Hosp Pract.* 1998;33:95-114.

- The estimated prevalence of neuropathic pain, based on the US population of approximately 270 million, depends on individual estimates for a wide range of etiologies⁴
- An American Pain Society (APS) survey of 805 adults experiencing non-cancer-related pain found that 56% of those with chronic, moderate to severe pain have been suffering for more than 5 years⁵
- Back pain is the most common cause of limited activity in adults <45 years of age⁶
 - Second most frequent reason for physician visits⁶
 - Fifth-ranking cause of admission to the hospital⁶
 - Third most common cause of surgical procedures⁶
 - Annual US prevalence rate ranges from 15% to 45%⁶
 - If only 1 in 10 cases of back pain has a neuropathic component, the prevalence of neuropathic pain more than doubles to more than 4 million⁴
- Whereas back pain is the leading cause of neuropathic pain, following in order of prevalence are⁴:
 - Diabetic neuropathy (~600,000)
 - Postherpetic neuralgia (~500,000)
 - Cancer-related pain (~250,000)
- Moderate to severe pain in ~50% of cancer patients is partly or completely neuropathic in origin⁴

Slide 6

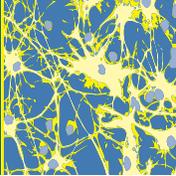
US Survey: Pain and Productivity



Most lost productivity is from reduced performance (77%), not absence

N=28,902.
Stewart WF et al. *JAMA.* 2003;290:2443-2454.

- In a random sample of 28,902 working adults in the United States⁷:
 - Approximately 13% lost productive time because of common pain conditions (arthritis, back pain, headache, other musculoskeletal pain)
- The lost productive time was⁷:
 - Expressed in hours per worker per week (mean, 4.6 h/wk)
 - Calculated in US dollars (\$1.2 billion/wk)
- Lost productive time during a 2-week period due to pain was⁷:
 - Headache, 5.4%
 - Back pain, 3.2%
 - Arthritis, 2.0%
 - Other musculoskeletal pain, 2.0%
- Most of the lost productive time (77%) was due to reduced performance at work and not to absence



Slide 7

Impact of the Undertreatment of Pain

- **Economic impact**
 - \$61.2 billion/y lost productivity¹
- **Quality of life**
 - Persistent pain reduces quality of life^{2,3}
 - Pain is associated with psychologic disorders (eg, depression, anxiety)^{3,4}
- **Health outcomes**
 - Pain is a predictor of poor health and depression⁵
- **Families with ≥1 migraineur have⁶**
 - 70% higher total unadjusted medical costs
 - 80% higher outpatient costs

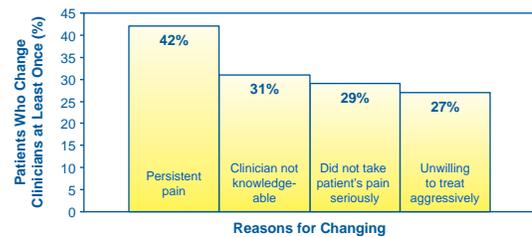
1. Stewart WF et al. *JAMA*. 2003;290:2443-2454. 2. Skevington SM. *Pain*. 1998;76:395-406. 3. Elliott TE et al. *Pain Med*. 2003;4:331-339. 4. McWilliams LA et al. *Pain*. 2004;111:77-83. 5. Reyes-Gibby CC et al. *Pain*. 2002;95:75-82. 6. Stang PE et al. *Am J Manag Care*. 2004;10:313-320.

- Undertreatment of pain affects productivity, quality of life, and other health outcomes, including mental health
- Effective treatment of chronic pain is important to economic, social, psychologic, and emotional domains
- Pain results in lost US workforce productivity costing \$61.2 billion per year⁷
 - This figure represents just 27% of the total estimated work-related cost of pain⁷
- Pain has a significant negative impact on perceptions of quality of life ($P < .001$)⁸
- Persistent pain affects psychologic health as well as quality of life⁹
 - A study of 242 patients with chronic noncancer pain (SF-36 Health Survey) found correlations between chronic pain, depression, and quality of life
 - All patients with chronic pain had low quality-of-life scores
 - The type of depression was highly correlated with quality-of-life scores ($r = -.567$; $P < .001$)
 - The prevalence of major depressive disorder was 52%
- A recent study found that the associations between pain conditions and anxiety disorders were even larger than those between the pain conditions and depression¹⁰
- Pain is a predictor of poor health. A study of community-dwelling older adults reported that those who often have pain were more than twice as likely (odds ratio [OR]=2.63; confidence interval=2.35, 2.95; $P < .001$) to perceive their health status as poor³
- Migraine families (≥1 migraineur) incur higher direct and indirect medical costs than do nonmigraine families¹¹

Slide 8

APS Survey: Reason for Changing Providers

- 94% with moderate to severe chronic pain seek medical care
- 47% change clinicians at least once



APS=American Pain Society.

APS. Chronic pain in America: roadblocks to relief. Available at: http://www.ampainsoc.org/whatsnew/summary2_road.htm. Accessed March 9, 2006.

- A survey conducted by the American Pain Society found that 94% of people with moderate to severe chronic pain sought medical care for pain relief⁵
- Patients changed clinicians at least once because (patients were able to choose more than 1 reason)⁵:
 - They had persistent pain (42%)
 - Clinician was not knowledgeable about pain management (31%)
 - Clinician did not take the patient's pain seriously (29%)
 - Clinician was unwilling to provide aggressive treatment (27%)

Slide 9

Disparities in Pain Management

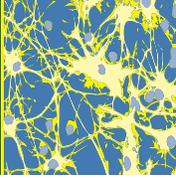
Age	<ul style="list-style-type: none"> Older nursing home patients received appropriate pain assessment only 3.9% of the time¹ 26% of older patients with daily pain did not receive any analgesic agents²
Ethnicity	<ul style="list-style-type: none"> Emergency department study <ul style="list-style-type: none"> Black patients: 57% received analgesics³ White patients: 74% received analgesics³ Hispanic patients: half as likely to receive analgesics as non-Hispanic white patients⁴
Gender	<ul style="list-style-type: none"> Women received less medication for cancer pain than men⁵ Women received more sedatives than men (men received pain medication instead)⁶

1. Baier RR et al. *J Am Geriatr Soc.* 2004;52:1988-1995. 2. Bernabei R et al. *JAMA.* 1998;279:1877-1882. 3. Todd KH et al. *Ann Emerg Med.* 2000;35:11-16. 4. Todd KH et al. *JAMA.* 1993;269:1537-1539. 5. Cleeland CS et al. *N Engl J Med.* 1994;330:592-596. 6. Unruh AM. *Pain.* 1996;65:123-167.

- Based on results from several studies, there are significant disparities in pain management with regard to gender, ethnicity, and age
 - Women receive less pain medication than do men, overall (OR=1.5), and less medication for pain resulting from cancer¹²
 - Women in pain clinics were more likely to receive sedatives, whereas men were more likely to receive pain medication.¹³ Black patients presenting to an emergency department received analgesics 57% of the time, compared with 74% for white patients¹⁴
 - Hispanic patients were twice as likely not to receive analgesics as non-Hispanic white patients in emergency room settings¹⁵
 - 26% of older patients with daily pain received no analgesics¹⁶
 - Less than 4% of older nursing home patients were appropriately assessed for pain¹⁷

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Slide 1

Understanding Pain Mechanisms

Slide 2

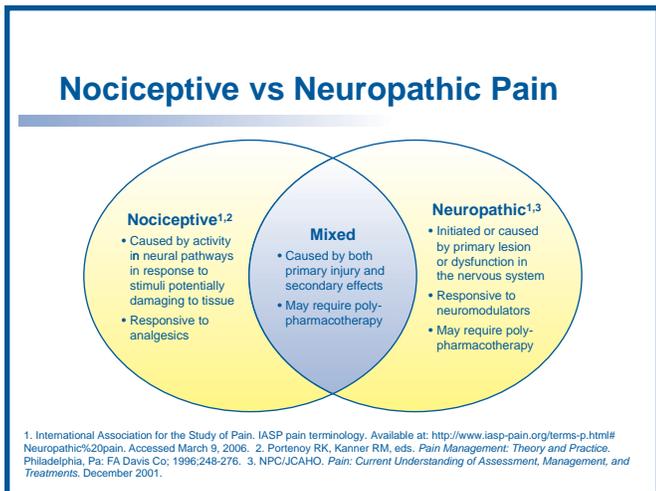
Differences Between Acute and Chronic Pain

Acute (Nociceptive) Pain	Chronic Pain
<ul style="list-style-type: none">• Has biologic function¹• Acts as warning system indicating tissue injury¹• Recent onset²• Finite duration (days to weeks)²• Remits when underlying pathology resolves¹	<ul style="list-style-type: none">• No biologic value¹⁻³• Detrimental effects¹⁻³• Persists beyond usual course of acute illness or injury (months to years)¹⁻³• Chronic pathologic process; can recur at intervals¹⁻³

1. Brookoff D. *Hosp Pract*. 2000;35:45-52:59. 2. Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Co; 1996:248-276. 3. Turk DC, Meizack R, eds. *Handbook of Pain Assessment*, 2nd ed. New York: The Guilford Press; 2001:3-11.

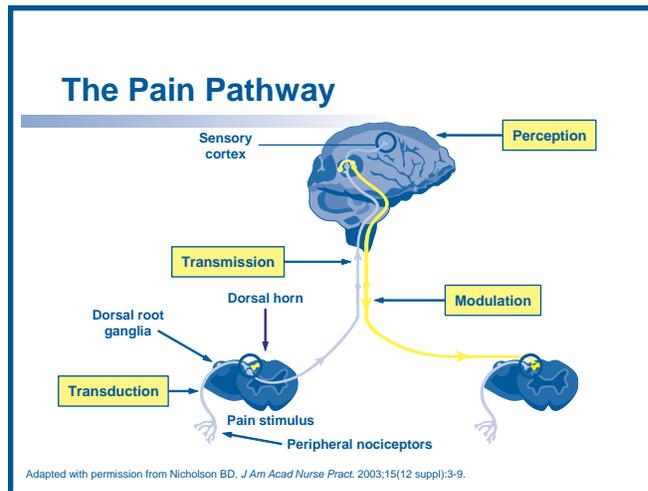
- Pain can be acute or chronic
- *Acute pain* has a biologic function, alerting us to tissue injury¹
- Ability to sense pain keeps us alive and functioning¹
 - Acute pain from tissue injury is expected to end in days to weeks following injury²
 - Remits when the underlying pathology heals¹
- *Chronic pain* has little or no biologic value, is detrimental for the patient, and/or is associated with a chronic pathologic process¹⁻³
 - Chronic pain persists or recurs¹⁻³
 - Acute recurrent (may recur at intervals for months to years [eg, migraine headaches, sickle cell anemia])
 - Chronic progressive (eg, cancer, chronic obstructive pulmonary disease)
 - Chronic nonprogressive or slowly progressive (eg, neuropathic pain such as postherpetic neuralgia or polyneuropathy, osteoarthritis)
 - Laboratory induced
 - Chronic pain is not just a prolonged version of acute pain¹
 - Neural pathways undergo physiochemical changes that make them hypersensitive to pain signals and resistant to antinociceptive input
 - Signals can become embedded in the spinal cord

Slide 3

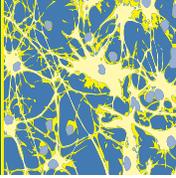


- Pain may be classified as nociceptive, neuropathic, or mixed
- Nociceptive pain results from activity in neural pathways caused by stimuli that are potentially damaging to tissue^{2,4}
 - Examples include postoperative pain, mechanical low back pain, sickle cell crisis, and sports or exercise injuries
 - Also included are chronic pain such as arthritis and some types of cancer pain
- Neuropathic pain is caused by a primary lesion or dysfunction in the peripheral and/or central nervous systems^{2,5,6}
 - Examples of peripheral neuropathic pain include:
 - Human immunodeficiency virus-related sensory neuropathy
 - Postherpetic neuralgia
 - Painful diabetic neuropathy
 - Stump pain
 - Examples of central neuropathic pain include:
 - Central poststroke pain
 - Spinal cord injury pain
 - Trigeminal neuralgia
 - Multiple sclerosis pain
 - Phantom limb pain
- Mixed pain occurs when components of continued nociceptive pain coexist with a component of neuropathic pain
 - Migraine headaches may represent a mixture of neuropathic and nociceptive pain
 - Also included are myofascial pain and low back pain

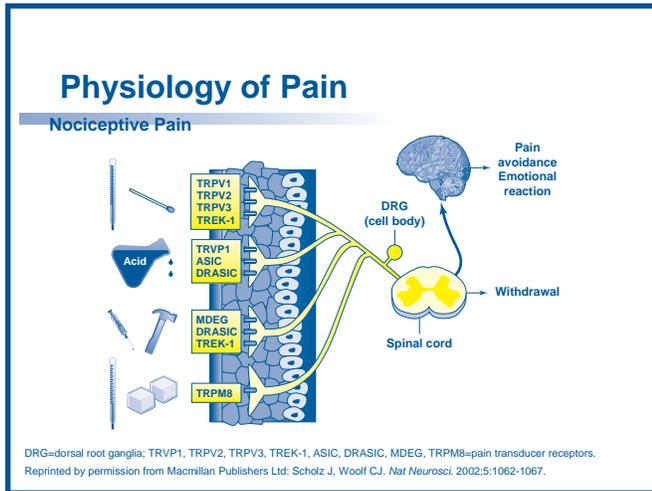
Slide 4



- Nociceptors are the peripheral endings of primary sensory neurons and are particularly reactive to noxious stimuli. Following acute trauma, nociceptors convert the energy from the stimulus into nerve impulses (transduction). These impulses travel along small myelinated A δ and unmyelinated C nerve fibers to the dorsal horn of the spinal cord and then to the thalamus and cerebral cortex (transmission), where the pain is perceived⁷⁻⁹
- At each point in the pathway, the signal may be modulated by intrinsic neurons or by descending input from higher centers; descending input from the brain influences nociceptive transmission at the spinal cord level (modulation), eventually causing protective muscle spasms¹⁻³

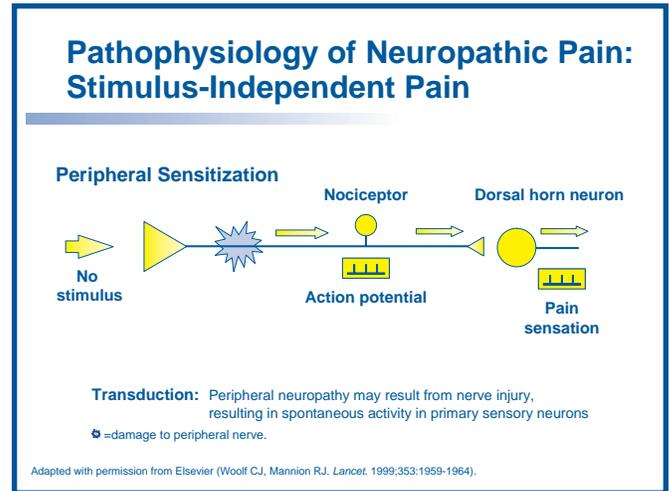


Slide 5



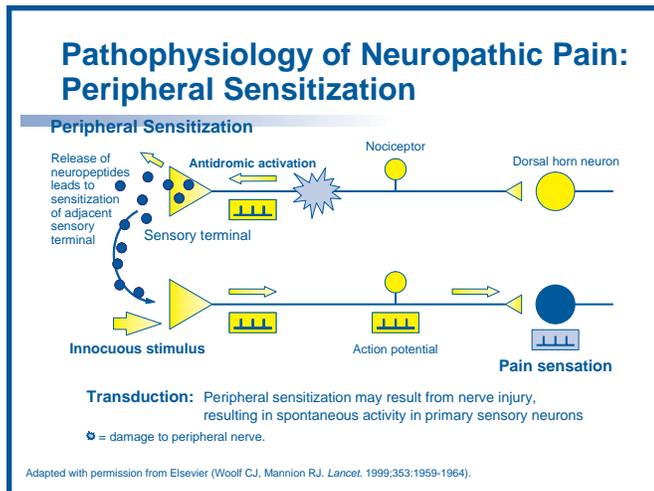
- Noxious stimulus is transduced by a nociceptor into electrical impulses that are transmitted to the spinal cord and then to the central nervous system¹⁰
- Pain is sensed¹⁰

Slide 6



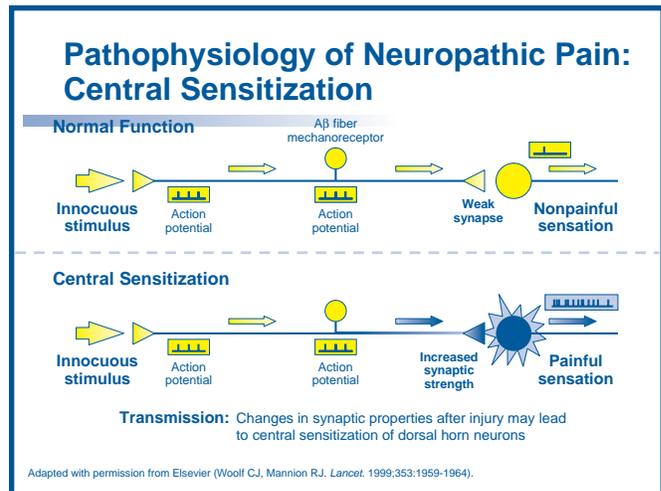
- Damage to a peripheral nerve, illustrated by the starburst, can cause hyperexcitability in the nerve¹¹
 - Nerve injury may cause accumulation of both tetrodotoxin (TTX)-sensitive and TTX-insensitive sodium channels at the neuroma site, at the tips of injured axons, along the length of the axon, and at the dorsal nerve root ganglia
 - The accumulated channels produce foci of hyperexcitability and initiation of ectopic action potentials in the axon and cell body of injured neurons
 - This process may result in stimulus-independent pain

Slide 7

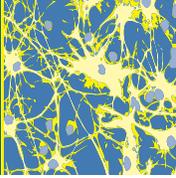


- Increased sensitization of peripheral nociceptors to external mechanical and thermal stimuli contributes to neuropathic pain by initiating an exaggerated response to these stimuli¹¹
- The figure illustrates how damage to a peripheral nerve (the starburst) can cause algescic substances to be released from the peripheral nerve terminal via antidromic nerve impulses¹¹
 - The algescic substances may induce action potentials in the surrounding, intact neurons
- Injured C-fiber nociceptors can develop new adrenergic receptors and sensitivity that contribute to sympathetically maintained pain¹²
- Nerve injury may also mediate deafferentation of Schwann cells, causing loss of the axon-insulation and myelin-production capabilities of these cells¹¹
- Other causes of peripheral sensitization are ephaptic (nonsynaptic) communication between neurons¹
 - Sprouting of new terminal branches on the large myelinated nerves (A fibers) that normally carry the sense of touch
- New terminal branches communicate with pain-sensing cells in the superficial layers of the dorsal horn rather than with touch-sensing cells located deeper in the spinal cord¹
- The result is that nonnoxious stimuli are perceived as painful (allodynia)¹¹

Slide 8



- The upper portion of the slide illustrates normal function of an Aβ nerve fiber and its dorsal horn connection¹¹
 - An innocuous brush-evoked stimulus activates the fiber's mechanoreceptor
 - The stimulus is not adequate to activate the dorsal horn pain pathway across a weak synapse, so sensation is perceived as nonpainful
- The lower portion illustrates central sensitization by increased nociceptor drive of the dorsal horn neuron (represented by the starburst)¹¹
 - A stimulus that is normally too weak to reach firing threshold becomes an irritating stimulus
 - The Aβ fiber input is now sufficient to activate spinal cord pain pathways
- Central sensitization can manifest as¹¹:
 - Enlargement of the area in the periphery where a stimulus activates neurons
 - An exaggerated response to a stimulus that meets the activation threshold
 - A stimulus that is too weak to satisfy the activation threshold, which becomes an irritating stimulus
- Disinhibition of dorsal horn neurons, resulting from peripheral nerve injury, may increase the likelihood that a dorsal horn neuron will fire spontaneously or in an exaggerated way in response to primary afferent input¹¹
- Brush-evoked allodynia can occur from central disinhibition, A-fiber sprouting in the spinal cord, or A-fiber phenotypic switching after peripheral nerve injury¹¹



Slide 9

Understanding Causes and Symptoms of Neuropathic Pain Can Aid in Selecting Therapy

Mechanism	Symptoms	Therapeutic Target/Agents
Transduction Changes in Na channel accumulation, redistribution, expression	Spontaneous pain, paresthesia	Na channels/local anesthetics (lidocaine, bupivacaine); antiepileptics, antiarrhythmics
Transduction Peripheral sensitization	Pressure or thermal hyperalgesia, spontaneous pain, neurogenic inflammation	Vallinoid R-1-desensitization, neurokinin 1, NGF, TTXR-Na channels/capsaicin, local anesthetics, NGF
Transmission Central sensitization	Tactile or cold hyperalgesia, pinprick hyperalgesia, allodynia	NMDA-R, neurokinin 1-R, neuronal nitric oxide synthase, protein kinase-γ/ketamine, dextromethorphan, amantidine, NMDA antagonists
Modulation Reduced inhibition	Spontaneous pain, hyperalgesia	N-type Ca-channel receptors/conotoxin, opiates, gabapentin

NGF=nerve growth factor; TTXR=tetrodotoxin resistant; NMDA=N-methyl-D-aspartate; R=receptor.
Adapted with permission from Elsevier (Woolf CJ, Mannion RJ. *Lancet*. 1999;353:1959-1964).

- A symptom-based analysis of neuropathic pain is important for assessment of disease progression
- Knowledge of symptoms must be supplemented with an understanding of the pathologic processes responsible for the pain
- Accurate diagnosis of pain mechanisms will aid in developing treatment strategies, but only if the mechanisms can be targeted with specific therapies

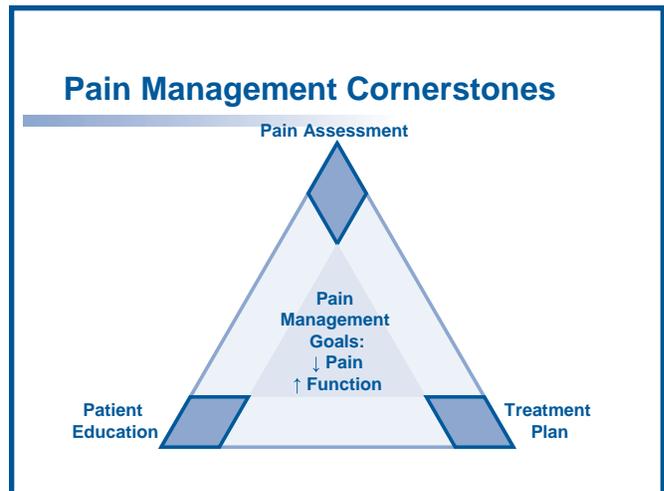
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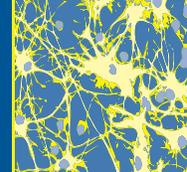
Slide 1



Slide 2



- The formulation of a successful pain management plan can be conceptualized as a pain-oriented problem list
- Assessment yields detailed information about the nature of the pain and its relationship to other organic and psychologic disturbances that contribute to the disability or suffering
- A multimodal treatment plan can be developed from the information received during the assessment, which will help prioritize the patient's concerns
- Patient education is critical to establishing realistic goals and managing patient expectations
 - Patient education can help redefine the patient's agenda so that it conforms to the opportunities presented by treatment



Slide 3

Assessment Challenges

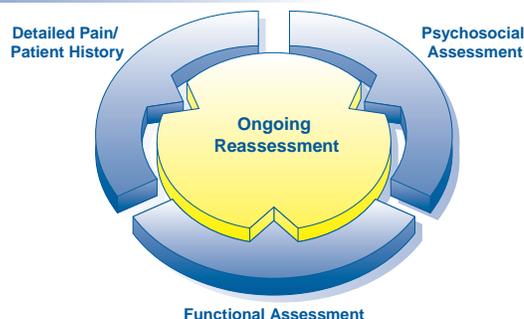
Pain is subjective ^{1,2}	<ul style="list-style-type: none"> • No satisfactory objective measures^{1,2} • Gold standard for pain assessment <ul style="list-style-type: none"> – Patient's self-report²
Pain is multidimensional	<ul style="list-style-type: none"> • Clinician must consider multiple aspects of the pain experience <ul style="list-style-type: none"> – Sensory, affective, cognitive^{3,4} – Chronic or acute – Quality of pain (eg, shooting, throbbing)
Special populations require different approaches ⁵	<ul style="list-style-type: none"> • Infants and children,⁶ elderly patients,⁷ and language and cultural factors present communication challenges⁷

1. APS. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 5th ed. Glenview, Ill: American Pain Society; 2003. 2. McCaffery M, Pasero C, eds. Pain: Clinical Manual. 2nd ed. St. Louis, Mo: Mosby, Inc; 1999:36-102. 3. NPC/ICAHO. Pain: Current Understanding of Assessment, Management, and Treatments. December 2001. 4. Galer BS et al. Clin J Pain. 2002;18:297-301. 5. Ramelet A-S et al. Aust Crit Care. 2004;17:33-45. 6. Craig KD et al. Clin Perinatol. 2002;29:445-457. 7. Davis MP, Srivastava M. Drugs Aging. 2003;20:23-57.

- Although appropriate assessment of pain is necessary for adequate treatment of pain, pain assessment is challenging
- Pain is subjective^{1,2}; therefore, each patient's experience of pain is different
 - There are no satisfactory objective measures of pain^{1,2}
 - The gold standard for assessing the existence and intensity of pain is the patient's self-report^{1,2}
- The experience of pain is multidimensional
 - It includes sensory, affective, and cognitive components^{3,4}; the clinician should consider each aspect carefully
- Different patient populations may require different approaches to pain assessment
 - For a pain measure to be useful clinically, it must be adapted to the developmental age of the target population⁵
 - Infants have limited behavioral repertoires, which makes identification of specific needs difficult^{5,6}
 - Older patients may have cognitive impairments that interfere with their ability to adequately express their pain⁷
 - Language or cultural factors may make communication difficult⁷

Slide 4

Components of a Comprehensive Pain Assessment



- The importance of a comprehensive pain assessment cannot be overstated³
- It is reasonable to expect that the most effective treatment of pain can be accomplished only when the patient's pain has been completely and accurately assessed
- There are 3 components to a comprehensive pain assessment
 - A detailed history of the pain and the patient's medical history
 - A functional assessment that addresses such issues as limits to range of motion and activities of daily living³
 - A psychosocial assessment that addresses the patient's mood, level of emotional success, and psychologic state
- Ongoing reassessments are necessary to monitor the results of pain therapy and intervention

Slide 5

Pain Assessment Tools

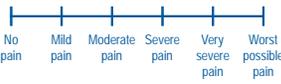
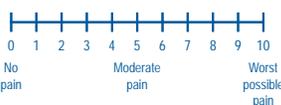
 <p>Unidimensional scales¹</p>	<ul style="list-style-type: none"> • Numeric Rating Scale • Verbal Rating Scale • Visual Analog Scale • Faces Pain Rating Scale
 <p>Multidimensional scales</p>	<ul style="list-style-type: none"> • Brief Pain Inventory¹ • McGill Pain Questionnaire¹ • Neuropathic Pain Scale²

1. Brunton S. *J Fam Pract.* 2004;53(suppl 10):S3-S10. 2. Galer BS et al. *Clin J Pain.* 2002;18:297-301.

- There are a variety of pain assessment tools available, including unidimensional and multidimensional scales⁸
- Unidimensional scales measure the severity or intensity of pain⁸
- Multidimensional scales assess several aspects of the patient's pain experience⁸
 - The Brief Pain Inventory measures the sensory dimension (pain intensity) and reactive dimension (interference with function)⁹
 - The McGill Pain Questionnaire provides information about the sensory and affective dimensions of pain¹⁰
 - The patient assigns a level of pain intensity (0 for no pain to 5 for excruciating pain) to 20 groups of descriptive words
 - The patient also identifies the temporal aspects of his or her pain (brief to constant)
- The Neuropathic Pain Scale is designed to assess distinct qualities associated with neuropathic pain¹¹

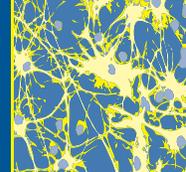
Slide 6

Unidimensional Pain Assessment Scales

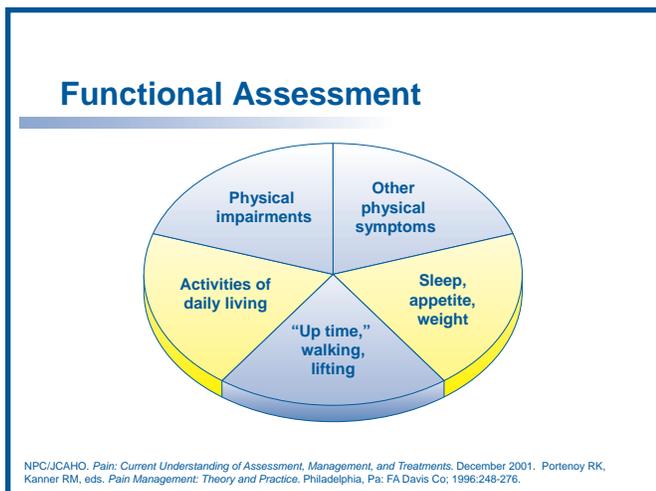
<p>Verbal Pain Intensity Scale</p> 	<p>Visual Analog Scale</p> 
<p>0-10 Numerical Rating Scale</p> 	<p>Faces Rating Scale</p> 

Adapted from McCaffery M, Pasero C, eds. *Pain: Clinical Manual*, 2nd ed. St. Louis, Mo: Mosby, Inc; 1999:36-102 with permission from Elsevier.

- Accurate assessment of pain intensity is the most important aspect of effective treatment
- Differences between the clinician's pain ratings and those of the patient can lead to inadequate pain management^{12,13}
- Because pain is subjective, assessment tools have been devised to more objectively evaluate pain and to compare patient's pain levels at different time points²
- The Verbal Pain Intensity Scale is used to describe the intensity of pain according to 6 specified degrees
- The Visual Analog Scale (VAS) is a 10-centimeter line along which patients mark the point that best indicates their pain intensity²
 - The distance from the "no pain" point to the patient's line, measured in millimeters, is the VAS score²
- On the Numerical Rating Scale, patients rate their pain from 0 (no pain) to 10 (worst possible pain)²
 - This scale can be administered in person or over the phone to facilitate follow-up
- The Faces Rating Scale, used for adults and children, provides a way for patients to characterize their pain nonverbally²

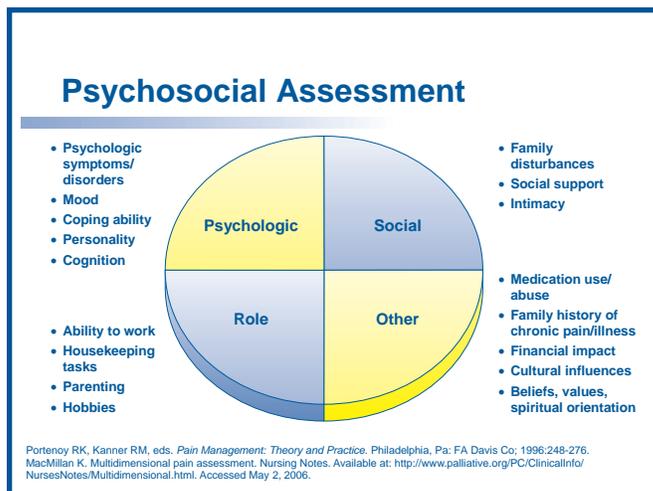


Slide 7



- A functional assessment evaluates the impact of pain in several areas
 - Physical impairments, such as paresis
 - Physical symptoms other than pain (eg, tachycardia, grimacing)
 - The ability to perform activities of daily living
 - “Up time,” walking, and lifting
 - Sleep quality, appetite, and weight

Slide 8



- A psychosocial assessment should consider the patient's ability to function psychologically, socially, and within his or her various roles, as well as other issues related to medication use, lifestyle influences, and family history¹⁴
- When evaluating psychological functioning, the clinician should identify:
 - Current and past psychiatric disorders
 - Coping styles and ability to adapt
 - Personality variables
 - Cognitive factors
- Questions regarding social functioning should focus on:
 - Family disturbances
 - Social support system and risk of social isolation
 - Close or intimate relationships
- Regarding role functioning, the clinician should ask about the patient's ability to:
 - Work and perform housekeeping tasks
 - Perform his or her parental role
 - Engage in hobbies or interests
- Other psychosocial factors to be considered include:
 - Patient's history of substance use (prescription, over-the-counter, illicit)
 - Family history of chronic pain or illness
 - Financial impact of pain
 - Cultural influences such as the ethnocultural backgrounds and expression (eg, stoic versus expressive)
 - Patient's beliefs, values, and spiritual orientation

Slide 9

Physical Examination for Pain



- Examine painful area to determine if palpation or manipulation exacerbates pain
- Evaluate common sites of origin of referred pain
- Look for behaviors that would indicate pain (eg, restricted movement of limb, abnormal posture)
 - Absence of pain behaviors does not mean there is no pain

- Pain should be assessed periodically to evaluate pain intensity and effectiveness of the pain management plan

APS. Guideline for the Management of Cancer Pain in Adults and Children. Glenview, Ill: American Pain Society; 2005.

- The clinician should perform a physical examination to determine the type of pain the patient is experiencing¹⁵
 - Determine if palpation or manipulation of the site exacerbates the pain
 - Evaluate common sites of origin of referred pain
 - Look for behaviors that would indicate pain (eg, restricted movement of limb, abnormal posture)
 - If the patient does not exhibit these behaviors, it should not be interpreted that the patient has no pain
- Pain should be assessed periodically to evaluate pain intensity and overall effectiveness of the pain management plan¹⁵

Slide 10

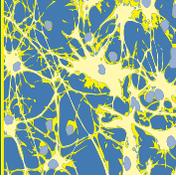
Diagnostic Tests for Pain



- Diagnostic tests (eg, CT or MRI scans) determine
 - Cause of pain
 - Extent of disease
- Results should be related to physical findings to ensure
 - Appropriate areas were imaged
 - Identified abnormalities explain the pain
- Tests should be repeated if pain worsens or there is a new source of pain

APS. Guideline for the Management of Cancer Pain in Adults and Children. Glenview, Ill: American Pain Society; 2005.

- Diagnostic testing (eg, computed tomography [CT] or magnetic resonance imaging [MRI] scans) is performed to determine the cause of pain and the extent of disease¹⁵
- Tests should be evaluated to ensure that appropriate areas were imaged and that abnormalities identified can explain the pain¹⁵
- Pain may indicate disease recurrence or progression and may occur before changes are evident on imaging studies¹⁵
- Diagnostic tests should be repeated if pain worsens or if there is a new source of pain, even if the initial tests were negative¹⁵



Slide 11

Ongoing Reassessment of Pain

- **Use valid, reliable, and consistent assessment tools¹**
 - eg, NRS, BPI
- **Perform reassessment at appropriate intervals²**
- **Document assessments²**
 - Pain relief
 - Changes in pain intensity
 - Interference with function
 - Adherence to pain management plan
 - Adverse effects of medication

NRS=Numeric Rating Scale; BPI=Brief Pain Inventory.

1. McCaffery M, Pasero C, eds. *Pain: Clinical Manual*. 2nd ed. St. Louis, Mo: Mosby, Inc; 1999:36-102. 2. APS. *Guideline for the Management of Cancer Pain in Adults and Children*. Glenview, Ill: American Pain Society; 2005.

- The third component of pain assessment is ongoing reassessment
- Use valid, reliable, and consistent assessment tools²
 - The same tool should be used with the same patient each time pain is assessed
- Perform reassessments at appropriate intervals¹⁵
- Document pain intensity¹⁵
 - Extent to which pain interferes with function
 - Pain relief (lower pain rating from one visit to the next) is a distinct parameter of pain assessment
 - Adherence to and effectiveness of pain management plan
- If a patient reports both persistent and breakthrough pain, include both types of pain in the reassessment¹⁵
- Patient pain management tools (eg, daily diary and pillbox) may help patients gain some control of their pain¹⁵
 - Patients can record their pain intensity, pain relief, and use of analgesic medications daily in a pain management diary
 - Patients can use a pillbox to keep track of their medications

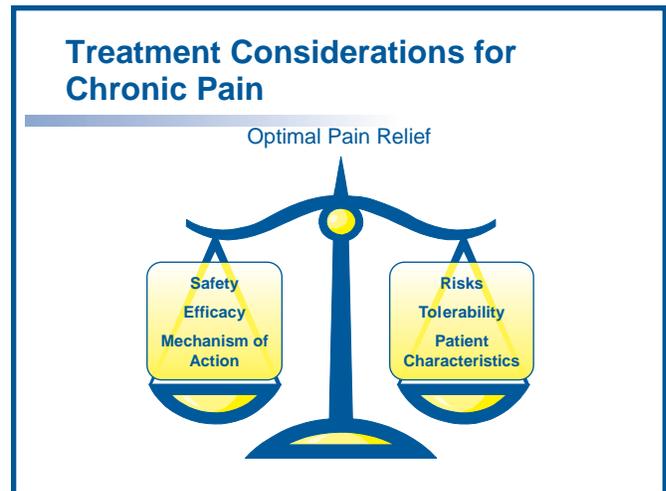
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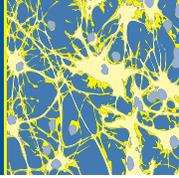
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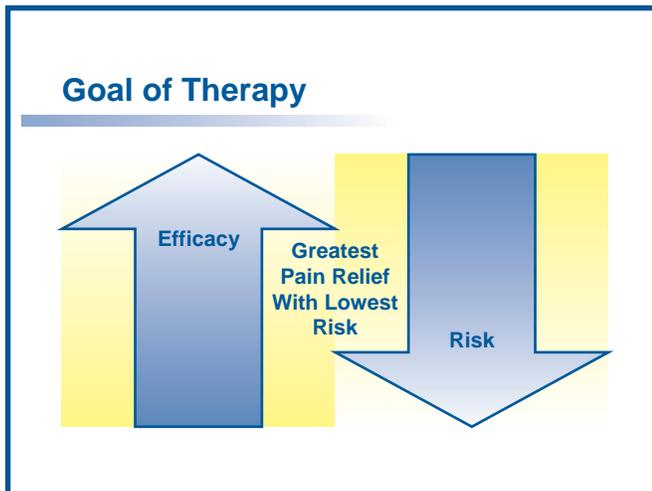
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- All pharmacologic interventions carry a balance of benefits and burdens¹
- In addition to efficacy, the clinician needs to consider and balance the characteristics of the particular patient; issues of risk, safety, and tolerability; and the mechanism of action of any given pain treatment approach¹
- The clinician must choose the most effective, most appropriate, and safest pain treatment for the patient's condition¹
- Medications, doses, use patterns, efficacy, and adverse effects should be regularly reviewed¹

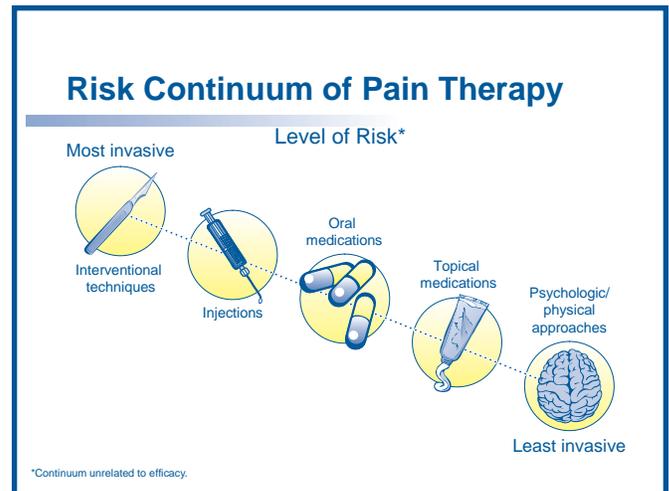


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- The goal of therapy is to obtain the greatest pain relief while exposing the patient to the lowest possible risk
- Complete pain relief is uncommon among patients with chronic pain; therefore, realistic goals should be discussed openly and agreed upon with the patient²
- All treatments carry some level of risk, which should be balanced against their clinical benefit

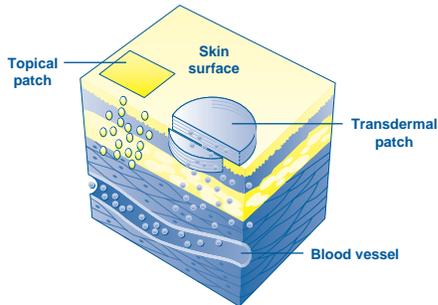
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- The risk continuum of pain therapy ranges from nonpharmacologic treatments (eg, psychologic/physical approaches), which pose the least amount of risk, to interventional techniques, which pose a greater relative risk
- Patients may need to progress to treatments with greater risk in order to achieve adequate pain relief
- Psychologic approaches include such treatments as relaxation therapy, imagery, and hypnosis; physical approaches include physical exercise or physical therapy, and the application of heat or ice
- Topical medications include the lidocaine patch 5%,^{3,4} capsaicin, and a variety of custom-compounded topical agents prepared by pharmacists
- Oral medications include over-the-counter nonsteroidal anti-inflammatory drugs and acetaminophen
- Prescription oral medications, including anticonvulsants (eg, gabapentin), tricyclic antidepressants, opioids, and miscellaneous agents (eg, mexiletine, baclofen), are systemic agents and, therefore, carry a greater risk of adverse effects⁵ and drug interactions
- Injections include nerve blocks and local infiltrations that are usually administered with local anesthetics and/or steroids
- Interventional techniques, which require referral to a specialist, include spinal cord stimulation, spinal analgesia, brain stimulation, and neurosurgical procedures such as dorsal root entry zone lesions⁶

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Pathway for Absorption: Topical vs Transdermal Skin Patch



- Topical and transdermal patch delivery systems differ in⁷:
 - Systemic activity
 - Application site
 - Serum levels of drug
 - Likelihood of systemic effects
- Topical analgesics (eg, the lidocaine patch 5%) exert localized pharmacologic activity at the pain site, are associated with minimal systemic absorption, and provide a targeted approach to delivering analgesia with low risk of systemic effects or drug interactions⁸
- Transdermal systems (eg, the fentanyl patch) may be applied anywhere on the body that a patch will adhere, need systemic absorption to exert their activity, and, as such, may cause systemic side effects and drug interactions⁷
 - It is important to note that improper use of the fentanyl patch can cause harm. Patients are advised not to use heat sources such as heating pads, electric blankets, heat lamps, saunas, hot tubs, heated waterbeds, or hot baths and not to sun bathe when using the fentanyl patch. All of these can make a patient's temperature rise and cause too much of the medication to be released at once⁹
 - Patients are advised to wear gloves when handling the patch, as the medication in the drug reservoir may come in accidental contact with the skin. If it does, the skin must be immediately flushed with large amounts of water to clean off the medication. Soap, alcohol or other solvents must not be used, as they may increase the drug's ability to penetrate the skin⁹
 - Patients must also be advised not to cut or damage the patch, as it can expose the patient to the contents of the patch, which contains a potentially fatal dose of medication. Patients are advised not to wear more than one patch at a time, unless their healthcare provider tells them to do so⁹
 - Once removed, the patch should be folded in half so that the adhesive backing is folded together and adheres to itself. Appropriate disposal of both a used and an unused patch can be accomplished by flushing down a toilet connected to a municipal sewage treatment facility.⁹ Disposal of a patch down a toilet connected to a septic field or septic tank is not recommended, and it is questionable from an environmental view. In these cases, it is advised that patients obtain a secure container (childproof and tamperproof) to dispose of the patch. Do not put the used patches in a garbage can

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Optimal Management of Chronic Pain Often Requires Multimodal Approach^{1,2}

Pharmacotherapy Cornerstone of Treatment

- Nonopioid analgesics
- Opioid analgesics (eg, morphine, oxycodone)
- Adjuvant analgesics, topical analgesics

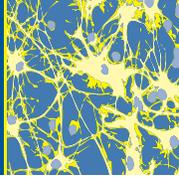
Nonpharmacologic Therapy Adjuvant to Pharmacotherapy

- Cognitive-behavioral approaches
- Physical therapy
- Surgery

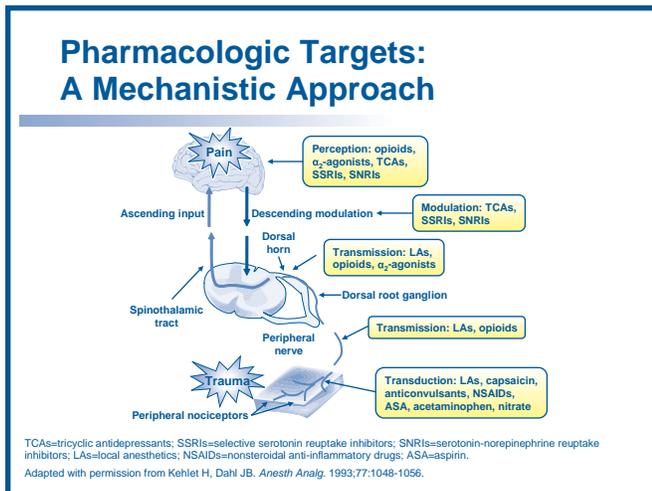
Both approaches have important, complementary roles in optimal pain management and reduction of adverse events

1. Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Co; 1996:248-276.
2. Reissner L. *Curr Pain Headache Rep*. 2003;7:24-33.

- A multimodal approach, using both pharmacologic and nonpharmacologic interventions, is an ideal method to obtain optimal pain relief with minimal side effects
- Pharmacotherapy remains the cornerstone of treatment
 - Medication choices include nonopioid analgesics (eg, acetaminophen, nonsteroidal anti-inflammatory drugs), opioid analgesics (eg, morphine-like agonists), topical analgesics (the lidocaine patch 5%), other topical agents (eg, capsaicin), and adjuvant analgesics (eg, anticonvulsants)^{3,4,7,8,10,11}
- Adjuvant analgesics are drugs used primarily for conditions other than pain, but which may be analgesic in selected circumstances
 - Some examples are tricyclic antidepressants and certain anticonvulsants^{8,10}
- Other analgesics used as primary pain therapeutics in some conditions, such as postherpetic neuralgia (eg, the lidocaine patch 5%), are also used as adjuvant therapies³
- Nonpharmacologic interventions include cognitive-behavioral approaches (eg, patient education, relaxation, imagery, hypnosis, biofeedback), physical therapy (eg, superficial heat/cold, massage, exercise, immobility, electroanalgesia), and surgery
 - These are usually supplemental to, rather than replacements for, pharmacotherapy

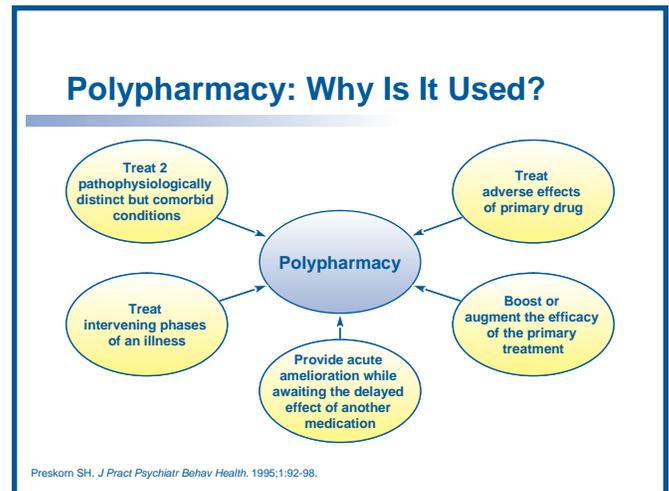


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- It is often necessary to employ a mechanistic approach to drug selection, with less emphasis on therapeutic class stratification and more attention to efficacy related to the underlying cause.^{11,12} This may allow for rational polymodal selection of therapeutic agents and improved patient outcomes¹²
- Opioids, tramadol, tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors can enhance the descending inhibitory pathways from the brain
- Opioids activate receptors that result in reducing the release of neurotransmitters (eg, norepinephrine, glutamate, serotonin, substance P, acetylcholine)¹¹
- Some antidepressants inhibit reuptake of biogenic amines (eg, norepinephrine, serotonin). Tricyclic antidepressants are strong sodium-channel modulators¹⁰
- Two groups of agents modulate central sensitization at the spinal cord:
 - Drugs that inhibit calcium flux, such as anticonvulsants
 - Drugs that affect *N*-methyl-D-aspartate (NMDA) receptors. This second group contains agents whose primary indications are unrelated. These drugs modulate central sensitization via effects on NMDA receptors and are still under study for analgesic use¹¹
- Drugs that modulate peripheral sensitization by inactivating voltage-dependent sodium channels include carbamazepine, oxcarbazepine, topiramate, and lidocaine. Gabapentin has no effect on Na⁺ channels; however, it inhibits Ca⁺⁺ channel current in a voltage-dependent manner. Capsaicin acts at vanilloid receptors, causing initial short-term receptor activation followed by long-term Ca⁺⁺-dependent desensitization¹²
- Topical analgesic patches offer some advantages over oral agents, the primary one being reduced systemic side effects⁷
 - Medication administration via the patch helps avoid chemical or metabolic degradation of the agent in the gastrointestinal tract
 - The patch can also be removed easily from the skin to limit adverse events if they occur
 - Removal of the patch will halt drug infiltration

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- Polypharmacy is the intentional, concomitant use of more than 2 medications to treat either a patient with a single disorder or a patient with more than 1 pathophysiologically distinct illness¹³

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Approach to Chronic Pain Management: Rational Polypharmacy

- Common for patients to have partial response to first-line medication alone
- Combinations of ≥ 2 first-line medications recommended when there is partial response
- Also recommended at beginning of treatment
- Consider complementary mechanisms of action when adding analgesics
 - Combine a systemic agent with a peripherally acting agent
- Disadvantages include increased risk of adverse events



Dworkin RH et al. Arch Neurol. 2003;60:1524-1534.

- The use of 2 or more agents with complementary mechanisms of action is often required to achieve effective analgesia in chronic pain conditions¹⁴
- A disadvantage of combination therapy is the increased risk of adverse effects; therefore, it is prudent to consider side-effect profiles and potential drug interactions when employing polypharmacy

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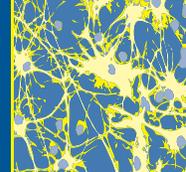
Role of Patient Education in Pain Management

- Critical component of an effective management plan
- Increases patient
 - Understanding of etiology
 - Understanding of the management plan
 - Adherence with the analgesic regimen
- Provides information in writing
- Encourages questions
- Involves family member/caregiver
- Encourages patients to complete a pain management diary



APS. Guideline for the Management of Cancer Pain in Adults and Children. Glenview, Ill: American Pain Society; 2005.

- Patient education and counseling are critical components of an effective pain management plan
- Education takes time but provides long-term benefits
- Be aware that the patient may not fully comprehend the information when he or she is not functioning to capacity because of pain
- A patient with chronic pain should understand the reason for the pain as well as the management techniques that will be employed (eg, side-effect management, regular assessments, pain diary)
- Patient education is especially important for patients with chronic diseases that may result in severe pain, such as osteoarthritis and cancer
- It is helpful to provide written as well as verbal information
- Patients should be encouraged to ask questions and to contact the clinician if they have further questions or need clarification
- It is also important to include a family member or caregiver in these discussions¹⁵



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13. Preskorn SH. Polypharmacy: when is it rational? Available at: <http://www.preskorn.com/columns/9507.html>. Accessed April 14, 2006.
14. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol.* 2003;60:1524-1534.
15. American Pain Society. *Guideline for the Management of Cancer Pain in Adults and Children. APS Clinical Practice Guideline Series, No. 3.* Glenview, Ill: American Pain Society; 2005.

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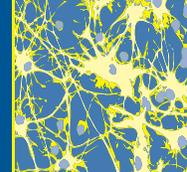


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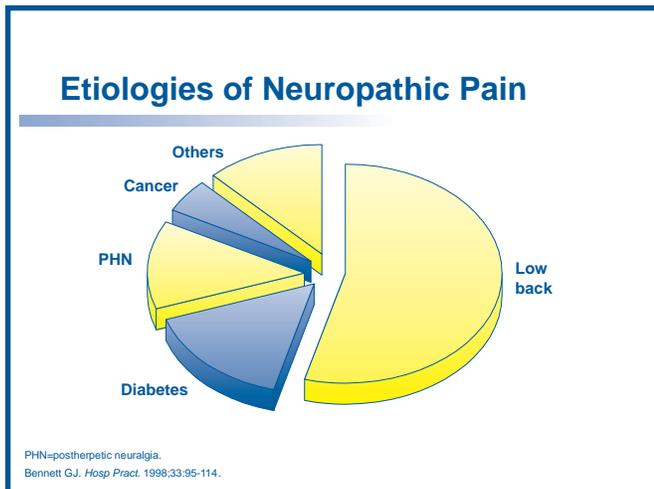
Chronic Neuropathic Pain

- **Initiated or caused by primary lesion or dysfunction in the nervous system**
- **Pathologic**
 - Serves no physiologic purpose
- **Mechanisms not completely understood**
 - Complex in nature
 - Often has multiple mechanisms

NPC/JCAHO. Pain: Current Understanding of Assessment, Management, and Treatments. December 2001.



Slide 3



- Even if it is assumed that as few as 10% of patients with low back pain have pain that is primarily neuropathic in origin, low back pain is clearly the most prevalent neuropathic pain syndrome, and the US prevalence of neuropathic pain is approximately 1.5%¹
- The classification of neuropathic pain is difficult. Not all patients with any particular illness will develop neuropathic pain. In some cases, 1 mechanism could be responsible for many different symptoms. In other cases, only a few patients may be affected. There are no predictors to indicate which patients will develop neuropathic pain²

Slide 4

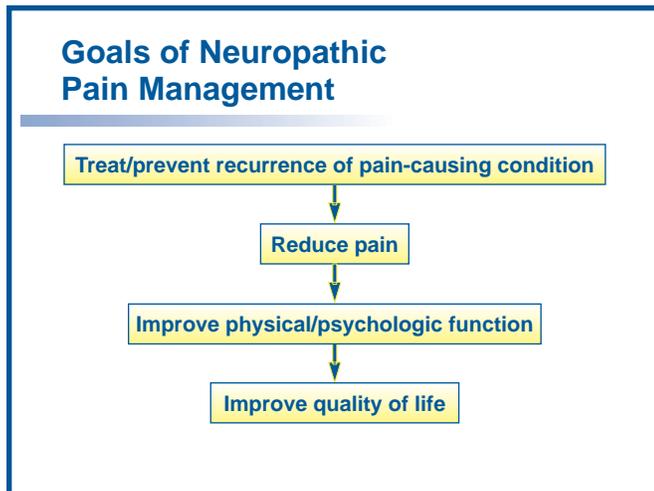
Neuropathic Pain: Issues and Challenges

- **Common**
 - ~3 million people with painful diabetic neuropathy¹
 - ~1 million people with postherpetic neuralgia²
- **Underassessed and undertreated**
- **Complex pathophysiology**
 - Multiple mechanisms
 - Emotional element of pain
 - Clinicians may doubt pain is “real” since there is no apparent tissue damage
- **Patients respond differently to treatment**

1. Schmader KE. *Clin J Pain.* 2002;18:350-354. 2. Bowsher D. *Eur J Pain.* 1999;3:335-342.

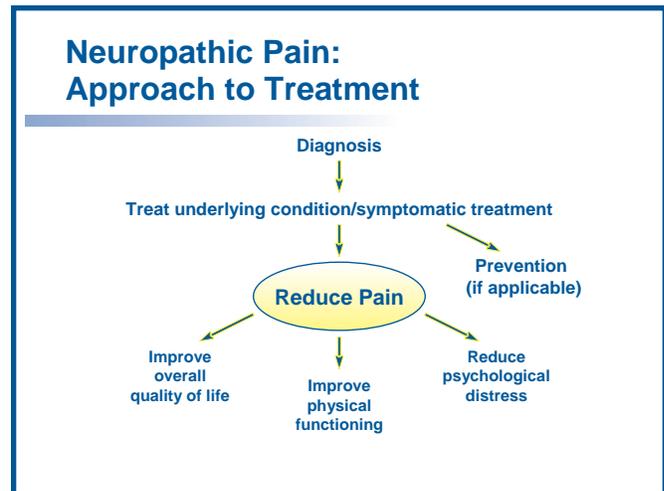
- Although there are no precise estimates, chronic neuropathic pain is fairly common
 - ~3 million people are affected by painful diabetic neuropathy³
 - ~1 million people are affected by postherpetic neuralgia⁴
- In clinical practice, it comprises a large number of all visits to pain clinics; yet, it is underassessed and undertreated
 - One reason is the complex pathophysiology of neuropathic pain
 - Patients often are not believed because there appears to be no tissue damage
 - Patients often experience emotional reactions associated with their pain

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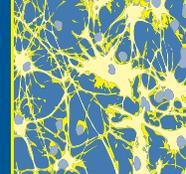


- There is a tendency to view pain syndromes as if they are acute problems. It may be more appropriate to view them as acute recurrent problems characterized by flare-ups⁵
- Management of neuropathic pain includes treating the underlying condition that has resulted in pain, providing symptomatic relief from pain and disability, and preventing recurrence
- If the underlying condition cannot be corrected, the primary goal of treatment should be relief of pain, which may improve physical functioning, reduce psychological distress, and improve overall quality of life
- In some cases, pain relief may be achieved through surgical release of an entrapped nerve,⁶ epidural steroids for lumbar radiculopathy,⁷ or antivirals for herpes zoster⁶
- For some types of neuropathic pain, preventive measures are available
 - Maintaining glycemic control for patients with painful diabetic neuropathy⁶
 - Providing antiviral agents for patients with acute herpes zoster to prevent postherpetic neuralgia⁶
- Symptomatic treatment should also be provided since treating the primary cause (herpes zoster, diabetes) may not relieve symptoms
- It is important for clinicians and patients to have appropriate expectations for the outcome of treatment
 - Patients should be aware that, although it is unlikely their pain will be completely eliminated, treatment can relieve pain and improve quality of life

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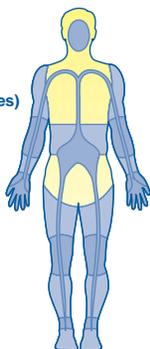
- It is unrealistic to expect all neuropathic pain to be eliminated. However, by identifying and effectively treating the underlying conditions, pain intensity can be reduced, thereby improving quality of life and physical functioning and reducing psychological stress



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Common Peripheral Neuropathies

- Painful diabetic neuropathy (hands and feet)
- Postherpetic neuralgia (commonly lower trunk)
- Complex regional pain syndrome (arms and legs)
- Mechanical neuropathies (commonly upper extremities)
 - Entrapment neuropathies
 - Nerve compressions
- HIV-related sensory neuropathy (feet and ankles)
- Idiopathic sensory neuropathy (distal/proximal)
- Phantom limb
- Posttraumatic neuralgias
- Trigeminal neuralgia (facial)
- Cancer-chemotherapy–induced neuropathies (hands and feet)



HIV=human immunodeficiency virus.
Dworkin RH et al. *Arch Neurol*. 2003;60:1524-1534.

- Some of the common peripheral neuropathies include⁸:
 - Painful diabetic neuropathy, which involves the hands and feet
 - Postherpetic neuralgia, which frequently involves the lower trunk
 - Complex regional pain syndrome, which occurs at the site of injury (most often the arms and legs)
 - Mechanical neuropathies, commonly of the upper extremities, which include entrapment neuropathies (eg, carpal tunnel syndrome, nerve compressions)
 - Human immunodeficiency virus–related sensory neuropathy, which often begins in the soles of the feet and moves up to the ankles; it rarely occurs in the fingers or hands
 - Idiopathic sensory neuropathy, which can occur in both distal and proximal locations
 - Phantom limb, which often involves an amputated leg
 - Posttraumatic neuralgias, which occur at any site where there is injury
 - Trigeminal neuralgia, which involves the nerves of the face
 - Cancer-chemotherapy–induced neuropathies, which usually occur in the hands and feet

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Common Central Neuropathies

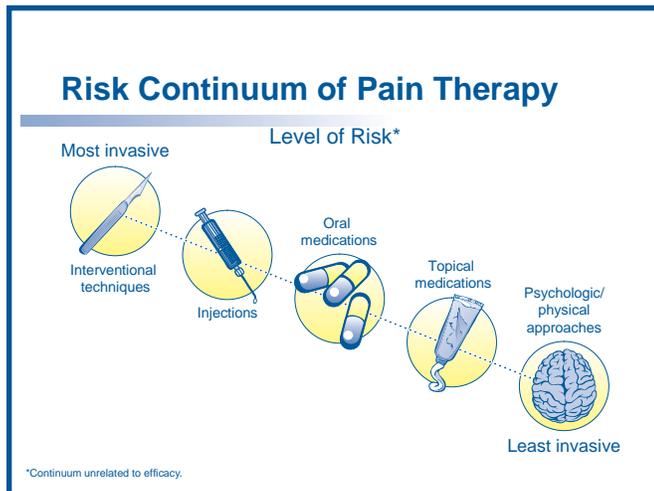
- Compression myelopathy from spinal stenosis (radiating arm, fingers, lower back, radiating leg)
- HIV myelopathy
- Pain related to multiple sclerosis and Parkinson's disease
- Postischemic and postradiation myelopathy
- Poststroke pain (face, arm, leg, or trunk on side of stroke)



HIV=human immunodeficiency virus.
Dworkin RH et al. *Arch Neurol*. 2003;60:1524-1534.

- Neuropathic pain can originate from lesions in the central nervous system
- Depending on the location of compression (cervical or lumbar), compression myelopathy associated with spinal stenosis may cause radiating arm pain, with numbness and paresthesia in the involved fingers; lower back pain; or radiating leg pain
- HIV myelopathy manifests clinically with slowly progressive spastic paraparesis, hyperreflexia and extensor plantar responses, sensory ataxia, incontinence, and, rarely, asymmetric features and involvement of upper extremities
- Other examples of central neuropathies include⁸:
 - Pain related to multiple sclerosis and Parkinson's disease
 - Postischemic and postradiation myelopathy
 - Poststroke pain, which can occur in the face, arm, leg, and trunk on the side of the body where the stroke occurred

Slide 9



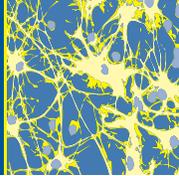
- Treatment should begin at an appropriate point along the risk continuum, based on the patient, disease process, patient characteristics, and safety considerations
- With neuropathic pain, psychological and physical approaches alone are not likely to significantly reduce the pain but may be useful as supportive therapy
- Topical medications, including the lidocaine patch 5%, capsaicin, and a variety of custom-compounded topical agents of undetermined effectiveness, may be appropriate for postherpetic neuralgia, diabetic peripheral neuropathy, low back pain, osteoarthritis, and musculoskeletal pain⁸⁻¹¹
- Prescription oral medications, including anticonvulsants (eg, gabapentin), tricyclic antidepressants, opioids, and miscellaneous agents (eg, mexiletine, baclofen), carry risk of systemic side effects or drug interactions but are often needed^{8,12}
- Interventional techniques, which are most invasive and necessitate referral to a specialist, may be required

Slide 10

Neuropathic Pain: Nonpharmacologic Treatment Options

- **Cognitive-behavioral strategies**
 - Meditation
 - Imagery
 - Biofeedback
 - Relaxation therapy
- **Physical rehabilitation**
- **Acupuncture**
- **Transcutaneous electrical nerve stimulation**

- Nonpharmacologic strategies may be useful in reducing pain and improving function, especially if used adjunctively with pharmacologic treatments¹³
 - Nonpharmacologic strategies are rarely sufficient to replace pharmacotherapies, especially in the case of chronic neuropathic pain^{13,14}
- Cognitive-behavioral strategies, including meditation, biofeedback, relaxation, and imagery, are most appropriate for patients who express interest in the modality, have anxiety or inordinate fears about pain, or experience persistent or recurrent pain that may benefit from combined pharmacologic and cognitive-behavioral strategies¹⁵
- Physical rehabilitation is appropriate for patients with persistent nonmalignant pain. In addition to relieving pain, physical therapy may reduce fear and anxiety, improve physical function, and alter physiologic response¹⁵
- Transcutaneous electrical nerve stimulation can ameliorate chronic neuropathic pain^{15,16}
 - The equipment may be difficult for some patients to operate
 - The treatment is time consuming



Slide 11

Topical vs Transdermal Delivery Systems

Topical (eg, lidocaine patch 5%)	Transdermal (eg, fentanyl patch)
Peripheral tissue activity	Systemic activity
<ul style="list-style-type: none"> Applied directly over painful site Insignificant serum levels Systemic side effects unlikely 	<ul style="list-style-type: none"> Applied away from painful site Serum levels necessary Possible systemic side effects

- Although systemic analgesics play a significant role in the treatment of pain, their use may be limited by issues of tolerability
- Topical analgesics provide a nonsystemic approach to manage peripherally generated pain of a localized nature
- Topical and transdermal patch delivery systems differ in:
 - Systemic activity
 - Application site
 - Serum levels of drug produced
 - Likelihood of systemic effects
- Since numerous types of neuropathic pain are peripherally generated, topical analgesics provide a useful treatment approach
- Topical analgesics, such as the lidocaine patch 5%, exert localized pharmacologic activity at the pain site, are associated with minimal systemic absorption, and provide a targeted approach to delivering analgesia, with low risk of systemic effects or drug interactions
- Transdermal systems, such as the fentanyl patch, may be applied anywhere on the body to which a patch will adhere, require systemic absorption to exert their activity, and, as such, may cause systemic side effects and drug interactions

Slide 12

Neuropathic Pain: First-Line Pharmacologic Treatments

- Gabapentin*¹
- Lidocaine patch 5%*¹
- Opioid analgesics¹
- Tramadol¹
- Tricyclic antidepressants¹
- Recently approved agents
 - Duloxetine²
 - Pregabalin³

*FDA-approved for the treatment of postherpetic neuralgia. †Not FDA-approved for analgesia. Carbamazepine: FDA-approved for trigeminal neuralgia. ‡FDA-approved for the treatment of painful diabetic neuropathy.

FDA=Food and Drug Administration

1. Dworkin RH et al. *Arch Neurol*. 2003;60:1524-1534. 2. FDA news, 2004. Available at: <http://www.fda.gov/bbs/topics/news/2004/NEW01113.html>. Accessed March 29, 2006. 3. Lesser H et al. *Neurology*. 2004;63:2104-2110.

- Dworkin et al identified pharmacologic agents with positive results from multiple randomized clinical trials as first-line treatment for neuropathic pain: gabapentin, lidocaine patch 5%, opioid analgesics, tramadol hydrochloride, and tricyclic antidepressants³
- Two additional agents, duloxetine and pregabalin, have been approved by the Food and Drug Administration (FDA) for the treatment of painful diabetic neuropathy and will likely be integrated into the revised guidelines currently in development
- Other medications with FDA-approved indications for neuropathic pain include carbamazepine for trigeminal neuralgia and both the lidocaine patch 5% and gabapentin for postherpetic neuralgia
- When selecting a pharmacologic treatment regimen, clinicians should consider safety and tolerability factors such as side-effect profiles and the potential for drug interactions
 - Because of its nonsystemic mechanism of action, the lidocaine patch 5% has the least potential for adverse side effects or drug interactions
 - Among systemic agents, gabapentin has a favorable safety and tolerability profile³
- Gabapentin, desipramine, tramadol, and controlled-release oxycodone also have demonstrated safety and tolerability profiles that are more favorable than those of earlier agents such as amitriptyline, endocannabinoids, phenytoin, and carbamazepine, among others¹⁷⁻²²

Slide 13

FDA-Approved Drugs for PHN

Drug	Gabapentin	Lidocaine Patch 5%	Pregabalin
Class	Anticonvulsant ¹	Topical analgesic for localized painful patch ^{2,3}	Anticonvulsant with analgesic and anxiolytic properties ^{4,5}
Mechanism of action	Uncertain mechanism ¹	Na ⁺ channel blocker; inhibits ionic fluxes required for initiation and propagation of impulses ⁶ ; physical barrier against allodynia	Uncertain mechanism; may reduce excitatory neurotransmitter release ⁶
Pharmacokinetics	Limited intestinal absorption ¹ Peak time: 2-3 h; elimination half-life: 5-7 h ¹	Clinically insignificant serum levels ^{2,3}	Peak concentrations reached in 1.3 h; elimination half-life: 4.6-6.8 h ⁶
Side effects/interactions	Usually well tolerated Serious adverse events rare ^{1,7} Few drug interactions ⁷	Systemic side effects and drug interactions unlikely Most common side effect: application-site sensitivity; should be used with caution with class I antiarrhythmics	Well tolerated; adverse events (dizziness, somnolence, peripheral edema) were mild to moderate and did not result in withdrawal ^{4,8,9,10}
Dosage	Range: ≤3600 mg/d (tid/qid)	≤3 patches applied once daily to cover painful site ⁴ ; 12 h on, 12 h off ²	150-600 mg/d ^{4,8,9,10}
Indications/FDA approval	PHN ¹	PHN ²	PHN, PDP ⁶

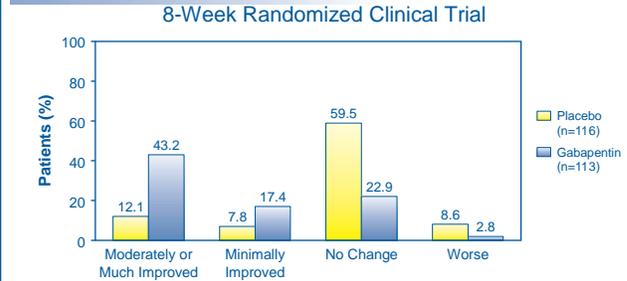
FDA=Food and Drug Administration; PHN=postherpetic neuralgia; PDP=painful diabetic neuropathy.

1. Neurontin® (gabapentin). *Physicians' Desk Reference*. 58th ed. Montvale, NJ: Thomson PDR; 2004:2559-2564. 2. Lidoderm® (lidocaine patch 5%). *Physicians' Desk Reference*. 58th ed. 2004:1238-1239. 3. Sammitoni AR et al. *Am J Health Syst Pharm*. 2002;59:2215-2220. 4. Rosenstock J et al. *Headache*. 2005;45:95. 5. Lesser H et al. *Neurology*. 2004;63:2104-2110. 6. Frampton JE, Foster RH. *Drugs*. 2005;65:111-118. 7. Yu TN. *Curr Pain Headache Rep*. 2004;8:15-18. 8. Dworkin RH et al. *Neurology*. 2003;60:1274-1283. 9. Rosenstock J et al. *Pain*. 2004;110:628-638. 10. Sabatowski R et al. *Pain*. 2004;109:26-35.

- Gabapentin, lidocaine patch 5%, and pregabalin have been approved by the Food and Drug Administration for the treatment of postherpetic neuralgia⁸
- Pregabalin has been approved for the treatment of painful diabetic neuropathy
- All of these agents are well tolerated^{8,23,24}
- The lidocaine patch 5% does not result in clinically significant blood levels, so systemic side effects and drug interactions are unlikely^{8,9}

Slide 14

Gabapentin for the Treatment of PHN

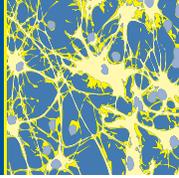


PHN=postherpetic neuralgia.

Average daily pain score was reduced compared with placebo; $P<.001$.

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- Rowbotham and colleagues conducted a large, multicenter, randomized, double-blind, placebo-controlled clinical trial of gabapentin for the treatment of postherpetic neuralgia in 225 patients¹⁷
- Patients received either gabapentin or placebo. Gabapentin was titrated over 4 weeks to a maximum dosage of 3600 mg/d; treatment was continued for an additional 4 weeks at the maximum tolerated dosage¹⁷
- The primary endpoint was average daily pain score¹⁷
- Responses to the Subjects' Global Impression of Change Questionnaire indicated that gabapentin provided valuable pain relief for many subjects, in contrast to patients treated with placebo¹⁷
- At the final week of therapy, patients treated with gabapentin had a statistically significant reduction (determined by means of an intent-to-treat analysis) in average daily pain score, compared with subjects receiving placebo (6.3 to 4.2 points vs 6.5 to 6.0 points, respectively; $P<.001$)¹⁷



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Gabapentin: Improvement in QOL for PHN

	Baseline Mean	Week 8 Mean	P Value	Mean Change From Baseline
Physical Functioning				
Gabapentin	61.7	66.2	.01	4.5
Placebo	57.6	57.5		-0.1
Bodily Pain				
Gabapentin	42.9	57.4	<.001	14.5
Placebo	42.7	47.3		4.7
Mental Health				
Gabapentin	67.9	74.6	<.001	6.7
Placebo	69.2	69.9		0.7
Total Mood Disturbance				
Gabapentin	31.9	16.9	<.001	-15.0
Placebo	30.6	27.7		-2.9

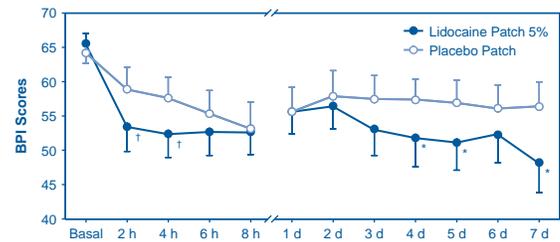
PHN=postherpetic neuralgia; QOL=quality of life.

Reprinted with permission from Rowbotham M et al. JAMA. 1998;280:1837-1842. © 1998, American Medical Association. All rights reserved.

- Among the secondary efficacy endpoints in the Rowbotham Study were patient quality of life and mood states, as measured by the Short Form-36 (SF-36) Quality-of-Life Questionnaire and the Profile of Mood States¹⁷
- Patients who received gabapentin had significantly better improvements than did patients who received placebo in 3 of the SF-36 indicators: physical functioning, bodily pain, and mental health as well as the Profile of Mood States measure of total mood disturbance¹⁷
- Gabapentin also produced significantly greater improvements ($P<.01$) in the SF-36 role-physical and vitality and the Profile of Mood States depression-dejection, anger-hostility, fatigue-inertia, and confusion-bewilderment measures¹⁷

Slide 16

Efficacy of Lidocaine Patch 5% in PHN



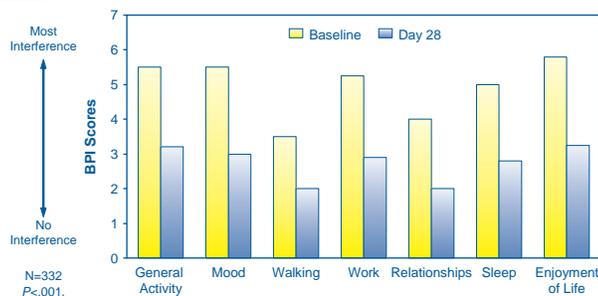
Change of basal scores (VAS) for ongoing pain throughout the first 8 hours and 7-day treatment period after patch application; mean (±SEM); lidocaine patch vs placebo patch. * $P<.05$ and † $P<.01$; n=40. The decrease in ongoing pain intensity and allodynia was statistically significant in the lidocaine group ($P<.001$) compared with the pretreatment (basal) values at all time points of the assessment.

PHN=postherpetic neuralgia; BPI=Brief Pain Inventory; VAS=Visual Analog Scale; SEM=standard error of the mean. Reprinted with permission from Meier T et al. Pain. 2003;160:151-158.

- A randomized, double-blind, placebo-controlled study was conducted by Meier and colleagues to investigate the efficacy of the lidocaine patch 5% in postherpetic neuropathy and in other peripheral neuropathic pain syndromes²⁵
 - 40 patients with various forms and localizations of peripheral neuropathic pain syndromes were evaluated²⁵
- Change of basal scores on the Visual Analog Scale for ongoing pain and allodynia were measured²⁵
- Decrease in ongoing pain intensity and allodynia was highly significant in the lidocaine group ($P<.001$) and significant in the placebo group ($P<.05$), compared with the pretreatment (basal) values at all time points of the assessment²⁵
- Study results demonstrated significant reduction in ongoing pain ($P=.017$) and allodynia ($P=.023$) during the first 8 hours of application²⁵
 - Patches also reduced pain over a period of 7 days ($P=.018$) in diverse focal peripheral neuropathic pain syndromes²⁵

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Lidocaine Patch 5%: QOL Indicators in PHN



QOL=quality of life; PHN=postherpetic neuralgia; BPI=Brief Pain Inventory.
Adapted with permission from Katz NP et al. *Pain Med.* 2002;3:324-332.

- The effect of the lidocaine patch 5% on quality-of-life indicators in 332 patients with postherpetic neuralgia persisting or starting ≥ 1 month from the onset of herpes zoster was evaluated in a multicenter, open-label study²⁶
- Pain was assessed using the short form of the Brief Pain Inventory, which includes 0 to 10 numeric rating scales of the following domains of quality of life²⁶:
 - General activity
 - Mood
 - Walking ability
 - Work
 - Relationships
 - Sleep
 - Enjoyment of life
- Treatment with the lidocaine patch 5% significantly reduced ($P<.001$) pain interference with quality of life at day 28 compared with baseline values for all 7 domains²⁶

Slide 18

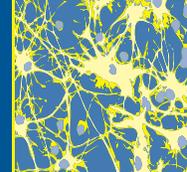
Pregabalin Clinical Studies in PHN and DPN

No./Type of Studies	• 12 double-blind, placebo-controlled ¹⁻⁸ – 5 in DPN; 6 in PHN; 1 in both
Total No.	• >2500 ¹⁻⁸
Study Length	• 6-14 weeks
Outcomes	• Decreases in mean pain score ($P<.001$) • Improvements in sleep interference ($P<.001$) ^{5,6} • 26%-50% of patients achieved a 50% decrease in pain ($P=.001$) ^{2,5,7}

PHN=postherpetic neuralgia; DPN=diabetic peripheral neuropathy.

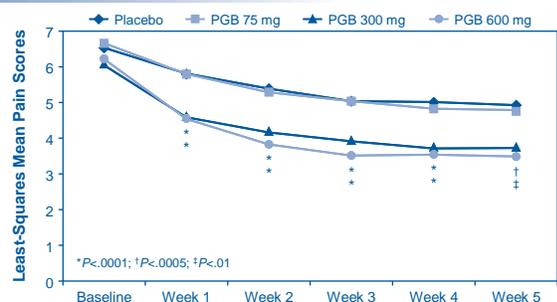
1. Rosenstock J et al. *Headache.* 2005;45:95. 2. Lesser H et al. *Neurology.* 2004;63:2104-2110. 3. Frampton JE, Foster RH. *Drugs.* 2005;65:111-118. 4. Frampton JE, Scott LJ. *Drugs.* 2004;24:2813-2820. 5. Dworkin RH et al. *Neurology.* 2003;60:1274-1283. 6. Rosenstock J et al. *Pain.* 2004;110:628-638. 7. Sabatowski R et al. *Pain.* 2004;109:26-35. 8. *Prescrire Int.* 2005;14:203-206.

- In 12 double-blind, placebo-controlled clinical trials that ranged from 6 to 14 weeks,^{23,24,27-32} >2500 patients with either postherpetic neuralgia or painful diabetic peripheral neuropathy reported significant decreases in mean pain and improvements in sleep interference^{29,30,32}
- In these studies, between 26% and 50% achieved a 50% decrease in pain^{24,29,31,32}



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Pregabalin for Treatment of Painful DPN



DPN=diabetic peripheral neuropathy; PGB=pregabalin.

Reprinted with permission from Lesser H et al. *Neurology*. 2004;63:2104-2110.

- Patients with a 1- to 5-year history of painful diabetic peripheral neuropathy and an average weekly pain score >4 on an 11-point numeric pain rating scale were enrolled in a 5-week, double-blind, multicenter, placebo-controlled study²⁴
- Patients were randomized to receive 1 of 3 doses of pregabalin (75, 300, or 600 mg/d) or placebo²⁴
- Patients in the 300- and 600-mg/d groups showed improvements in endpoint mean pain score versus placebo ($P<.0001$)²⁴
- Improvements in pain and sleep were seen as early as the first week of treatment and were sustained throughout the 5 weeks²⁴
- The authors concluded that pregabalin demonstrated early and sustained improvement in pain in patients with painful diabetic peripheral neuropathy and had a beneficial effect on sleep²⁴
- Pregabalin was well tolerated at all doses studied in the trial²⁴

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Neuropathic Pain: Emerging Treatments

Class/Drug	Current Indications*	Under Investigation
Anticonvulsants		
• Gabapentin ^{1,2}	• PHN	• PDN, HIV-related, MS, disc herniation, ³ deafferentation neuropathy of the face ⁴
• Pregabalin ⁵	• PHN, PDN	• Neuropathic pain conditions
• Carbamazepine ^{5,6}	• Trigeminal neuralgia	• PHN, PDN, migraine prophylaxis, central pain after stroke
Topical analgesics		
• Lidocaine patch 5% ⁶	• PHN	• LBP, PDN, OA, carpal tunnel syndrome

*FDA-approved indication.

PHN=postherpetic neuralgia; PDN=painful diabetic neuropathy; HIV=human immunodeficiency virus; MS=multiple sclerosis; LBP=low back pain; OA=osteoarthritis; FDA=Food and Drug Administration.

1. Rowbotham M et al. *JAMA*. 1998;280:1837-1842. 2. LaSpina J et al. *Eur J Neurol*. 2001;8:71-75. 3. Solaro C et al. *Mult Scler*. 2000;6:192-193. 4. Rosner H et al. *Clin J Pain*. 1996;12:56-58. 5. Vu T-N. *Curr Pain Headache Rep*. 2004;8:15-18. 6. Dworkin RH et al. *Arch Neurol*. 2003;60:1524-1534.

- Numerous treatments are being evaluated for the management of neuropathic pain
 - Gabapentin has been approved for the treatment of postherpetic neuralgia, and is being evaluated for use in painful human immunodeficiency virus-related neuropathy^{33,34}
 - Gabapentin also has been investigated for pain related to multiple sclerosis³⁵⁻³⁷ and has been reported anecdotally to be effective in patients with disc herniation, sciatic-like pain in both legs, and deafferentation neuropathy of the face³⁴
 - Pregabalin, a more potent analogue of gabapentin, has been approved for treatment of postherpetic neuralgia and painful diabetic neuropathy³⁸
 - Carbamazepine is approved by the Food and Drug Administration for the treatment of trigeminal neuralgia and examined with postherpetic neuralgia, painful diabetic neuropathy, and mono- and polyneuropathies^{9,39}
 - The topical analgesic lidocaine patch 5% has been examined for treatment of painful diabetic neuropathy⁴⁰ and as concomitant treatment with gabapentin in patients with focal peripheral neuropathic pain syndromes²⁵
 - The lidocaine patch 5% also has been studied as adjuvant therapy in the treatment of neuropathic pain qualities in low back pain⁴¹

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Neuropathic Pain: Emerging Treatments (cont)

Class/Drug	Current Indications*	Under Investigation
Other Anticonvulsants		
<ul style="list-style-type: none"> Levetiracetam¹ Oxcarbazepine^{1,2} Lamotrigine^{1,2} 	<ul style="list-style-type: none"> Trigeminal neuralgia Epilepsy, bipolar disorder 	<ul style="list-style-type: none"> Neuropathic pain conditions Neuropathic pain conditions Painful neuropathy with HIV/AIDS, PDN
Opioids^{3,4}		
<ul style="list-style-type: none"> CR oxycodone Tramadol 	<ul style="list-style-type: none"> PDN PDN, painful polyneuropathy, OA (sustained-release tramadol)⁵ 	
Antidepressants^{1,2,5}		
<ul style="list-style-type: none"> Tricyclics Duloxetine 	<ul style="list-style-type: none"> PDN, migraine PHN, neuropathic pain 	
Neurotoxin^{6,7}		
<ul style="list-style-type: none"> Botulinum toxin 	<ul style="list-style-type: none"> Chronic low back pain 	

*FDA-approved indication.

HIV=human immunodeficiency virus; AIDS=acquired immune deficiency syndrome; PDN=painful diabetic neuropathy; CR=controlled release; OA=osteoarthritis; PHN=postherpetic neuralgia; FDA=Food and Drug Administration.

1. Dworkin RH et al. *Arch Neurol*. 2003;60:1524-1534. 2. Vu T-N. *Curr Pain Headache Rep*. 2004;8:15-18. 3. Watson CPN, Babul N. *Neurology*. 1998;50:1837-1841. 4. Gimbel JS et al. *Neurology*. 2003;60:927-934. 5. Reisner L. *Curr Pain Headache Rep*. 2003;7:24-33. 6. Difazio M, Jabbari B. *Clin J Pain*. 2002;18(6 suppl):S155-S162. 7. Thant Z-S, Tan E-K. *Med Sci Monit*. 2003;9:RA40-RA48. 8. Foster L et al. *Neurology*. 2001;56:1290-1293. 9. Ellis R, Hou J. Available at: <http://www.pharmexc.com/pharmexc/content/printContentPopUp.jsp?id=136704>. Accessed March 23, 2006.

- The efficacy of levetiracetam and oxcarbazepine, second-generation anticonvulsants, for the treatment of neuropathic pain has not been fully defined⁸
- Oxcarbazepine, a keto-analog of carbamazepine, has been shown to be equally effective as carbamazepine in the treatment of trigeminal neuralgia and may have a more favorable side-effect profile³⁸
- Lamotrigine has been studied for the treatment of numerous neuropathic pain conditions; it is generally well tolerated, but it interacts with other anticonvulsants³⁸
- Other treatments utilized for the treatment of neuropathic pain include opioids^{8,20,42,43} and antidepressants^{8,38,44}
- Placebo-controlled and randomized clinical trials of controlled-release oxycodone have shown that it is effective and well tolerated in patients with painful diabetic neuropathy^{42,43}
- Tricyclic antidepressants act in part by inhibiting the reuptake of norepinephrine and serotonin into presynaptic nerves; however, the different potencies result in significant variability in efficacy, tolerability, and dosage⁴⁴
 - Although tricyclic antidepressants have been commonly used to relieve neuropathic pain,³⁸ they do not have Food and Drug Administration approval for this indication
- Botulinum toxin is being investigated for the treatment of low back pain⁴⁵⁻⁴⁸
- In one study, the paravertebral administration of botulinum toxin type A in patients with chronic low back pain relieved pain and improved function at 3 and 8 weeks after treatment⁴⁷
- Botulinum toxin is also in phase II trials for migraine and tension headache^{48,49}

Slide 22

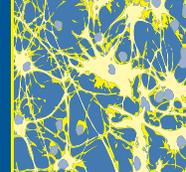
Neuropathic Pain: Emerging Treatments (cont)

Class/Drug	Under Investigation
Bisphosphonate	
<ul style="list-style-type: none"> Pamidronate 	Phase III trials for the management of malignant bone pain ¹
Novel Analgesic	
<ul style="list-style-type: none"> Bicifadine Ziconotide (Conus snail venom peptide) 	Under clinical investigation for chronic low back pain (LBP) ¹ In clinical development for chronic LBP and cancer, neuropathic, and postoperative pain ^{1,2}
NMDA-Receptor Antagonist	
<ul style="list-style-type: none"> Memantine 	Currently being studied for neuropathic pain syndromes ³ (approved for treatment of Alzheimer's disease)
Cannabinoid-Receptor Agonist	
	Under investigation for cancer, neuropathic, and postoperative pain (UK); neuropathic pain (Canada) ⁴

NMDA=N-methyl-D-aspartate.

1. Ellis R, Hou J. Available at: <http://www.pharmexc.com/pharmexc/content/printContentPopUp.jsp?id=136704>. Accessed March 23, 2006. 2. Wermeling D et al. *J Clin Pharmacol*. 2003;43:624-636. 3. Lipton SA. *J Alzheimers Dis*. 2004;6(6 suppl):S61-S74.

- Pamidronate, a bisphosphonate, is currently used off-label for cancer pain when cancer has metastasized to bone⁴⁸
 - It is a potent inhibitor of bone resorption, thereby maintaining bone mineral density
 - It is thought to prevent the attachment of osteoclast precursor cells to bone
 - It is currently used to treat osteoporosis and other bone disorders, and it is in phase III trials in the United States for the management of malignant bone pain
- Bicifadine, a novel analgesic with an unknown mechanism of action, is under development for a broad pain indication and has been under clinical investigation for chronic low back pain⁴⁸
- Ziconotide, under clinical development for chronic pain, including low back, cancer, neuropathic, and postoperative pain, is a synthetic form of a Conus snail venom peptide^{48,50}
 - It blocks N-type calcium channels of the central nervous system
- Memantine, an N-methyl-D-aspartate receptor antagonist currently approved for Alzheimer's disease, is under investigation for treatment of neuropathic pain syndromes⁵¹
- A cannabinoid-receptor agonist administered as a mouth spray is under development for cancer, neuropathic, and postoperative pain in the United Kingdom and for neuropathic pain in Canada⁴⁸

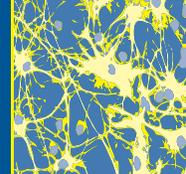


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50. Wermeling D, Drass M, Ellis D, et al. Pharmacokinetics and pharmacodynamics of intrathecal ziconotide in chronic pain patients. *J Clin Pharmacol*. 2003;43:624-636.
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Slide 1



Slide 2

Cancer Pain: Etiology

- **Common causes of pain**
 - Direct tumor involvement (up to 75%)^{1,2}
 - Pain resulting from cancer treatment^{1,2}
 - Surgery
 - Chemotherapy
 - Radiation therapy
 - Pain unrelated to cancer or cancer treatment¹
 - Comorbidities (ie, PHN)
 - Psychologic factors³⁻⁵
 - Anxiety, depression, anger⁵

PHN=postherpetic neuralgia.
1. Portenoy RK, Lesage P. *Lancet*. 1999;353:1695-1700. 2. Katz N. *Clin J Pain*. 2000;16(2 suppl):S41-S48. 3. Cousins MJ. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*. 3rd ed. Philadelphia, Pa: Lippincott-Raven; 1998:675-699. 4. Gamsa A. *Pain*. 1994;57:5-15. 5. Gamsa A. *Pain*. 1994;57:17-29.

- Up to three fourths of chronic cancer pain syndromes result from the direct effects of cancer; others are related to the treatments administered to treat the cancer or to unrelated disorders¹
- Pain associated with direct tumor involvement is caused by spinal cord compression; bone pain due to primary or metastatic lesions; headache and facial pain related to primary or metastatic lesions of the brain, skull, or cranial nerves; plexopathies or neuropathies; visceral pain; or paraneoplastic syndromes (eg, gynecomastia)^{1,2}
- Acute or chronic pain associated with cancer treatment may be a result of:
 - Surgery
 - Chronic pain following surgery for cancer is a well-known neuropathic complication and in many cases may be due to injury to intercostal nerves²
 - Acute postoperative pain is common; postsurgical pain syndromes after radical neck dissection, mastectomy, nephrectomy, thoracotomy, and limb amputation are often reported^{1,2}
 - Chemotherapy
 - Pain can be caused by oral mucositis, painful extravasation, or peripheral neuropathy associated with vinca alkaloids, taxanes, platinum-type compounds, or thalidomide¹
 - Peripheral neuropathy is usually dose related; it can be associated with dysesthesias and hyporeflexia²
 - Radiation therapy
 - Painful mucositis or esophagitis, plexopathies, radiation myelopathy, chronic radiation enteritis or proctitis, or osteoradionecrosis^{1,2}
- Cancer patients also can experience pain unrelated to cancer or cancer therapy, for example, from comorbidities such as postherpetic neuralgia and from psychological factors such as anxiety, depression, and anger³⁻⁵

Slide 3

Classes of Chronic Cancer Pain

Somatic	<ul style="list-style-type: none"> • Tumor invades bone, muscle, or connective tissue • Experienced as localized aching pain
Visceral	<ul style="list-style-type: none"> • Tumor encroachment on internal organs • Poorly localized colic and referred pain
Neuropathic pain from actual nerve damage	<ul style="list-style-type: none"> • Deafferentation pains and complex pain syndromes

Portenoy RK, Lesage P. *Lancet*. 1999;353:1695-1700.

- Recognizing pain syndromes can help the clinician:
 - Identify the specific etiology responsible for the pain
 - Suggest whether there is need for further evaluation
 - Suggest specific therapies
 - Help assess patient outcome
- The 3 classes of chronic cancer pain are somatic, visceral, and neuropathic¹
- Somatic pain results when a tumor invades the bone, muscle, or connective tissue, and primary afferent nerves become activated¹
 - This occurs commonly as a result of metastases and is experienced as localized aching pain
- Visceral pain results from tumor encroachment on internal organs and from activation of viscera afferents¹
 - This is experienced as poorly localized colic with referred pain, for instance, back and epigastric pain that is related to the pancreas and the liver
- Neuropathic cancer pain is caused by actual nerve damage that results in several subtype syndromes¹
 - Deafferentation pains, peripheral mononeuropathies and polyneuropathies, and complex regional pain syndromes

Slide 4

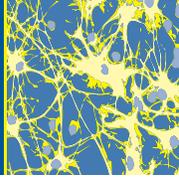
Managing Cancer Pain

- **Assess the pain**
- **Initiate pain management plan**
- **Reassess effectiveness of the plan and modify as necessary**
- **Patients with cancer pain may experience breakthrough pain**
 - Initiate prompt treatment with analgesics while awaiting assessment/diagnostic workup

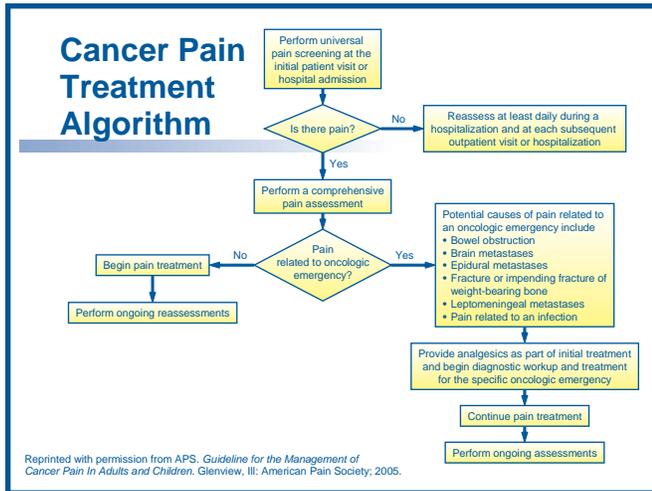


APS. *Guideline for the Management of Cancer Pain in Adults and Children*. Glenview, Ill: American Pain Society; 2005.

- There are 3 essential components to the management of cancer pain⁶
 - Assessing the pain
 - Initiating a pain management plan
 - Ongoing reassessment of the effectiveness of the plan with appropriate modification
- It is important to recognize that patients with cancer pain may experience breakthrough pain as a result of their disease or treatment⁶
 - This pain warrants prompt treatment with analgesic medications while the patient waits for an assessment and diagnostic workup



Slide 5



- Until recently, the World Health Organization analgesic ladder has been the recommended treatment guideline for managing cancer pain
- The American Cancer Society, the National Comprehensive Cancer Network, and, most recently, the American Pain Society recommend the use of an algorithm-based treatment approach
 - Cancer pain rarely progresses in the stepwise fashion that the World Health Organization ladder implies⁶
- Treatment algorithms can be challenging as they are often complex and not easily depicted graphically
- The key consideration is the need to determine if the pain is coming from an oncologic emergency that requires immediate treatment

Slide 6

Principles of Chronic Opioid Therapy for Cancer Pain

- Opioid analgesics are the medication of choice for severe cancer-related pain¹
- Titrate dose to optimize efficacy and minimize side effects²
- Fixed-dose regimens are generally preferred over PRN regimens¹
 - Short-acting opioids
 - Long-acting opioids
- Document treatment plan and outcomes
 - Control adverse effects with appropriate management²
- Understand distinctions between addiction, tolerance, physical dependence, and pseudoaddiction¹

PRN=as needed.

1. Cherry NJ, CA—*Cancer J Clin*. 2000;50:70-116. 2. APS. *Guideline for the Management of Cancer Pain in Adults and Children*. Glenview, Ill: American Pain Society; 2005.

- Opioid analgesics are an effective treatment option in cancer-related pain. Although these agents may pose some risks for patients, the risks can be prevented or circumvented with proper dosing and titration^{6,7}
 - The clinician has a choice of short-acting or long-acting opioids
- Most adverse effects from opioids can be controlled with appropriate specific management (eg, prophylactic bowel regimens)⁷
- Addiction has been defined as a biopsychosocial disorder characterized by continued compulsive use of a substance despite harm.⁸ Extended discussion of addiction and risk is presented in the section on opioids
- Tolerance means that a greater amount of drug is needed to maintain a therapeutic effect⁷
 - Tolerance also may apply to side effects, which may be beneficial⁸
- Physical dependence is a pharmacologic effect characterized by a withdrawal syndrome when the drug is discontinued, the dose is substantially reduced, or if an antagonist is administered⁷
- Pseudoaddiction has been defined as behavior suggestive of addiction that is often caused by undertreatment of pain^{7,8}

Slide 7

Choosing an Opioid: Factors to Consider

- Patient's pain intensity
- Coexisting disease (eg, hepatic, renal impairment)
- Patient's response to previous opioid treatment
- Pharmacokinetics
- Formulary considerations



- Opioid analgesics are the medication of choice for severe cancer-related pain⁶
- The choice of opioid depends on the patient's pain intensity, coexisting disease, the patient's response to previous treatment with opioids, the pharmacokinetics of the agent, and formulary considerations⁷
- Effective opioid management includes choosing the most efficacious route of administration and dosing schedule (ie, around-the-clock dosing or dosing as needed)⁷

Slide 8

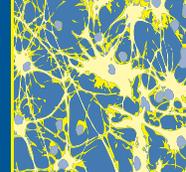
Categories of Opioid Analgesics

Category	Benefits	Drugs*
Short acting: Used to manage intermittent and breakthrough pain ¹	<ul style="list-style-type: none"> • Easier to titrate • More rapidly attained steady-state plasma concentrations² 	<ul style="list-style-type: none"> • Morphine sulfate • Codeine • Hydrocodone • Oxycodone • Hydromorphone • Fentanyl • Oxymorphone • Levorphanol
Long acting: For treating chronic pain in patients with consistent pain levels ^{3,4}	<ul style="list-style-type: none"> • Makes around-the-clock therapy possible • Dosing convenience and flexibility • Relative steady-state concentrations of opioid concentrations in the blood^{3,4} 	<ul style="list-style-type: none"> • Morphine (sustained-release) • Oxycodone (sustained-release) • Transdermal fentanyl • Hydromorphone (sustained-release) • Methadone • Hydrocodone • Oxymorphone • Levorphanol

*All but codeine are full agonists at μ -receptor.

1. NPC/JCAHO. Pain: Current Understanding of Assessment, Management, and Treatments. December 2001. 2. Cherny NI. CA—Cancer J Clin. 2000;50:70-116. 3. McCarberg BH, Barkin RL. Am J Ther. 2001;8:181-186. 4. AGS Panel on Chronic Pain in Older Persons. J Am Geriatr Soc. 1998;46:635-651.

- Opioids are first-line analgesic treatment for moderate to severe cancer pain.⁹ These agents provide analgesia by binding to receptors in the central nervous system to inhibit the transmission of nociceptive input from the periphery to the spinal cord, by activating descending inhibitory pathways that modulate transmission in the spinal cord, and by altering limbic system activity⁹
- Short-acting opioids are used to manage intermittent and breakthrough pain.⁹ Because they have a shorter half-life, they are easier to titrate and more rapidly attain steady-state plasma concentrations⁷
- The most effective opioids have full agonist properties at the μ receptor.¹⁰ Full μ agonists (eg, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone, levorphanol, fentanyl, methadone) do not exhibit a ceiling effect with increasing dose (ie, analgesia increases with all higher doses of opiate)^{7,9}
- Long-acting opioids can be used in chronic pain patients with consistent pain levels.^{9,11} Long-acting, controlled-release, oral formulations of opioids, which have a predictable duration of action lasting 8 hours or 12 to 24 hours,¹² make around-the-clock therapy possible and offer dosing convenience, flexibility, and relative steadiness of the opioid concentrations in the blood



Slide 9

Opioid Rotation

- Sequential trial of different opioids to obtain the most favorable balance between analgesia and adverse effects^{1,2}
- Reasons for opioid rotation³:
 - Substantial variability in patient response
 - Inadequate analgesia
 - Intolerable adverse effects
 - Chronic sedation



1. Fine PG. *J Pain Palliat Care Pharmacother.* 2004;18:75-79. 2. Bruera E, Kim HN. *JAMA.* 2003;290:2476-2479. 3. Fine PG, Portenoy RK. *A Clinical Guide to Opioid Analgesia.* Minneapolis, Minn: McGraw-Hill; 2004.

- A technique called “opioid rotation” may be appropriate to optimize therapy^{10,13,14}
- Opioid rotation usually involves abrupt discontinuation of the initial opioid and replacement with an equivalent dose of an alternative opioid¹⁴
- Based on factors such as genetics, demographic and disease-related variables, as well as comorbidities, there is substantial variation in how patients respond to opioids
 - In some patients, the opioid dose required to maintain analgesia also causes chronic sedation
 - Patients who become nauseated from oral therapy may benefit from transdermal administration
 - Responsiveness to opioid treatment may be impaired if the analgesic effect declines rapidly, resulting in the need to escalate the dose to an intolerable level
 - Metabolism of the drugs is variable. For example, codeine is metabolized to the active metabolite of morphine by the cytochrome P-450 hepatic enzyme system, where about 7% of the US population are slow metabolizers; as a result, poor codeine responsiveness may occur¹⁰
- Poor responsiveness to one opioid does not predict response to another
- When switching from one opioid to another, calculated equianalgesic doses are used as a starting point to reduce the risk of overdosing or underdosing¹⁰

Slide 10

Opioid Adverse Effects

System/Type	Adverse Effect
Gastrointestinal	Constipation ¹⁻³ Nausea and vomiting ^{1,3}
Central nervous system	Sedation ^{1,3} Cognitive impairment ^{1,3} : “mental clouding”/confusion
Respiratory	Respiratory depression ^{1,3}
Dermal	Pruritus ³
Endocrine	Decrease in libido ^{4,5,7} Hypogonadism ^{4,6,7}

1. Cherny NI. *CA—Cancer J Clin.* 2000;50:70-116. 2. Pappagallo M. *Am J Surg.* 2001;182(SA suppl):11S-18S. 3. NPC/JCAHO. *Pain: Current Understanding of Assessment, Management, and Treatments.* December 2001. 4. Abs R et al. *J Clin Endocrinol Metab.* 2000;85:2215-2222. 5. Rajagopal A, Bruera ED. *Pain Med.* 2003;4:379-383. 6. Finch PM et al. *Clin J Pain.* 2000;16:251-254. 7. Roberts LJ et al. *Clin J Pain.* 2002;18:144-148.

- The development of adverse effects from opioid analgesics depends on a number of factors, including patient age, extent of disease, concurrent organ dysfunction, other medications administered, prior opioid exposure, and the route of administration⁷
- Opioid bowel dysfunction, including constipation, is the most common adverse effect of chronic opioid therapy^{7,10,15}
- Other adverse effects may include nausea, vomiting, sedation, respiratory depression, itching, endocrine dysfunction, decrease in libido, and addiction.^{7,10,16} Except for constipation, endocrine dysfunction, and addiction, tolerance to adverse effects typically occurs within a few days to weeks of therapy initiation¹⁰
- Central nervous system side effects generally are dose related
 - Sedation is common upon initiation of opioid therapy⁷
 - Some patients continue to have sedative effects that may interfere with daily activities
- Respiratory depression is potentially the most serious adverse effect of opioid therapy, but it is always accompanied by other signs of central nervous system depression, including sedation and mental clouding
 - Respiratory compromise accompanied by tachypnea and anxiety is never a primary opioid event⁷
- Long-term administration of intrathecal opioids may be associated with decreased libido, as a result of effects on the hypothalamic-pituitary-gonadal axis (hypogonadotropic hypogonadism^{17,18})
 - Potential metabolic effects of hypogonadism include undesirable changes in bone mineral density
 - Such patients may need endocrine monitoring¹⁸
- Confusion about dependence and addiction contributes to fears that lead to undertreatment of pain⁷

Slide 11

General Management of Opioid-Related Adverse Effects

- Expect constipation and treat preemptively
- Use preventive measures, particularly in high-risk patients
- Titrate doses slowly until pain relief is achieved
- Determine cause of symptoms (ie, opioid adverse effect or other cause)
- Consider change in regimen or route of administration to maintain steady-state blood levels
- Consider switching to another opioid (opioid rotation)
- Add medication to counteract adverse effect(s)

Fine PG, Portenoy RK. *A Clinical Guide to Opioid Analgesia*. Minneapolis, Minn: McGraw-Hill; 2004.

- Managing opioid-related adverse effects is an integral part of effective opioid pharmacotherapy
- Some general principles to follow¹⁰
 - Assume the patient will develop constipation, which is a very common side effect of opioid use, and treat it preemptively
 - Use preventive measures; think ahead, particularly in patients at higher risk for certain adverse effects
 - Titrate medication doses slowly until pain relief is achieved
 - Determine whether a symptom is caused by the opioid or some other problem
 - If a symptom results from opioid therapy, consider changing the dosing regimen or route of administration to maintain constant opioid blood levels
 - Switching to another opioid (opioid rotation) may alleviate the problem
 - Add a medication (eg, a mild stimulant, such as methylphenidate, during the day if sedation occurs) to counteract the adverse effect. Other psychostimulants are also commonly tried, and patients may react more positively to one drug over another

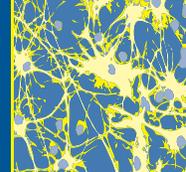
Slide 12

Managing Opioid-Related Adverse Effects

Adverse Effect	Treatment
Nausea and vomiting	Use antiemetics; switch opioids ¹
Constipation	Treat preemptively with diet and regular use of stool softeners and laxatives ²⁻⁴
Sedation	Reduce dose; add nonopioid or adjuvant analgesic; add mild stimulants ⁴
Mental clouding	Eliminate nonessential medications with central nervous system effects; consider neuroleptics for persistent delirium
Respiratory depression	Stop opioid and administer naloxone, only if strongly indicated
Pruritus	Switch opioids; use antihistamines ¹
Endocrine dysfunction/ decreased libido	Monitor endocrines; use replacement therapy, endocrine consultation ^{5,6}

1. Fine PG, Portenoy RK. *A Clinical Guide to Opioid Analgesia*. Minneapolis, Minn: McGraw-Hill; 2004. 2. AAPM/APS. *Clin J Pain*. 1997;13:6-8. 3. Pappagallo M. *Am J Surg*. 2001;182(SA suppl):11S-18S. 4. Cherny NI. CA—*Cancer J Clin*. 2000;50:70-116. 5. Abs R et al. *J Clin Endocrinol Metab*. 2000;85:2215-2222. 6. Finch PM et al. *Clin J Pain*. 2000;16:251-254.

- The adverse effects of opioid therapy can be managed as follows:
 - Nausea is generally transitory and often becomes less bothersome within a few weeks
 - Antiemetic medications may be sufficient to control nausea and vomiting¹⁰
 - Constipation should be treated preemptively with diet, stool-softening agents, and laxatives^{7,15,19}
 - Sedation is best managed with a stepwise approach⁷
 - Discontinue nonessential central nervous system medications
 - Reduce the dose of opioid by 25%
 - Add a psychostimulant (eg, methylphenidate)
 - Reassess opioid(s) being administered and consider opioid rotation, intraspinal route, or neurosurgical options
 - For patients with opioid-enhanced respiratory depression, physical stimulation may be enough to prevent significant hypoventilation
 - Pruritus can be treated with antihistamines
 - If itching continues, switching opioids may resolve the pruritus¹⁰
 - For endocrine dysfunction, consider replacement therapy and endocrine consultation^{17,20}



Slide 13

Opioid Dependence, Tolerance, Pseudoaddiction, and Addiction

What are the differences?

- **Physical dependence:** Withdrawal syndrome would occur if the medication is discontinued abruptly, dose is reduced rapidly, or an antagonist is administered^{1,2}
- **Tolerance:** A greater amount of medication is needed to maintain therapeutic effect, or loss of effect over time²
- **Pseudoaddiction:** Behavior suggestive of addiction caused by undertreatment of pain²; can be a major barrier to appropriate treatment of patients in pain
- **Addiction (psychologic dependence):** A biopsychosocial disorder characterized by continued compulsive use of a substance despite harm^{2,3}

1. APS. *Guideline for the Management of Cancer Pain in Adults and Children*. Glenview, Ill: American Pain Society; 2005.
2. Savage SR et al. *APS Consensus Statement*. Glenview, Ill: American Pain Society; 2001. 3. Fishbain DA et al. *Clin J Pain*. 1992;8:77-85.

- Opioid tolerance and physical dependence are expected physiologic adaptations to long-term opioid treatment and should not be confused with addiction (psychological dependence)
 - Misunderstanding these terms often leads to undertreatment of patients with chronic pain^{6,21}
- Physical dependence is expected in all patients who receive opioids for more than a few days⁶
- Physical dependence is manifested by a drug-class-specific withdrawal syndrome when the medication is stopped abruptly, the dose is reduced rapidly, the blood level of the medication drops, or an antagonist (eg, naloxone) is administered
 - Withdrawal can be avoided by tapering the dose of the opioid when therapy is discontinued^{6,21}
- Pseudoaddiction is a response to the patient's need for appropriate pain management
 - Pseudoaddiction may occur when a patient with severe pain that has not been managed effectively seems preoccupied with potent analgesics or is engaged in other drug-seeking behaviors.²¹ When the patient receives adequate medication, the behavior stops and the patient uses the medication as prescribed^{6,21}
- Addiction is a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors characterized by impaired control over medication use, compulsive use, continued use despite harm, and craving^{6,21}
- Physical dependence is not the same as addiction^{6,22}

Slide 14

Assessing Patients at Risk for Opioid Addiction: Screening for Substance-Abuse Potential

Predictive of Aberrant Behavior	Use Caution With
 Alcohol consumption	<ul style="list-style-type: none"> • Men who drink >4 alcoholic beverages per day or >16 per week • Women who drink >3 alcoholic beverages per day or >12 per week
 Drug use	<ul style="list-style-type: none"> • Persons who admit to recreational use of marijuana or hashish in the previous year
 Smoking Age	<ul style="list-style-type: none"> • Persons who are <40 years and smoke

Fear of abuse should not prevent adequate treatment of pain

Fine PG, Portenoy RK. *A Clinical Guide to Opioid Analgesia*. Minneapolis, Minn: McGraw-Hill; 2004.

- Clinicians who prescribe opioids must:
 - Incorporate risk assessment and, when necessary, risk management at the start of opioid therapy
 - Revisit these issues throughout the course of treatment
- Patients with a past history of substance abuse or addiction are at higher risk for opioid dependence¹⁰
- The Screening Instrument for Substance Abuse Potential is designed for use by a clinician with:
 - An established patient relationship
 - Sufficient collateral data to confirm the patient's responses
- This tool has a low false-negative rate but a fairly high false-positive rate (ie, high sensitivity and low specificity)¹⁰
- Note that screening tools are only one element of patient assessment and are not intended to "rule in or rule out" patients but rather to serve as an aid to the physician's clinical judgment

Slide 15

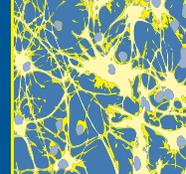
Risk Management Principles

Thorough Assessment and Appropriate Level of Monitoring

PROACTIVE STRATEGIES	REACTIVE STRATEGIES
<ul style="list-style-type: none"> • Written agreement • Long-acting drug without rescue dose • Frequent visits/limited prescription quantities/count pills at appointment • 1 pharmacy/no early refills or replacements • Require prior records/permission to contact prior providers • Referral for substance-abuse assessment for at-risk patients • Permission to get feedback from family members • Database query for electronic prescriptions 	<ul style="list-style-type: none"> • All proactive strategies • More specific written agreement • Discontinue rescue dose • Urine drug screens • Referral for substance-abuse assessment with follow-up treatment for problematic behaviors

Fine PG, Portenoy RK. *A Clinical Guide to Opioid Analgesia*. Minneapolis, Minn: McGraw-Hill; 2004.

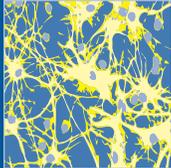
- Treatment strategies should be individualized to minimize the likelihood of misuse, abuse, addiction, or diversion; thorough assessment and an appropriate level of monitoring should reduce such outcomes¹⁰
- The clinician needs to assess the patient's level of risk of abuse and use proactive strategies; all patients taking opioids should be monitored for development of aberrant drug-related behaviors¹⁰
- If a patient engages in problematic behavior, it is important to reassess the patient to clarify the meaning of the behavior and to distinguish among addiction, pseudoaddiction, family problems, or criminal activity^{6,10}
- Proactive and reactive strategies include
 - A written agreement, which is more specific when assessing aberrant drug-related behaviors
 - Prescribing a long-acting drug without a rescue dose
 - Frequent visits, small prescription quantities, asking the patient to bring the pill bottle to appointments for a pill count
 - Using one pharmacy and allowing no early refills and no replacements without a police report documenting the loss of medication
 - Requiring all prior records of permission to contact the patient's prior healthcare providers
 - Mandatory referral to an addiction specialist when a patient is assessed to be at risk for substance abuse or behaviors suggest a potential problem
 - Mandatory permission to get feedback from spouse or family members¹⁰
 - Communicating the intention to perform a database query when using electronic prescription forms¹⁰



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20. Finch PM, Roberts LJ, Price L, Hadlow NC, Pullan PT. Hypogonadism in patients treated with intrathecal morphine. *Clin J Pain*. 2000;16:251-254.
21. Savage SR, Covington E, Heit H, Hunt J, Joranson DE, Schnoll S, eds. *Definitions Related to the Use of Opioids for the Treatment of Pain: A Consensus Document From the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine*. Glenview, Ill: American Pain Society; 2001.
22. Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. *Clin J Pain*. 1992;8:77-85.
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Slide 1



Low Back Pain

Slide 2

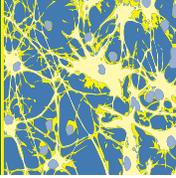
Low Back Pain: Epidemiology

- Prevalence estimates range from 7% to 33%¹
- Most common reason for workers' compensation claims²
- Total estimated US annual cost: \$25-\$50 billion³
- Widespread low back pain predicts long-term work disability⁴
- Among top 10 most costly physical health conditions for employers⁵



1. Kent, PM, Keating JL. *Chiropract Osteopath*. 2005;13:13. 2. Guo H-R et al. *Am J Public Health*. 1999;89:1029-1035. 3. Zagari MJ et al. *Pharmacoeconomics*. 1996;10:356-377. 4. Natvig B et al. *Scand J Public Health*. 2002;30:288-292. 5. Goetzel RZ et al. *J Occup Environ Med*. 2003;45:5-14.

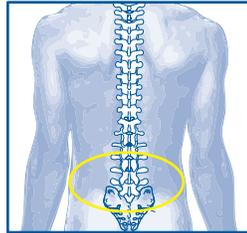
- The prevalence of low back pain is between 7% and 33% in industrialized countries, and the peak prevalence is found in patients 45 to 59 years of age¹
- Back pain is the most common reason for workers' compensation claims, accounting for about one fourth of all claims and one third of total compensation costs²
- The total annual cost for treating low back pain in the United States is estimated to be \$25 to \$50 billion³
- In a 4-year prospective study, low back pain in persons with widespread musculoskeletal pain predicted long-term work disability⁴
- A multiemployer database that links medical, prescription drug, absence, and short-term disability data at the patient level was analyzed to uncover the most costly physical and mental health conditions affecting American businesses⁵
 - Data for more than 350,000 employees from 6 large employers were analyzed
 - Low back pain was among the top 10 most costly physical health conditions



Slide 3

Etiology of Low Back Pain

- **Mechanical causes^{1,2}**
 - Overuse, trauma, physical deformity, osteoarthritis, lumbar strain or sprain, age-related degeneration of disks and facets, herniated disk, and spinal stenosis
- **Systemic causes³**
 - Inflammatory, endocrine/metabolic, blood, infectious, and neoplastic disorders
- **Pathophysiologic causes**
 - Peripheral mechanisms
 - Central mechanisms
 - Psychologic factors⁴⁻⁷

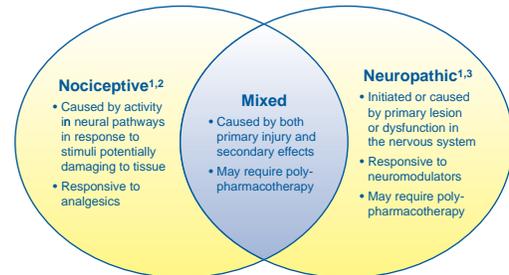


1. Cohen RI et al. *Geriatrics*. 2001;56:38-47. 2. Deyo RA, Weinstein JN. *N Engl J Med*. 2001;344:363-370. 3. Jarvik JG, Deyo RA. *Ann Intern Med*. 2002;137:586-597. 4. Andersson GB. *Lancet*. 1999;354:581-585. 5. Atkinson JH et al. *Pain*. 1991;45:111-121. 6. Leino P, Magni G. *Pain*. 1993;53:89-94. 7. Polatin PB et al. *Spine*. 1993;18:66-71.

- Low back pain can originate in the spine or it can be referred pain resulting from abdominal or visceral disease
- Low back pain is most often related to mechanical causes, including overuse, trauma, physical deformity, osteoarthritis, lumbar strain or sprain, age-related degeneration of disks, herniated disk, and spinal stenosis^{6,7}
- Low back pain can also result from systemic causes such as inflammatory, endocrine/metabolic, blood, infectious, or neoplastic disorders⁸
- The pathophysiology of low back pain involves both peripheral and central mechanisms of pain; psychological factors may also play a role⁹⁻¹²

Slide 4

Nociceptive vs Neuropathic Pain



1. International Association for the Study of Pain. IASP pain terminology. Available at: <http://www.iasp-pain.org/terms-p.html#Neuropathic%20pain>. Accessed March 9, 2006. 2. Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Co; 1996:248-276. 3. NPC/JCAHO. *Pain: Current Understanding of Assessment, Management, and Treatments*. December 2001.

- The etiology of low back pain is often complex and multifaceted
 - Low back pain may be purely nociceptive, representing a response in neural pathways to tissue-damaging stimuli such as sports or exercise injuries or internal disk disruption
 - Other causes of low back pain, such as sciatica, can be purely neuropathic
 - The majority of cases of chronic low back pain are of mixed etiology, having both nociceptive and neuropathic characteristics

Slide 5

Clinical Assessment and Diagnostic Evaluation of Low Back Pain

Proper evaluation is essential and should include

- Medical history
- Physical examination
- Neurologic examination
- Social or psychologic factors
- Neuroanatomic imaging

Deyo RA, Weinstein JN. *N Engl J Med.* 2001;344:363-370.

- A comprehensive clinical assessment and diagnostic evaluation should determine if a systemic disease is causing the pain, if there is a neurologic compromise that requires surgical evaluation, or if there is social or psychological distress
- Medical history: Clues to underlying systemic disease include the patient's age, history of cancer, unexplained weight loss, injection-medication use, chronic infection, duration of pain, presence of nighttime pain, and response to prior therapy; sciatic pain or pseudoclaudication may indicate neurologic involvement
- Physical examination: Fever (possible infection), vertebral tenderness (possible infection), limited spinal motion, and chest expansion (<2.5 cm: possible ankylosing spondylitis) should be investigated
- Neurologic examination: Ipsilateral and cross-legged/straight-leg raising tests, ankle and great toe dorsiflexion strength, plantar flexion strength, ankle and knee reflexes, and dermatomal sensory loss yield important neurologic function information
- Social/psychologic factors: Many patients with low back pain have no radiculopathy or anatomic abnormalities that explain their symptoms; antidepressant drug therapy may be useful for the one third of patients with low back pain who also have depression
- Neuroanatomic imaging: Plain radiography should be limited to patients with clinical findings suggestive of systemic disease or trauma. Computed tomography and magnetic resonance imaging are more sensitive than plain radiography for detecting early spinal infection and cancers, herniated disks, and spinal stenosis. Computed tomography and magnetic resonance imaging should be reserved for patients with a strong clinical impression of underlying infection, cancer, or persistent neurologic deficit

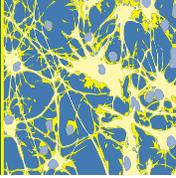
Slide 6

Treatment of Chronic Low Back Pain

- There are no evidence-based guidelines/recommendations for *chronic* low back pain
- Clinical trials have been small or have poor study design
 - Faulty randomization procedures
 - Lack of control group
 - Nonblinded assessments
- Choose treatments based on
 - Efficacy established through published multicenter, randomized, controlled studies
 - Consensus statements
- Clinical experience

Koes BW et al. *Ann Rheum Dis.* 1997;56:214-223.

- Chronic low back pain presents a challenge to clinicians
 - Whereas there are treatment guidelines for managing acute low back pain (AHCPR Guidelines for Assessment and Treatment of Acute Low Back Pain in Adults, ACP Appropriate Criteria for Acute Low Back Pain-Radiculopathy, and ICSI Healthcare Guidelines for Acute Low Back Pain), no expert organization has developed evidence-based guidelines for managing chronic low back pain^{13,14}
- In the absence of evidence-based clinical practice guidelines, clinicians may choose approaches in which efficacy has been established through published multicenter, randomized, controlled studies or through consensus statements by reputable professional groups¹³
- Clinicians often need to rely on an empiric approach to treatment, as well as clinical experience



Slide 7

General Management Principles for Low Back Pain

- Diagnose and treat the underlying disease
- Perform a comprehensive pain assessment
- Determine the best pain management approach for the type and level of pain
 - Nonpharmacologic
 - Pharmacologic (systemic and/or topical)
 - Interventional
- Provide adequate patient education



Cohen RI et al. *Geriatrics*. 2001;56:38-47.

- Diagnosis and treatment of the underlying disease and a comprehensive pain assessment will allow the clinician to determine the best management approach for the type and level of pain⁵
- Conservative treatment for low back pain includes nonpharmacologic and noninvasive therapies such as application of heat and cold, spinal manipulation, massage, and transcutaneous electrical nerve stimulation⁶
- Most patients with low back pain will need pharmacologic intervention, which may include systemic and/or topical analgesics⁵
- Some will require more invasive approaches such as trigger point injections or surgery⁵
- Patient education is an important component of treatment⁵
 - This includes recommendations for exercise, instruction for changes in daily habits, and instruction on proper nutrition

Slide 8

Nonpharmacologic Treatment Options for Low Back Pain

- Physical approaches
 - Physical therapy^{1,2}
 - Weight control³
 - Back strengthening exercises and increased physical activity^{1,3}
 - Prolonged bed rest lacks significant scientific merit⁴



1. Bogduk N. *Med J Aust*. 2004;180:79-83. 2. Cherkin DC et al. *Ann Intern Med*. 2003;138:898-906. 3. Deyo RA, Phillips WR. *Spine*. 1996;21:2826-2832. 4. Nadler SF. *J Am Osteopath Assoc*. 2004;104(suppl 8):S6-S12.

- Physical approaches to improve low back pain include physical therapy, exercise, and weight control¹⁴⁻¹⁶
- Prolonged bed rest in the treatment of low back pain is without significant scientific merit¹⁷

Slide 9

Nonpharmacologic Treatment Options for Low Back Pain

Complementary and Alternative Approaches

Approach	Effectiveness
Massage ^{1,2}	More effective than self-care educational materials, acupuncture, muscle relaxation, and remedial exercises
Spinal manipulation ^{2,3}	Minimal advantage over transcutaneous electrical nerve stimulation and massage
Transcutaneous electrical nerve stimulation ³	More advantageous than massage and acupuncture
Biofeedback ⁴	Limited evidence that it is effective for up to 3 months
Multimodal ⁵	Stress management, coping skills training, cognitive restructuring, relaxation therapy

1. Bogduk N. *Med J Aust.* 2004;180:79-83. 2. Cherkin DC et al. *Ann Intern Med.* 2003;138:898-906. 3. Cohen RI et al. *Geriatrics.* 2001;56:38-47. 4. Nielson WR, Weir R. *Clin J Pain.* 2001;17(4 suppl):S114-S127. 5. Astin JA. *Clin J Pain.* 2004;20:27-32.

- Controlled trials have shown that massage is more effective than self-care educational materials, acupuncture, muscle relaxation, and remedial exercises^{14,15}; however, compared with transcutaneous electrical nerve stimulation and manipulation therapy, massage therapy is not advantageous⁶
- Spinal manipulation has shown minimal advantage over transcutaneous electrical nerve stimulation^{6,15}
- There is limited evidence (level 3) that electromyogram feedback is effective for chronic low back pain for up to 3 months¹⁸
- Although acupuncture may relieve chronic low back pain, no evidence suggests that acupuncture is more effective than other active therapies. More research is needed¹⁹
- Based on evidence from randomized controlled trials, multicomponent mind-body approaches that include some combination of stress management, coping skills training, cognitive restructuring, and relaxation therapy may be an appropriate adjunctive treatment for chronic low back pain²⁰
- Complementary therapies include massage, spinal manipulation, and transcutaneous electrical nerve stimulation

Slide 10

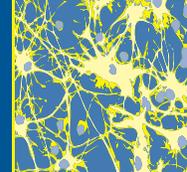
Pharmacologic Treatment Options for Low Back Pain

Drug Type	Use/Benefit	Examples
Nonsteroidal anti-inflammatory drugs ¹	• Short-term benefit	Celecoxib, naproxen, ibuprofen, diclofenac
Opioids ¹⁻⁴	• Average effect ≤ 10 -pt reduction on 100-pt scale	Codeine, morphine, oxycodone
Anticonvulsants ²	• Successful in neuropathic pain • Safe in patients taking multiple medications or at risk for drug interactions	Gabapentin, pregabalin, lamotrigine
Antidepressants ² (tricyclics, SSRIs, SNRIs) ²	• Dose range significantly less than for treating depression	Amitriptyline, desipramine, fluoxetine, paroxetine
Muscle relaxants ²	• Acute period	Cyclobenzaprine, carisoprodol
Topical analgesics ⁴	• Low risk of systemic effects and drug interactions	Lidocaine patch 5%, topical NSAIDs (eg, diclofenac, ibuprofen)

SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor; NSAID=nonsteroidal anti-inflammatory drug.

1. Bogduk N. *Med J Aust.* 2004;180:79-83. 2. Cohen RI et al. *Geriatrics.* 2001;56:38-47. 3. Jamison RN et al. *Spine.* 1998;23:2591-2600. 4. Argoff CE. *Curr Pain Headache Rep.* 2004;8:261-267.

- Effective options for the treatment of low back pain are listed here
- Nonsteroidal anti-inflammatory drugs (NSAIDs) may be of short-term benefit for low back pain.¹⁴ Studies have demonstrated an increase in pain relief; however, the use of NSAIDs has been called into question because of the withdrawal of rofecoxib and valdecoxib, both cyclooxygenase-2-selective NSAIDs, from the market due to their adverse cardiovascular event profile. Celecoxib also may be associated with negative cardiovascular effects. The Food and Drug Administration has asked manufacturers of all NSAIDs to revise their labeling to include a boxed warning highlighting the potential for increased risk of cardiovascular and gastrointestinal events²¹
- Opioids are more effective than naproxen or placebo for relieving chronic low back pain,²² but the average effect is not more than a 10-point reduction on a 100-point scale¹⁴
- It has been recommended that opioids have a role in the treatment of low back pain when other treatments have failed. They should be prescribed as part of a multimodal and, ideally, interdisciplinary treatment plan²³
- Anticonvulsants have been used successfully for the management of neuropathic pain. Gabapentin, which is approved for treatment of postherpetic neuropathy, has been used successfully for treating low back pain.⁶ Because gabapentin is neither hepatically metabolized nor protein-bound, it is relatively safe for older patients who are taking multiple medications and are at risk for drug interactions⁶
- Tricyclic antidepressants such as amitriptyline appear to have analgesic efficacy for low back pain; the dose range for analgesia may be significantly less than that required to treat depression⁶
- A muscle relaxant such as cyclobenzaprine is often useful in the acute period⁶
- Topical analgesics such as the lidocaine patch 5% or a topical NSAID can be applied locally to the peripheral site of the pain. Topical analgesics have a lower risk of systemic side effects and drug interactions than do orally administered agents, and they may be particularly suited to peripherally generated pain²⁴



Slide 11

Invasive Treatments for Low Back Pain

← Minimally Invasive Most Invasive →

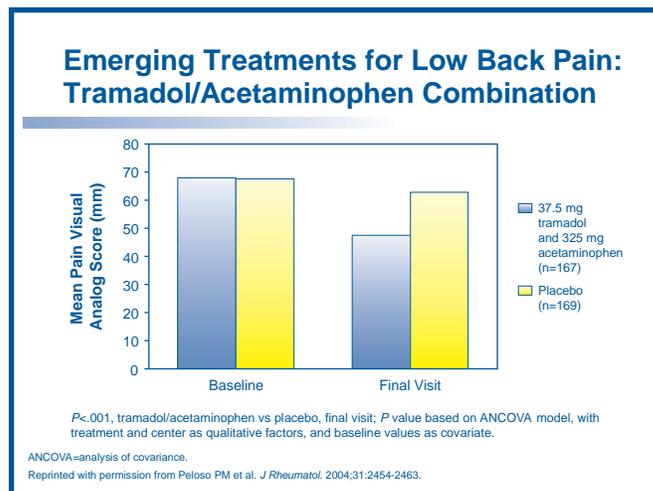
Minimally Invasive	Most Invasive
<ul style="list-style-type: none"> • Acupuncture^{1,2} • Injections <ul style="list-style-type: none"> – Trigger points² – Botulinum toxin type A³⁻⁵ – Facet/SI joints² – Epidurals – Selective nerve root 	<ul style="list-style-type: none"> • Rhizotomy • Fusion/instrumentation² • Spinal cord stimulation^{2,4} • Intrathecal infusion • Annuloplasty (IDET)⁴ • Percutaneous discectomy (nucleoplasty)² • Vertebroplasty

SI=sacroiliac; IDET=intradiskal electrothermal therapy.

1. Cherkin DC et al. *Ann Intern Med.* 2003;138:898-906. 2. Cohen RI et al. *Geriatrics.* 2001;56:39-47. 3. Thant Z-S, Tan E-K. *Med Sci Monit.* 2003;9:RA40-RA48. 4. Bogduk N. *Med J Aust.* 2004;180:79-83. 5. Foster L et al. *Neurology.* 2001;56:1290-1293.

- After traditional methods and noninvasive treatments have been tried and found not to provide adequate relief, invasive treatments such as injections may provide relief^{6,15}
- Invasive modalities are beneficial only for specific diagnoses and should be used for selected patients
- Procedural therapies may include trigger point, epidural, and facet injection of a local anesthetic and/or a depo-steroid injection⁶
- Prolotherapy (injection of sclerosing agents into tender ligaments) has shown mixed results and may be no more effective than placebo¹⁴
- Botulinum toxin is more effective than placebo at 8 weeks, but no long-term studies have been conducted^{14,25,26}
- Patients with a structural or mechanical cause of pain (eg, herniated disk or nerve compression due to foraminal encroachment) may benefit from surgery⁶
- Partial pain relief lasting 3 years has been demonstrated with spinal cord stimulation⁶
- Decompressive laminectomy can be a good option for severe symptoms caused by spinal stenosis⁶
 - Medication may be effective for treating the pain associated with spinal stenosis; however, medication cannot reverse the loss of proprioception and strength associated with this condition⁶
- Discectomy for herniated intervertebral disks appears to have initial benefit, but a clear advantage cannot be demonstrated 10 years postoperatively⁶
- With intradiskal electrothermal therapy, the fissures of a painful disk are coagulated percutaneously with flexible electrodes introduced into the disk; complete pain relief sustained for 2 years occurs in about 20% of patients, and an additional 30% obtain >50% relief, enabling them to return to work¹⁴

Slide 12

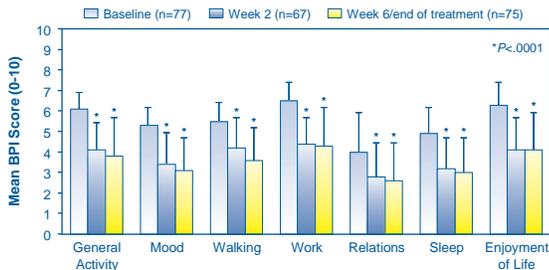


- Although there are not many well-controlled trials, there is empiric evidence for the effectiveness of opioids for low back pain
- Emerging treatments in pharmacologic management include the use of new combinations of older medications, for example, ibuprofen plus hydrocodone and acetaminophen plus tramadol
- When opioids are combined with other pain-relief agents such as acetaminophen²⁷:
 - The combination may provide better pain relief than either agent alone
 - A lower dose of each medicine may be used for effective pain relief
- Two double-blind, randomized, placebo-controlled studies in the United States and Canada looked at the efficacy and safety of the opioid combination tramadol/acetaminophen for chronic low back pain. Patients with moderate, chronic low back pain had a 3-week analgesic washout period, then were randomized to either tramadol/acetaminophen or placebo for 91 days. By day 10, patients had been titrated to 4 tablets/d of tramadol 37.5 mg and acetaminophen 325 mg^{28,29}
 - Pooled study results for 654 patients found that patients taking tramadol/acetaminophen scored significantly better than placebo on pain rating scales (*P* < .001)^{28,29}
 - Cumulative discontinuation rates due to insufficient pain relief were significantly better for tramadol/acetaminophen than for placebo (*P* < .001)^{28,29}
- The most common treatment-limiting adverse effects were nausea and dizziness

Slide 13

Emerging Treatments for Low Back Pain: Lidocaine Patch 5% Add-On Therapy

QOL Interference Indicators for Chronic Low Back Pain



QOL=quality of life; BPI=Brief Pain Inventory.
Reprinted with permission from Gimbel J et al. *Am J Ther.* 2005;12:311-319.

- A 6-week, prospective, multicenter, nonrandomized pilot study was conducted to evaluate the efficacy and safety of the lidocaine patch 5% in patients with moderate to severe low back pain (subacute, acute, short-term, and long-term chronic)³⁰
- Patients applied ≤ 4 patches as add-on therapy once daily to the area of maximal low back pain through week 2, with the option to taper concomitant analgesics during weeks 3 to 6
- Using the Brief Pain Inventory, significant decreases in pain intensity were seen at weeks 2 and 6 ($P \leq .001$), and significant improvements in pain interference with function were noted for all Brief Pain Inventory measures of quality of life at weeks 2 and 6 for acute and subacute ($P \leq .007$) and long-term chronic ($P < .0001$) low back pain groups
- Fifty-eight percent of patients reported being satisfied or very satisfied with the treatment
 - The patches were well tolerated; common adverse events were dizziness and rash (n=5; 3.8%); most adverse events were mild to moderate in intensity

Slide 14

Emerging Treatments for Low Back Pain: Opioids

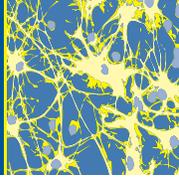
• Transdermal fentanyl

- Study of impact on functional disability (n=122)¹
 - Significant improvements on Oswestry Disability Index and numeric rating scale of pain intensity*
- Transdermal fentanyl vs oral morphine (n=680)²
 - Provided comparable pain relief with similar adverse event rates
 - Mean composite pain relief/constipation scores were significantly better for transdermal fentanyl†



*P<.001 for both. †P=.028.
1. Brennan M et al. *J Pain.* 2004;5(suppl 1):74. Abstract 864. 2. Allan L, Kalso E. *J Pain.* 2004;5(suppl 1):69. Abstract 844.

- Transdermal fentanyl is a synthetic opioid with short-acting analgesic activity delivered via a skin patch system to release medication systemically at a constant rate³¹
- One study of transdermal fentanyl measured its impact on the functional disability of 122 patients³²
 - This observational, naturalistic study at 17 US clinical centers measured patient responses on the Oswestry Disability Index, and with a numeric rating scale of pain intensity at baseline and after a minimum of 9 weeks of treatment
- High baseline disability scores showed moderate improvement at follow-up ($P < .001$), meeting the criteria for a clinically significant improvement in functioning; pain intensity scores also showed clinically significant improvement ($P < .001$)³²
- In another study that compared transdermal fentanyl with oral morphine, both treatments provided comparable pain relief; however, mean composite pain relief/constipation scores were significantly better for transdermal fentanyl than for oral morphine³³
 - This is a significant improvement since a common side effect of opioids is constipation



Slide 15

Emerging Treatment for Low Back Pain: Botulinum Toxin Type A

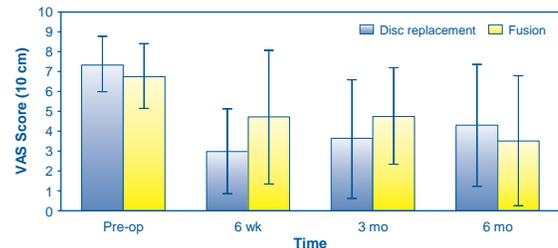
- **Randomized, double-blind, placebo-controlled trial¹**
 - N=31 (15 men, 16 women)
 - Age ≥18 years
 - 3 weeks (VAS): 73.3% had >50% pain relief vs placebo ($P=.012$)
 - 8 weeks (VAS): 60% had relief vs placebo ($P=.009$)
 - 8 weeks (OLBPQ): 66.7% were improved ($P=.011$)
- **2 retrospective analyses**
 - BTX-A appeared to be effective in patients with significant, long-term LBP who failed surgery and other modalities²
 - BTX-A appeared to be efficacious for patients with highly refractory chronic LBP³
- **Small number of patients in studies; further studies warranted**

VAS=Visual Analog Scale; OLBPQ=Oswestry Low Back Pain Questionnaire; BTX-A=botulinum toxin type A; LBP=low back pain.
 1. Foster L et al. *Neurology*. 2001;56:1290-1293. 2. Edwards K, Dreyer M. *J Pain*. 2004;5(suppl 1):63. Abstract 817.
 3. Edwards K, Dreyer M. *J Pain*. 2003;4(suppl 1):28. Abstract 710.

- In a study by Foster and colleagues of patients with chronic low back pain, 15 patients received 200 units of botulinum toxin type A, 40 units/site, and 16 patients received normal saline²⁶
 - Pain and disability were documented using the Visual Analog Scale and the Oswestry Low Back Pain Questionnaire²⁶
 - Evaluations took place at 3 and 8 weeks (Visual Analog Scale) and 8 weeks (Oswestry Low Back Pain Questionnaire)
 - At 3 weeks, 11 of 15 patients who received botulinum toxin type A (73.3%) had >50% pain relief versus 4 of 16 patients (25%) in the saline group ($P=.012$)
 - At 8 weeks, 9 of 15 patients (60%) and 2 of 16 (12.5%) had relief ($P=.009$) in the botulinum toxin type A and placebo groups, respectively
 - Repeat Oswestry Low Back Pain Questionnaire assessments at 8 weeks showed improvement in 10 of 15 patients (66.7%) in the botulinum toxin type A group versus 3 of 16 patients (18.8%) in the saline group ($P=.011$)
- In a retrospective chart review of 17 patients treated with botulinum toxin type A, reductions in pain using the Visual Analog Scale, McGill Short Form, and Present Pain Intensity were shown³⁴
 - Botulinum toxin type A appeared to be effective in patients with significant, long-term low back pain who failed surgery and other modalities
- A second retrospective analysis of 12 patients treated with botulinum toxin type A also showed reductions using the Visual Analog Scale, McGill Short Form, and Present Pain Intensity³⁵
 - Botulinum toxin A appeared to be efficacious for patients with highly refractory chronic low back pain
- Although results are promising, additional studies are warranted

Slide 16

Emerging Treatments for Low Back Pain: Lumbar Disk Replacement



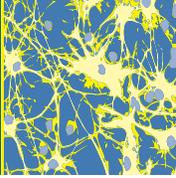
Mean and standard deviations of pain as measured by the VAS for patients treated with artificial disk compared with those treated with fusion procedure. Patients reported less initial pain and disability with artificial disk replacement, but differences disappeared by 6 months.

VAS=Visual Analog Scale.
 Reprinted with permission from Delamarter R et al. *Spine*. 2003;28:S167-S175.

- The standard of care for low back pain refractory to nonsurgical treatments such as rest, heat, medications, and physiotherapy has been spinal fusion³⁶
 - Problems associated with this approach include donor-site morbidity, pseudoarthrosis, degeneration at disks adjacent to the surgery, and loss of movement at one or more levels^{36,37}
- An artificial lumbar disk was developed by Thierry Marnay in the late 1980s³⁶; the Food and Drug Administration approved an investigational device exemption to study its efficacy and safety
- Compared with spinal fusion surgery, artificial disk replacement has resulted in³⁶:
 - Significant early reduction in pain and disability following surgery ($P<.05$)
 - Greater motion at vertebral segments L4-L5 ($P<.05$)
- Lumbar disk replacement allows for significantly greater motion, which exerts a protective effect, reducing the risk of adjacent segment disease and further surgeries^{36,37}

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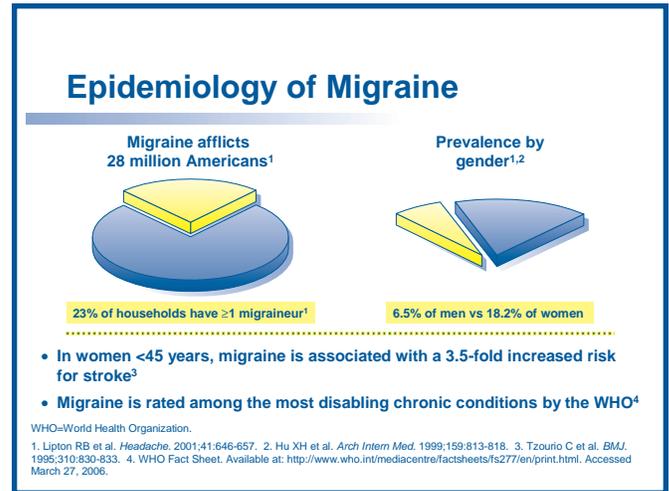
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Slide 1



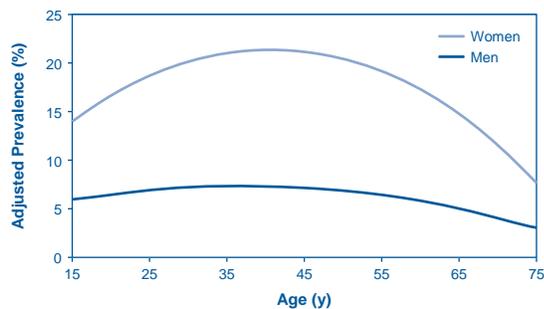
Slide 2



- Migraine is a common affliction, affecting 28 million Americans¹
- About 1 in 4 households has a member who suffers from migraine¹
- 6.5% of men and 18.2% of women suffer from migraine pain^{1,2}
- In women <45 years of age, migraine is associated with a 3.5-fold increased risk for stroke³
- The World Health Organization lists severe migraine among the most disabling chronic conditions⁴

Slide 3

Prevalence of Migraine Peaks in Reproductive Years



Reprinted with permission from Current Medicine, Philadelphia. Bigal ME et al. *Curr Neurol Neurosci Rep.* 2004;4:98-104.

- Although both men and women are affected by migraines, women experience them more frequently⁵
- This graph from a meta-analysis of migraine prevalence studies shows the increase of migraine prevalence in men and women until approximately age 40 years, after which it declines⁵
- Researchers are unclear as to the causes of decline after age 40 years, but it is believed to be a combination of factors including hormonal fluctuation (particularly estrogen), lifestyle, sociodemographic factors, and gender-based issues

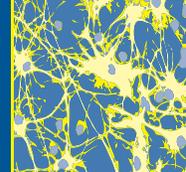
Slide 4

Societal Impact of Migraine

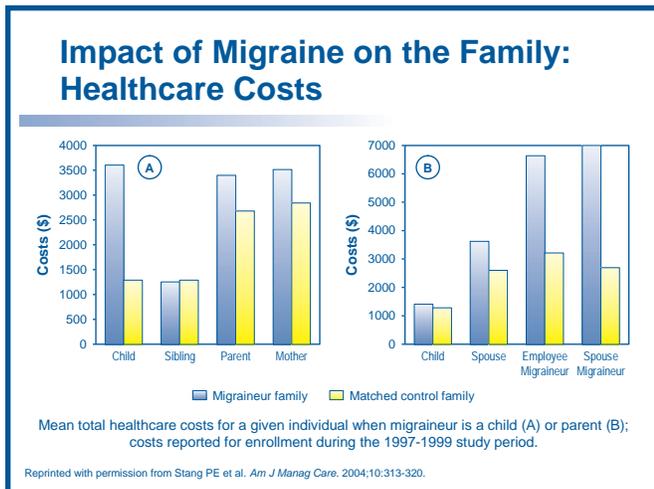
- **Migraine impairs ability to perform daily activities**
 - 53% of migraineurs reported substantial impairment in daily activities and may have required bed rest¹
 - Decreased work/school productivity¹
 - Increased work-related disability
 - 31% miss ≥ 1 day of work or school because of migraine in a 3-month period¹
- **Migraine-related absenteeism and reduced productivity**
 - \$13 billion per year²
 - 68.9 million lost workdays²
- **>\$1 billion in annual US healthcare costs²**

1. Lipton RB et al. *Headache.* 2001;41:646-657. 2. Hu XH et al. *Arch Intern Med.* 1999;159:813-818.

- Patients suffering with migraines experience a diminished quality of life
 - More than half (53%) of patients reported a substantial impairment in daily activities and may have required bed rest¹
 - Almost one third (31%) reported ≥ 1 day of work or school missed because of migraine¹
- The economic impact of migraine is significant, with an estimated cost of \$13 billion per year and 68.9 million lost workdays²
- Migraine pain has resulted in more than \$1 billion in annual healthcare costs in the United States²



Slide 5



- Stang et al investigated the impact of migraine on families⁶
 - A migraine case was defined as any subject having an *International Classification of Diseases, Ninth Revision* diagnosis code for migraine (346.xx) or a pharmaceutical claim for an ergot, a triptan, or isometheptene
 - Nonmigraineurs were matched to migraineurs in up to a 3:1 ratio on employer, age (5-year bands), number of family members, sex, and index date quarter
- Total healthcare costs of a family with a migraineur were 70% higher than those of the nonmigraine family⁶
 - Most of the difference occurred in outpatient and pharmacy costs⁶
- Comparing families with migraineurs, total healthcare costs for the family were about \$600 higher when the migraineur was a child versus a parent, and almost \$2500 higher when both a parent and a child were affected⁶

Slide 6

Migraine Headache: Etiology

- **Migraine is a paroxysmal neurologic disorder¹**
- **Inflammation and blood vessel changes²**
- **Possibly influenced by serotonin²**
- **Genetic component**
 - Migraine chromosomes have been discovered^{1,3,4}
 - Tendency to inherit a "sensitive" brain²
- **Two main types¹**
 - Migraine without aura: "common migraine"⁵
 - 4 subtypes
 - Migraine with aura: transient focal neurologic symptoms (usually visual)⁶
 - About 30% of migraineurs¹

1. Sandor PS et al. *Headache.* 2002;42:365-377. 2. Gallagher RM, Cutrer FM. *Am J Manag Care.* 2002;8(3 suppl):S58-S73. 3. Joutel A et al. *Nat Genet.* 1993;5:40-45. 4. Ophoff RA et al. *Histol Histopathol.* 1998;13:827-836. 5. IHS. *Cephalalgia.* 2004;24(suppl 1):9-160. 6. Breslau N, Rasmussen BK. *Neurology.* 2001;56(6 suppl 1):S4-S12.

- Migraine is a common, chronic, incapacitating neurovascular disorder characterized by episodic attacks of headache commonly associated with nausea, vomiting, photophobia, phonophobia, and aura⁷⁻⁹
- Research suggests that migraines are produced by abnormalities in central nervous system regulation of blood vessels^{7,9}
- Migraine headaches are believed to have a hereditary component⁸; genes have been identified for some types of migraine^{9,10}
- Migraines are defined as those with aura and those without aura^{7,11}; auras are focal neurologic (usually visual) symptoms that precede migraine and are reported by about 30% of migraineurs¹²

Slide 7

Migraine-Associated Comorbidity: Ischemic Stroke

- Increased risk (2.16) for ischemic stroke among individuals with all types of migraine (95% CI, 1.89 to 2.48)¹
- In migraine without aura, risk was 1.83 (95% CI, 1.06 to 3.5)¹
- Among women taking oral contraceptives, risk was 8-fold higher than for others¹
- Women <45 years with migraine have a 3.5-fold greater risk for stroke than those without migraine²

CI=confidence interval.

1. Etminan M et al. *BMJ*. 2005;330:63. 2. Tzourio C et al. *BMJ*. 1995;310:830-833.

- There appears to be an independent association between migraine and increased risk for ischemic stroke^{3,13}
- In a meta-analysis conducted by Etminan et al, there was an increased risk for ischemic stroke among individuals with all types of migraine (relative risk [RR], 2.16; 95% confidence interval [CI], 1.89 to 2.48)¹³
- In patients with migraine without aura, RR was 1.83 (95% CI, 1.06 to 3.5)¹³
- Women taking oral contraceptives had an 8-fold higher risk than others¹³
- Tzourio et al found that women with migraine aged <45 years have a 3.5-fold greater risk for stroke than those without migraine³

Slide 8

Diagnostic Criteria for Migraine Without Aura

General Diagnostic Criteria

- 5 attacks lasting 4-72 hours treated or unsuccessfully treated

• At least 2 characteristics

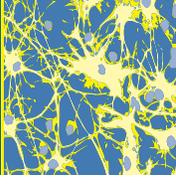
- Unilateral location
- Pulsating quality
- Moderate to severe pain intensity
- Aggravation by routine physical activity

• At least 2 during headache

- Nausea
- Vomiting
- Photophobia and phonophobia
- Osmophobia

IHS. *Cephalalgia*. 2004;24(suppl 1):9-160.

- Optimal management of patients with migraine involves first establishing the diagnosis, which is frequently missed¹⁴
- General diagnostic criteria for migraine without aura include experiencing at least 5 attacks, each lasting between 4 and 72 hours, with at least 2 of the following characteristics¹¹:
 - Unilateral location
 - Pulsating quality
 - Moderate to severe pain intensity
 - Aggravation by routine physical activity
- Also, at least 2 of the following will be occurring during the headache¹¹:
 - Nausea
 - Vomiting
 - Photophobia (extreme sensitivity to light) and phonophobia (extreme sensitivity to sound)
 - Osmophobia (aversion to odors or smells)



Slide 9

Diagnostic Criteria for Migraine Without Aura (cont)

Subtype Criteria

- **Pure menstrual migraine**

- Day 1 \pm 2 of menstruation
- 2 out of 3 menstrual cycles
- Occurs no other times of month

- **Menstrually related**

- Day 1 \pm 2 of menstruation
- 2 out of 3 menstrual cycles
- Also occurs other times of month

- **Nonmenstrual migraine**

- In a menstruating woman
- No menstrual relationship

IHS. *Cephalalgia*. 2004;24(suppl 1):9-160.

- Pure menstrual migraine occurs on Day 1 (plus or minus 2 days) of menstruation, in 2 out of 3 menstrual cycles, but does not occur at any other times during the month¹¹
- Menstrually related migraine occurs during the perimenstrual period and also at other times during the month¹¹
- Nonmenstrual migraine without aura may occur during menstruation but does not fit the International Headache Society criteria for pure menstrual or menstrually related migraine without aura¹¹

Slide 10

Diagnostic Criteria for Migraine With Aura



General Diagnostic Criteria

- **Aura: recurrent, focal neurologic symptoms develop 5-20 minutes before or at onset of headache and last <60 minutes**
- **Followed by features of migraine without aura**

IHS. *Cephalalgia*. 2004;24(suppl 1):9-160.

Aura picture reprinted with permission: Migraine Action Association and Boehringer Ingelheim.

- The criteria for migraine with aura include¹¹:
 - Focal neurologic symptoms that develop 5 to 20 minutes before or at onset of headache and last <60 minutes
 - All those for basic migraine without aura

Slide 11

Premonitory Signs vs Aura

Premonitory Signs	Aura
Occur over hours or days before headache onset	Symptoms develop 5-20 minutes before or at the onset of headache and last <60 minutes
Fatigue, difficulty in concentrating, repetitive yawning, neck stiffness, sensitivity to light/sound, nausea, blurred vision, pallor	Reversible focal neurologic symptoms (eg, visual symptoms such as flickering lights, spots, or loss of vision)
Can occur with or without aura	Visual auras may be accompanied by symptoms in the extremities (eg, numbness, "pins and needles")

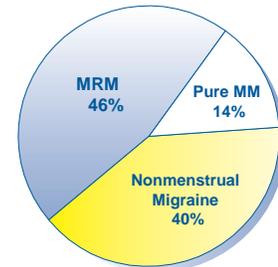
IHS. *Cephalalgia*. 2004;24(suppl 1):9-160.

- Some patients experience a premonitory phase, which can occur hours or days before a headache; the headache might also be followed by a similar resolution phase¹¹
- In the aura phase, symptoms develop 5 to 20 minutes prior to the onset of headache and usually last <60 minutes¹¹
- Premonitory symptoms include fatigue, difficulty in concentrating, repetitive yawning, neck stiffness, sensitivity to light/sound, nausea, blurred vision, and pallor¹¹
 - The premonitory phase can occur in migraines with and without aura
- In migraine with aura, there are reversible focal neurologic symptoms, such as visual symptoms of flickering lights, spots, or loss of vision¹¹
- Premonitory symptoms and aura are distinct features associated with the onset of migraine¹¹
- Many people who have migraine with aura also may experience migraine without aura¹¹

Slide 12

Migraine Classification in Women

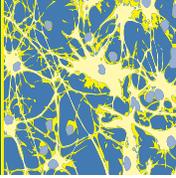
- **60% menstrual migraine**
 - 14% pure MM
 - 46% MRM
- **40% nonmenstrual migraine**



Female Migraineurs

MM=menstrual migraine; MRM=menstrually related migraine.
Mannix LK, Calhoun AH. *Curr Treat Options Neurol*. 2004;6:489-498.

- Approximately 60% of migraines experienced by women are menstrual migraines¹⁵
 - Of those 60%, 14% are considered to be pure menstrual migraine; the other 46% are considered menstrually related migraines



Slide 13

Characteristics of Menstrual Migraine

- Migraine without aura
- Severe intensity
- Long duration (≤ 72 hours)
- High recurrence rate
- Increased work-related disability
- Predictable timing



Allais G, Benedetto C. *Neurof Sci*. 2004;25(suppl 3):S229-S231.

- The characteristics of menstrual migraine include¹⁶:
 - Migraine without aura
 - Severe intensity
 - Long duration (≤ 72 hours)
 - High rate of recurrence
 - Increased work-related disability
 - Predictable timing

Slide 14

Evaluation of Menstrual Migraine

- Patient diaries are an effective tool to aid in diagnosis and can track
 - Frequency and onset
 - Menstrual cycle
 - Triggers in addition to menses
 - Response to current management



MacGregor EA, Hackshaw A. *Neurology*. 2004;63:351-353.

- When diagnosing patients with menstrual migraine, clinicians should recognize the importance of patient diaries in ensuring proper diagnosis

Slide 15

Menstrual Migraine Treatment Options

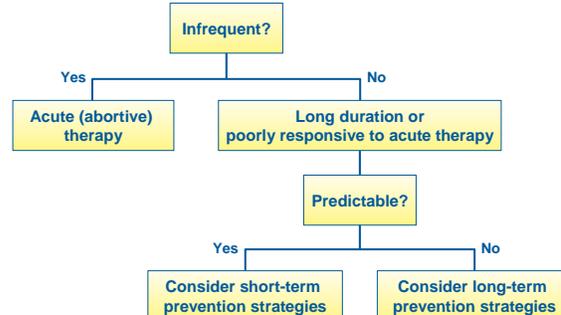
- **Acute treatment**
 - Aimed at treatment of pain after headache begins
- **Short-term prevention**
 - For patients to prevent migraine typically associated with the menstrual cycle (predictable)
- **Long-term continuous prevention**
 - Aimed at preventing the onset of pain
 - Ongoing prevention may be used for patients in whom migraine is frequent but not predictable or for patients with concomitant medical conditions

Martin VT. *Curr Pain Headache Rep.* 2004;8:229-237.

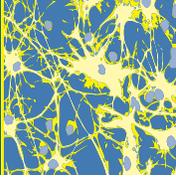
- Acute treatment is used to treat a patient after migraine has already begun¹⁷
- Short-term prevention is used to preemptively prevent a migraine from occurring¹⁷
 - Can be used when migraines occur in a regular, predictable cycle, such as with menstrual migraine
 - Treatment is begun a few days before the anticipated migraine attack
- Long-term continuous prevention is also used to preemptively prevent a migraine from occurring¹⁷
 - It is used for preventing migraines that occur throughout the cycle
 - It is also used for migraine patients with concomitant medical conditions

Slide 16

Migraine Pharmacologic Treatment



- Choosing the correct treatment plan depends on the frequency and predictability of migraines
- If migraines are infrequent, acute therapy is the usual treatment
- If migraines occur frequently, preventive strategies may be used
 - Short-term preventive therapies may be used when migraine occurrence is predictable
 - Menstrual migraines may benefit from short-term treatments
 - Long-term preventive strategies may be used when migraines occur frequently, but their occurrence is not predictable



Slide 17

Benefits of Early Migraine Treatment

- Reduced need for medication
- Reduced exposure to potential adverse events
- Reduced recurrence rates
- Reduced functional disability
- Reduced medical costs
- Faster resolution of pain

Landy SH, Lobo BL. *Expert Rev Neurother*. 2005;5:343-353. Lainez M. *Cephalalgia*. 2004;24(suppl 2):24-30.

- Evidence supports the benefits of early (soon after migraine begins) treatment for migraine pain^{18,19}
- When patients are treated soon after a migraine begins, they experience:
 - Faster resolution of pain
 - Less need for medication
 - Less exposure to potential adverse events
 - Lower recurrence rates
 - Reduced functional disability
 - Reduced medical costs

Slide 18

Overview of Acute Drug Therapy



- **Migraine-specific treatments**
 - Ergotamine, dihydroergotamine, triptans
- **Nonspecific treatments**
 - Aspirin, acetaminophen, NSAIDs, opiates, combination analgesics

NSAIDs=nonsteroidal anti-inflammatory drugs.

- Migraine-specific agents include dihydroergotamine, ergotamine, and triptans
- Common nonspecific treatments include aspirin, acetaminophen, nonsteroidal anti-inflammatory drugs, opiates, and combination analgesics

Slide 19

Emerging Concept: Short-term Prevention of Menstrual Migraine

- Agents tested in randomized clinical trials for short-term prevention

- Estrogen
- Triptans
 - Frovatriptan
 - Naratriptan
 - Sumatriptan
 - Zolmitriptan
- Naproxen sodium
- Magnesium

- A number of agents have been examined for short-term preventive treatment of menstrual migraine, including magnesium, naproxen sodium, triptans, and hormonal treatments (eg, estradiol gel or estradiol patch)
- This treatment approach targets the predictability of menstrual migraine by providing prophylactic therapy within the period of time that migraine is most likely to occur
- The benefits include a reduced exposure to medications and related side effects, as well as a reduced cost

Slide 20

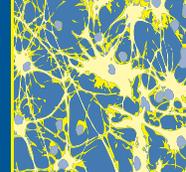
Short-term Prevention of MM: Naproxen Sodium

- Naproxen sodium versus placebo (N=40)

- Day -7 to day +6 (start of menses=day 1)
- Reduced headache intensity and duration, number of headache days
- 33% were headache free (none with placebo)

MM=menstrual migraine.
Sances G et al. *Headache*. 1990;30:705-709.

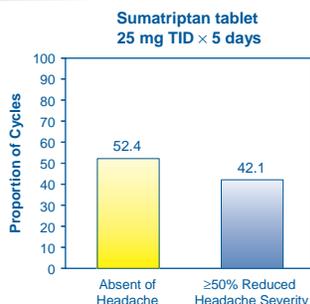
- The efficacy of naproxen sodium was tested in the prophylaxis of menstrual migraine²⁰
- Forty women suffering from menstrual migraine were admitted to a double-blind treatment protocol with naproxen sodium 550 mg twice each day by mouth or placebo for 3 months²⁰
 - In the following 3 months, all the women were treated with the active drug in an open study
- Headache intensity and duration, as well as the number of days of headache and the analgesic consumption, were reduced with naproxen sodium compared with placebo²⁰



Slide 21

Short-term Prevention of MM: Sumatriptan

- Open-label pilot study
 - Day -2 or day -3 before onset of treatment
- 20 patients treated for ≥ 1 cycle; median, 6 cycles
- 126 menstrual cycles treated



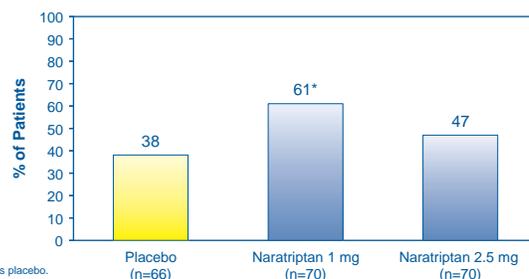
MM=menstrual migraine.
Newman LC et al. *Neurology*. 1998;51:307-309.

- This study was the first to examine whether triptans could be used for the short-term prevention of menstrual migraine²¹
- In this open-label study, oral sumatriptan (25 mg TID for 5 days) was administered premenstrually for use in short-term preventive therapy of menstrual migraine²¹
- 20 patients were treated for a total of 126 menstrual cycles²¹
- Study results reported headache was absent in 52.4% (66 of 126) of treated menstrual cycles and reduced in severity by $\geq 50\%$ in 42.1% (53 of 126) of treated cycles²¹
- Breakthrough headaches were rare and significantly reduced in severity compared with baseline headaches²¹

Slide 22

Short-term Prevention of MM: Naratriptan

Patients With $\leq 50\%$ Reduction in Perimenstrual Periods With Headache

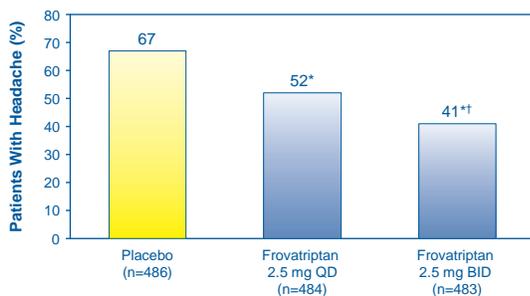


*P<.05 vs placebo.
MM=menstrual migraine.
Includes patients treating at least 1 perimenstrual period.
Newman L et al. *Headache*. 2001;41:248-256.

- A randomized, double-blind, parallel-group, placebo-controlled study was conducted in women (>18 years) with a history of migraine with or without aura of at least 6 months²²
- Two strengths of naratriptan (1 mg, 2.5 mg) or a placebo were administered BID for 5 days starting 2 days prior to the expected onset of menses. The primary endpoint was number of menstrually associated migraines²²
- Significantly more patients treated with naratriptan 1 mg reported menstrually associated migraine in 50% or less of their treated perimenstrual periods compared with the placebo-treated patients²²
- The researchers concluded that naratriptan 1 mg was an effective short-term, prophylactic treatment for menstrually associated migraine²²

Slide 23

Short-term Prevention of MM: Frovatriptan



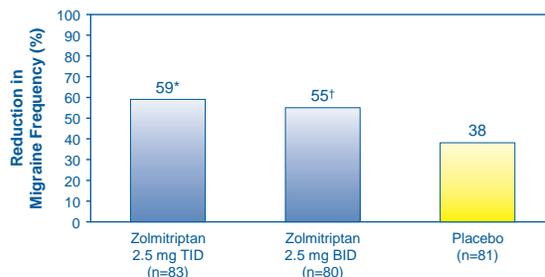
* $P < .0001$ vs placebo; † $P < .001$ vs 2.5 mg QD.
MM=menstrual migraine.
Silberstein SD et al. *Neurology*. 2004;63:261-269.

- Silberstein et al conducted a randomized, double-blind, placebo-controlled, 3-way crossover study in 546 women (mean age, 37.6 years)²³
 - Patients were treated during each of 3 perimenstrual periods with placebo, frovatriptan 2.5 mg QD, or frovatriptan 2.5 mg BID
- The 6-day treatment started 2 days before the anticipated start of menstrual migraine²³
 - Patients maintained a headache diary to identify the dates on which their menstrual migraine should occur
 - As this date varied among the patients, dosing could commence from day -4 to day +2 relative to the onset of menstruation
- The study demonstrated that use of frovatriptan reduced the occurrence of menstrually associated migraine headache²³
 - The incidence of migraine during the 6-day perimenstrual period was 67% for placebo, 52% for frovatriptan 2.5 mg QD, and 41% for frovatriptan 2.5 mg BID
 - Both frovatriptan regimens were superior to placebo ($P < .001$)
- The incidence and type of adverse events for both regimens were similar to those for placebo and consistent with those reported for short-term migraine management²³
- The researchers concluded that frovatriptan given prophylactically for 6 days during the perimenstrual period significantly reduced the incidence of menstrually associated migraine ($P < .0001$)²³

Slide 24

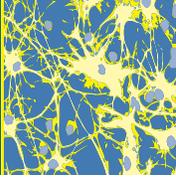
Short-term Prevention of MM: Zolmitriptan

Patients With $\geq 50\%$ Reduction in Perimenstrual Periods With Headache



* $P = .0007$; † $P = .002$ vs placebo.
MM=menstrual migraine.
Tuchman M et al. *Headache*. 2005;45:771-772.

- Tuchman et al conducted a multicenter randomized, double-blind, parallel-group, placebo-controlled trial in 244 women²⁴
- Two dosages of zolmitriptan (2.5 mg TID, 2.5 mg BID) or a placebo TID were administered²⁴
- Patients were treated for 3 consecutive cycles, started treatment 2 days prior to the expected onset of menses, and continued treatment for a total of 7 days per cycle²⁴
- The primary endpoint was the percentage of patients with a $\geq 50\%$ reduction in frequency and mean number of menstrual migraine headaches²⁴
- Researchers concluded that zolmitriptan 2.5 mg (TID $P = .0007$ or BID $P = .002$) showed superior efficacy to placebo in achieving a $\geq 50\%$ reduction in the frequency of menstrual migraine headaches²⁴



Slide 25

Migraine Pharmacotherapy: Long-term Continuous Prevention

- **Intended to prevent migraine or mitigate its effects when¹**
 - Patient has not responded to acute care
 - Frequent migraines with acute migraine treatment increases potential for rebound headache
- **Optimal for patients with concomitant medical conditions**
 - Migraine therapy would serve dual purpose
- **Medications include antiepileptics, antidepressants, β -blockers, botulinum toxin type A, topiramate, oral contraceptives¹⁻⁴**
- **Disadvantages include greater exposure to potential adverse events and increased medical costs**

1. Silberstein SD. *Neurology*. 2000;55:754-763. 2. Göbel H. *J Neurol*. 2004;251(suppl 1):1/8-1/11. 3. Mei D et al. *Neuro Sci*. 2004;25:245-250. 4. IHS. *Cephalalgia*. 2004;24(suppl 1):9-160.

- Prophylactic or long-term preventive treatment should be considered for patients²⁵:
 - Whose migraine has a substantial impact on their lives
 - Who have not responded to acute care
 - Whose frequency of migraine causes reliance on acute pain medications that would increase the potential for rebound headache
- Continuous prevention is optimal for patients with concomitant medical conditions for whom migraine therapy would serve a dual purpose
 - Tricyclic antidepressants can be administered to patients with frequent migraine who also suffer from depression
 - β -Blockers are useful in patients with recurring migraines and concurrent angina or hypertension
 - Calcium channel blockers are helpful for patients with concurrent hypertension and migraine
 - Antiepileptics are beneficial for patients with migraine who have concurrent epilepsy, anxiety disorder, or bipolar disorder
 - Oral contraceptives can be given to women with menstrual disorders and frequent migraine; however, in some cases, oral contraceptives can cause migraine¹¹
 - Patients must be evaluated for reactions to oral contraceptives before therapy is begun
 - Oral contraceptives also are associated with an increased risk for stroke³; when added to the increased risk for stroke associated with migraine, oral contraceptives may not be a desirable option

Slide 26

General Management Principles for Migraine

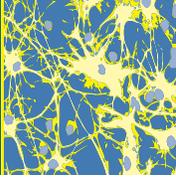
- **Establish a diagnosis through comprehensive assessment**
 - Headache diaries can help identify triggers and help differentiate menstrual migraine
- **Educate patients about migraine**
 - Discuss treatment rationale, how to use the medication, and potential adverse effects
- **Establish realistic expectations**
- **Create a formal management plan**
- **Encourage identification and avoidance of triggers**

Silberstein SD. *Neurology*. 2000;55:754-763.

- General principles for migraine management include²⁵:
 - Establishing a definitive diagnosis through comprehensive assessment
 - Encourage patients to maintain a headache diary. This will allow patients to identify triggers, allergies, health patterns, etc, and will help differentiate among the various types of menstrually related migraines. It will also help track the effectiveness of various medications and any associated side effects
 - Educating migraine sufferers about their condition and the treatment
 - Discuss the rationale for a particular treatment, how to use it, and what adverse events may occur
 - Establishing realistic patient expectations
 - Set appropriate goals; discuss the expected benefits of therapy and how long it will take to achieve these benefits
 - Developing a written and individualized formal management plan that considers the patient's response to, and tolerance for, specific medications
 - Consider comorbidities and coexisting conditions
 - Encourage patients to identify and avoid migraine triggers (eg, caffeine, chocolate, red wine)

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Slide 1

Osteoarthritis Pain

Slide 2

Epidemiology and Impact of Osteoarthritis

- **Prevalence of arthritis and musculoskeletal disorders is difficult to estimate¹**
- **Osteoarthritis affects 40 million Americans¹**
 - Estimated to affect 59.4 million people, or 18.2% of the US population, by 2020¹
 - >20 million people experience pain from osteoarthritis²
 - 7.1 million ambulatory care visits specific to osteoarthritis³
 - Leading cause of work-related disability in people aged 16-72 years¹
 - 80% of people >75 years have osteoarthritis⁴

1. Lawrence RC et al. *Arthritis Rheum.* 1998;41:778-799. 2. Lipman AG. *Curr Rheumatol Rep.* 2001;3:513-519. 3. Hootman JM et al. *Arthritis Rheum.* 2002;47:571-581. 4. Manek NJ, Lane NE. *Am Fam Physician.* 2000;61:1795-1804.

- Osteoarthritis is the most common joint disorder in the United States¹; however, prevalence is difficult to estimate because of the varying definitions used in the clinic setting
- Some conditions have no standard case definition; others have competing or evolving definitions based on symptoms, signs, or radiographic findings
- Estimates also can vary in the research setting, depending on the inclusion or exclusion of symptomatic, mild, or early disease and on how active the case finding process is
- Prevalence data, therefore, should be viewed as conservative estimates²
- Osteoarthritis causes pain for >20 million Americans³ and accounts for >7 million ambulatory care visits per year⁴
- It is a leading cause of work-related disability in individuals aged 16 to 72 years²
- About 80% of people older than 75 years have osteoarthritis¹

Slide 3

Joints Commonly Involved in Osteoarthritis



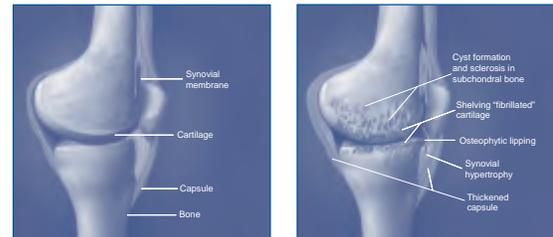
- Osteoarthritis principally affects weight-bearing joints in the knees and hips, but it also affects the feet, ankles, distal interphalangeal joints, proximal interphalangeal joints, first carpometacarpal joints, cervical spine, and lower spine

APS. *Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis*. 2nd ed. Glenview, Ill: American Pain Society; 2002.

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Slide 4

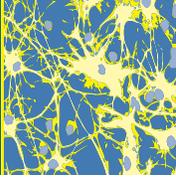
Etiology and Pathophysiology of Osteoarthritis



Normal

Osteoarthritis

- Osteoarthritis is a chronic, progressive, degenerative disease that involves the cartilage of weight-bearing joints⁵
- Osteoarthritis has a multifactorial etiology with both modifiable and nonmodifiable risk factors
 - Osteoarthritis begins with trauma-induced or idiopathic loss of integrity of the cartilage
 - A cascade of events occurs, characterized by a local inflammatory response of the tissues and, ultimately, mechanical and functional alterations⁶
 - When catabolism exceeds cartilage synthesis, osteoarthritis develops¹
- Osteoarthritis can occur as ligaments stretch and loosen, causing joints to become unstable; bones then move more freely, creating greater friction that wears away the cartilage protecting the bone. As the cartilage is worn away, the joint attempts to stabilize by growing more bone. Osteoarthritis of the knee is complicated by small pieces of cartilage that break off, causing inflammation and occasionally locking the joint
- Factors that contribute to the development of osteoarthritis include obesity, heavy exercise, trauma, and vitamin D deficiency⁷
- Before age 50, osteoarthritis is seen more commonly in men; after age 50, women are more likely to develop osteoarthritis⁷



Slide 5

Osteoarthritis Diagnosis

Assessment^{1,2}	<ul style="list-style-type: none"> • Medical and functional history¹ • Physical examination tool (eg, range of motion) • Functional assessment² (eg, Health Assessment Questionnaire and Arthritis Impact Measurement Scales³)
Signs and Symptoms³	<ul style="list-style-type: none"> • Morning stiffness (20-30 minutes) • "Gel" phenomenon (~20 minutes) • Occasionally local inflammation
Radiographic Evidence¹⁻³	<ul style="list-style-type: none"> • Joint space narrowing³ • Increased subchondral bony sclerosis³ • Subchondral cyst formation³ • Osteophytes³

1. Swagerty DL Jr, Hellinger D. *Am Fam Physician*. 2001;64:279-286. 2. Kantz ME et al. *Med Care*. 1992;30(suppl):MS240-MS252. 3. APS. *Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis*. Glenville, Ill: American Pain Society; 2002.

- Osteoarthritis is primarily assessed with a medical history and a physical examination⁸
- Obtaining a functional history by using a functional assessment tool is an important part of the assessment as well⁹
- Range-of-motion tools can be used to determine function and to provide objectivity for the physical examination
- People with osteoarthritis typically report stiffness lasting about 20 to 30 minutes, particularly on arising in the morning
- They also may experience a "gel" phenomenon when they are sitting or driving, a feeling of stiffness that goes away within 20 minutes, once they begin moving again
- Although the stiffness goes away, there is likely increased pain in the weight-bearing joints over the course of the day¹⁰
- Osteoarthritis can be confirmed and further differentiated from other processes using laboratory and radiographic findings
 - Plain radiographs are usually adequate to confirm diagnosis or assess severity if surgery is being considered⁸
- Radiographic evidence includes joint space narrowing, increased subchondral bony sclerosis, subchondral cyst formation, and osteophytes^{8,10}

Slide 6

Nonpharmacologic Interventions for Osteoarthritis

Primary Treatment Goal	<ul style="list-style-type: none"> • Minimize symptoms¹ • Increase function and QOL¹
Patient/Family Education	<ul style="list-style-type: none"> • Education about pain, pain management options, and self-management programs² • Personalized social support (phone)^{2,3}
Cognitive-Behavioral Therapy¹	<ul style="list-style-type: none"> • Reduce pain and psychological disability • Enhance self-efficiency and pain coping

QOL=quality of life.

1. Hinton R et al. *Am Fam Phys*. 2002;65:841-848. 2. APS. *Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis*. 2nd ed. Glenville, Ill: American Pain Society; 2002. 3. ACR. *Arthritis Rheum*. 2000;43:1905-1915.

- The primary goal of both nonpharmacologic and pharmacologic treatments is minimization of symptoms and improved function and quality of life⁶
- Nonpharmacologic therapies such as patient education and cognitive-behavioral therapy should be used concurrently with analgesic and anti-inflammatory medications¹¹⁻¹³
- Patient education should include information about pain, pain management options, and self-management programs, as well as personalized social support by telephone, which benefits patients who are having difficulty adjusting to pain and its management^{10,14}

Slide 7

Physical Interventions for Osteoarthritis

Exercise^{1,2}	<ul style="list-style-type: none"> • Range of motion and flexibility • Muscle strengthening • Aerobic (low impact, gravity limiting)
Maintain Ideal Body Weight^{1,2}	<ul style="list-style-type: none"> • Follow a balanced diet plan • If BMI >30 kg/m², follow weight management program
Physical Modalities²	<ul style="list-style-type: none"> • Physical therapy • Occupational therapy
Orthotics^{1,2}	<ul style="list-style-type: none"> • Assistive devices for walking and ADLs • Footwear and insoles, compression gloves, patellar taping, cane

BMI=body mass index; ADLs=activities of daily living.

1. APS. *Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis*. 2nd ed. Glenville, Ill: American Pain Society; 2002. 2. ACR. *Arthritis Rheum*. 2000;43:1905-1915.

- Physical interventions in arthritis are aimed at decreasing impairment and improving function
- Because of the chronic and fluctuating nature of arthritis and because self management pain-relief measures have been demonstrated to be effective, patients should be encouraged to use measures such as range-of-motion and flexibility exercises, muscle-strengthening exercises, and aerobic exercise^{10,14}
- Patients also should follow a balanced diet plan and lose weight if necessary (body mass index >30 kg/m²)^{10,14}
 - These recommendations should be accompanied by adequate demonstration, instruction, and follow-up¹⁰
- Physical interventions also include physical and occupational therapy and use of orthotics such as assistive and adaptive devices¹⁰

Slide 8

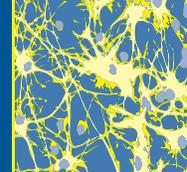
Complementary and Alternative Medicine for Osteoarthritis

Dietary Supplements^{1,2}	<ul style="list-style-type: none"> • Glucosamine sulfate • Chondroitin 4-sulfate
Physical Modalities¹	<ul style="list-style-type: none"> • Heat/cold application • TENS • Acupuncture • Magnets (insufficient evidence supporting use)

TENS=transcutaneous electrical nerve stimulation.

1. APS. *Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis*. 2nd ed. Glenville, Ill: American Pain Society; 2002. 2. Clegg DO et al. *N Engl J Med*. 2006;354:795-808.

- The role of nutrition in reducing or eliminating arthritis pain is not well understood; however, studies have shown that nutrition has an impact on inflammatory disease that results in an improvement in clinical symptoms in people with rheumatic diseases¹⁰
- There is some evidence that oral glucosamine sulfate is a chondroprotective agent that stimulates the production of cartilage matrix and provides nonspecific protection as an antioxidant against chemical damage¹⁰
 - Studies support the recommendation that adults with osteoarthritis be encouraged to take 1500 mg of oral glucosamine sulfate daily¹⁰
- In the Glucosamine/chondroitin Arthritis Intervention Trial, glucosamine and chondroitin sulfate alone or in combination did not reduce pain effectively in the overall group of patients with osteoarthritis of the knee. However, exploratory analyses suggested that the combination of glucosamine and chondroitin sulfate may be effective in the subgroup of patients with moderate to severe knee pain¹⁵
- Heat and cold can provide analgesia, promote relaxation, reduce muscle spasm, and enhance flexibility of muscle and periarticular structures, and is commonly used with other interventions such as stretching exercises.¹⁰ Cooling has a local analgesic effect and reduces inflammatory responses secondary to trauma¹⁰
- Transcutaneous electrostimulation stimulates afferent nerve fibers, which transmit or inhibit noxious input through the spinal cord to the brain; high-frequency or burst-mode transcutaneous electrostimulation appears to provide lasting relief (2.5 to 18 hours) and is considered an appropriate mode for pain reduction in arthritis¹⁰
- Acupuncture involves insertion of slender needles that may be heated with an herb (moxibustion) or electrified at specific points in the body; studies have yielded mixed results¹⁰
- There is currently insufficient evidence of the benefits of electromagnetic field (magnet) therapy to recommend its use in managing pain related to arthritis¹⁰



Slide 9

Pharmacologic Treatments for Osteoarthritis

Analgesics

- Acetaminophen¹⁻³
- NSAIDs¹⁻⁴
- COX-2 inhibitors^{*1,2}
- Topical agents (eg, capsaicin,^{1,2} lidocaine patch 5%⁴)
- Opioids
 - When all other analgesics have failed and as part of a biopsychosocial approach⁵

NSAIDs=nonsteroidal anti-inflammatory drugs; COX=cyclooxygenase.

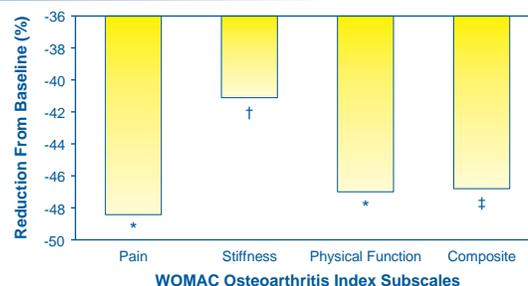
*Questions have been raised about adverse cardiovascular events.

1. ACR. *Arthritis Rheum*. 2000;43:1905-1915. 2. APS. *Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis*. 2nd ed. Glenview, Ill: American Pain Society; 2002. 3. Lipman AG. *Curr Rheumatol Rep*. 2001;3:513-519. 4. Gammaitoni AR et al. *Curr Med Res Opin*. 2004;20(suppl 2):S13-S19. 5. Kivitz A et al. EULAR 20th Annual Meeting, 2003.

- According to various guidelines, pharmacologic options for osteoarthritis include acetaminophen, nonsteroidal anti-inflammatory drugs, topical analgesics, and when these prove inadequate, opioids^{10,14}
- Acetaminophen is the medication of first choice for mild osteoarthritis pain^{3,10,14}
- For moderate to severe osteoarthritis pain and/or inflammation, a cyclooxygenase-2-selective nonsteroidal anti-inflammatory drug was considered first choice if there was no significant risk for hypertension or renal disorder; however, there is now concern regarding the use of coxibs and nonsteroidal anti-inflammatory drugs in patients at risk for cardiovascular events.¹⁶ Two cyclooxygenase-2 inhibitors, rofecoxib and valdecoxib, have been removed from the market
- Topical agents such as capsaicin and the lidocaine patch 5% have been recommended for use in osteoarthritis. The lidocaine patch 5% was found to reduce ongoing pain and allodynia in osteoarthritis, as both monotherapy and add-on therapy¹⁷
- Opioids should be used when other medications produce inadequate pain relief³
 - This is frequently the case, because neither acetaminophen nor nonsteroidal anti-inflammatory drugs consistently provide suitable pain relief in the treatment of osteoarthritis¹⁸

Slide 10

Emerging Pharmacologic Treatment: Lidocaine Patch 5%



2-week, open-label trial. N=20; *P<.001; †P=.003; ‡P<.01.

WOMAC=Western Ontario and McMaster Universities.

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- In an open-label, multicenter pilot study of 32 patients with osteoarthritis in 1 or both knees, the lidocaine patch 5% was used for 2 weeks; ≤4 patches/24 hours were applied. Treatment resulted in reduction in "worst" and "average" pain and "pain right now" ($P<.0001$); pain relief ($P<.001$), and least pain ($P<.01$); >50% reduction in "worst" and "average" pain was seen in 52% and 39% of patients, respectively¹⁹
 - Significant reductions were seen in all Western Ontario and McMaster (WOMAC) Universities osteoarthritis subscores and the composite index ($P<.0001$). Reductions >50% in pain, stiffness, physical function and composite index score were seen in 55%, 48%, 61%, and 61% of patients, respectively¹⁹
- A 2-week, open-label, multicenter, proof-of-concept study was conducted in 20 patients receiving the lidocaine patch 5% as monotherapy. At week 2, statistically significant improvements were seen for all WOMAC subscale scores of pain, including the composite index ($P<.01$). More than a 40% reduction was observed for all WOMAC subscale scores from baseline to week 2²⁰
- In a 2-week, prospective, multicenter, open-label pilot study of 137 patients, addition of the lidocaine patch 5% to analgesic therapy such as acetaminophen and nonsteroidal anti-inflammatory drugs significantly reduced pain intensity and improved function in patients with osteoarthritis in 1 or both knees ($P<.001$ and $P<.001$, respectively)²¹
- In all studies, the lidocaine patch 5% was well tolerated, with few treatment-related adverse events. Controlled clinical trials are needed to validate these findings

Slide 11

Pharmacologic/Invasive Treatments for Osteoarthritis



Injections

- Intra-articular glucocorticoid (3-4x/y)^{1,2}
- Hyaluronic acid viscosupplementation³



Surgery

- Total or resection arthroplasty, arthrodesis, arthroscopy, osteotomy (hip, ankle, knee)¹



Other

- Glucosamine sulfate, 1500 mg/d¹

1. APS. *Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis*. 2nd ed. Glenville, Ill: American Pain Society; 2002. 2. Hinton R et al. *Am Fam Physician*. 2002;65:841-848. 3. Manek NJ, Lane NE. *Am Fam Physician*. 2000;61:1795-1804.

- Local injections of glucocorticoids into arthritic joints offer relief for up to 4 weeks and are typically administered 3 or 4 times a year⁶
- Osteoarthritis of the knee can be treated with injections of hyaluronic acid-like products, a Food and Drug Administration-approved treatment.^{1,6} The treatment replaces damaged joint fluid
- In patients whose symptoms persist despite appropriate treatment, referral to an orthopedic surgeon should be considered
- Trials using glucosamine for osteoarthritis have shown some degree of efficacy, but the studies are believed to have methodologic problems and most likely overestimate the results²²
 - Further studies are needed to determine the clinical utility of glucosamine and chondroitin

Slide 12

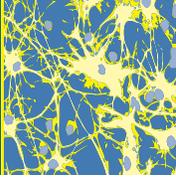
Intra-articular Injection of Hyaluronic Acid for Osteoarthritis

- Mechanism of action is unknown
- Animal studies show improvement in osteoarthritis and cartilage¹
- In vitro studies show beneficial molecular and cellular effects¹
 - Extracellular matrix, immune cells, inflammatory mediators
- Clinical studies²
 - Pain relief greater than placebo, comparable to oral NSAIDs, and comparable to or greater than glucocorticoid injections

NSAIDs=nonsteroidal anti-inflammatory drugs.

1. Moreland LW. *Arthritis Res Ther*. 2003;5:54-67. 2. ACR. *Arthritis Rheum*. 2000;43:1905-1915.

- Intra-articular injection of hyaluronic acid is indicated for use in patients who have not responded to a program of nonpharmacologic therapy and simple analgesics¹⁴
- Although the mechanism of intra-articular hyaluronic acid for the treatment of osteoarthritis pain is unknown, clinical studies have demonstrated various physiologic effects of exogenous hyaluronic acid¹⁴
- Hyaluronic acid can reduce nerve impulses and nerve sensitivity associated with osteoarthritis pain. Improvement in osteoarthritis with administration of hyaluronic acid has been shown in electrophysiology and animal pain models, and hyaluronic acid may have protective effects on cartilage. Additionally, in vitro studies have shown that hyaluronic acid has beneficial effects on extracellular matrix, immune cells, and inflammatory mediators²³
- In clinical trials, intra-articular injection of hyaluronic acid preparations resulted in pain relief significantly greater than that seen with placebo injections, comparable to that achieved with oral nonsteroidal anti-inflammatory drugs, and comparable to or greater than that obtained with intra-articular glucocorticoids. However, pain relief with hyaluronic acid injections takes longer but the effect may last considerably longer¹⁴



Slide 13

Future Treatments for Osteoarthritis



Nonpharmacologic

- Specific physical therapy programs
- Continued improvement in complementary and alternative approaches



Disease-modifying agents

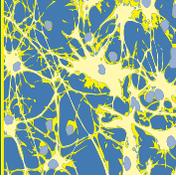
- Target-specific inflammatory mediators¹
- Target-specific genetic deficiencies²
 - Interleukin-1
 - Interleukin-6
 - Tumor necrosis factor- α
- Cartilage growth factor (Tgf-S)³
- Articular cartilage repair and transplantation⁴

1. Pelletier JP et al. *Rheum Dis Clin North Am*. 1993;19:545-568. 2. Goldring MB. *Connect Tissue Res*. 1999;40:1-11. 3. ACR. Cartilage Growth Factor (Tgf-S) in osteoarthritis. Available at: <http://www.rheumatology.org/publications/hotline/archive/0394cartilagegf.asp>. Accessed May 23, 2006. 5. Buckwalter JA, Mankin HJ. *Arthritis Rheum*. 1998;41:1331-1342.

- Emerging therapies in the nonpharmacologic management of osteoarthritis include specific swimming and physical therapy programs, as well as continued improvement in complementary and alternative therapies
- Future directions for the treatment of osteoarthritis are to further define the pathophysiology of this disease to allow for preventive measures
- Cytokines and growth factors are thought to play a role in the pathophysiology of osteoarthritis. Interleukin-1 and tumor necrosis factor- α may activate enzymes involved in proteolytic digestion of cartilage. Growth factor- β and insulin growth factor-1 may play a role in the body's attempts to repair cartilage through cartilage synthesis. Advances in therapies that target these pathways may be clinically useful^{24,25}
- Treatment with free transforming growth factor- β and liposome-encapsulated transforming growth factor- β is associated with cartilage repair that resembles normal hyaline cartilage; its integrity was found to persist at 1 year after surgery²⁶
- Experimental studies have revealed that transplantation of chondrocytes and mesenchymal stem cells; use of periosteal and perichondrial grafts, synthetic matrices, and growth factors; and other methods have the potential to stimulate the formation of a new articular surface. The long-term follow-up of a small group of patients indicates that the transplantation of osteochondral autologous grafts and allografts can be effective for the treatment of focal defects of articular cartilage in select patients²⁷

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Slide 1

Pain Management in Older Adults

Slide 2

Challenges in Pain Management: Older Adults

- **Population with most significant need for comprehensive pain management**
 - Serious comorbidities
 - Pharmacologic issues
 - Metabolize medications differently
 - Frequently on multiple medications, which increases risk of drug interactions and adverse events
 - Cognitive impairment affects ability to express degree of pain
 - Fewer economic resources to pay for analgesics
 - Compliance
 - May not take maximal doses

Davis MP, Srivastava M. *Drugs Aging*. 2003;20:23-57.

- Older patients need the most comprehensive pain management for chronic pain conditions such as osteoarthritis, low back pain, postherpetic neuralgia, and diabetic neuropathy.^{1,2} However, a survey of pain management and age shows that older patients present unique challenges to effective pain management because of²:
 - Serious comorbidities
 - Medication issues
 - Older patients metabolize medications differently and are frequently on multiple medications, which increases their risk of drug interactions and adverse events
 - Cognitive impairment^{1,2}
 - Affects the ability of older patients to express the degree of pain
 - Fewer economic resources to pay for analgesics

Slide 3

Common Conditions Causing Pain in Older Adults

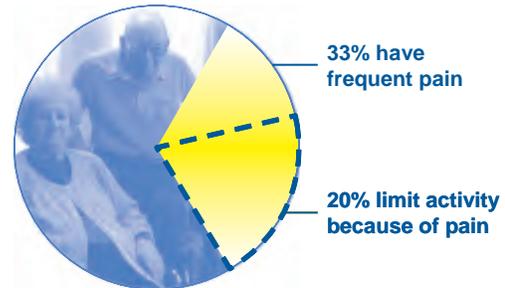
- Low back pain from facet joint arthritis and spondylosis
- Osteoarthritis
- Osteoporosis
- Previous bone fractures
- Rheumatoid arthritis
- Polymyalgia rheumatica
- Paget's disease
- Peripheral neuropathies
- Neuropathic pain associated with stroke
- Shingles, postherpetic neuralgia
- Diabetes
- Trigeminal neuralgia
- Nutritional neuropathies
- Peripheral vascular disease
- Coronary artery disease

Davis MP, Srivastava M. *Drugs Aging*. 2003;20:23-57.

Slide 4

Prevalence of Pain in Older Adults

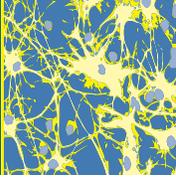
Survey: >5000 Community-Dwelling Older Adults



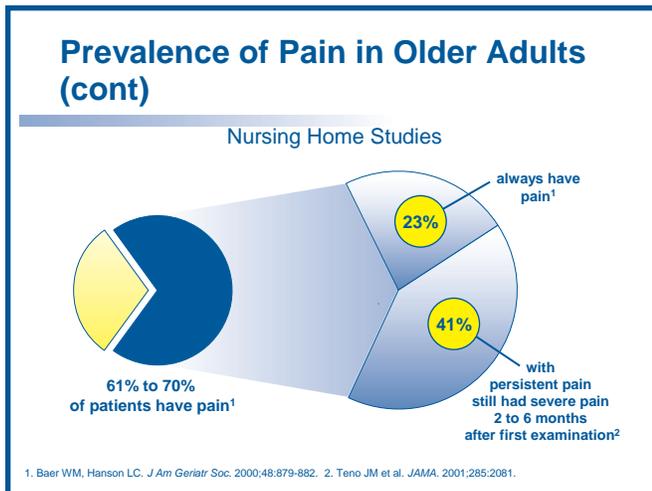
Reyes-Gibby CC et al. *Pain*. 2002;95:75-82.

- Generally, pain in older patients is located in the back, knee, foot, ankle, shoulder, neck, or wrist.¹ Common causes of pain in older persons include²:
 - Low back pain from facet joint arthritis and spondylosis
 - Osteoarthritis
 - Osteoporosis
 - Previous bone fractures
 - Rheumatoid arthritis
 - Polymyalgia rheumatica
 - Paget's disease
 - Peripheral neuropathies
 - Neuropathic pain associated with stroke
 - Shingles, postherpetic neuralgia
 - Diabetes
 - Trigeminal neuralgia
 - Nutritional neuropathies
 - Peripheral vascular disease
 - Coronary artery disease

- In a survey of >5000 community-dwelling older adults, 33% reported frequent pain, and 20% reported activity limitations directly related to pain³

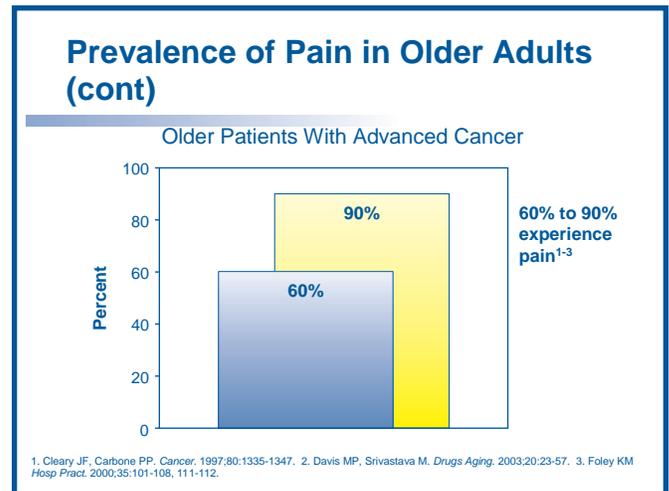


Slide 5



- A survey of nursing home hospice enrollees found that ~70% had moderate to severe pain in their last 3 months of life, and 23% had pain all of the time.⁴ In another study, 41% of residents with persistent pain had severe pain 2 to 6 months later⁵

Slide 6



- Pain from advanced cancer is also prevalent in the elderly population; 60% to 90% of patients with cancer experience pain^{2,6,7}

Slide 7

Pain in Older Adults Is Undertreated

- **Nursing home patients with cancer¹**
 - Aged >85 years less likely to receive analgesics
 - 24% in pain daily; 26% received no analgesics
- **Patients with hip fracture**
 - Received <25% of the mean prescribed amount of opioid analgesics²
 - Half of cognitively intact patients received inadequate analgesia³
 - 76% of cognitively impaired and 83% of cognitively intact patients had no standing order for analgesia³
- **Most older adults with pain do not see a pain specialist⁴**
 - Primary care clinicians need to be able to assess and treat pain

1. Bernabei R et al. *JAMA*. 1998;279:1877-1882. 2. Feldt KS et al. *J Am Geriatr Soc*. 1998;46:1079-1085. 3. Morrison RS, Siu AL. *J Pain Symptom Manage*. 2000;19:240-248. 4. Weiner DK. *Pain*. 2002;97:1-4.

- Pain in older adults is undertreated. Nursing home patients who have cancer are among the oldest patients (>85 years of age) and are less likely to receive analgesics for their pain. Bernabei and colleagues found that 24% of these patients experience pain daily, but that 26% of patients experiencing pain received no analgesics⁹
- In a prospective cohort study, analgesic administration was compared for cognitively intact patients (n=59) and patients with dementia (n=38), all of whom had hip fracture. Half of the cognitively intact patients who had moderate to very severe pain received inadequate analgesia for their level of pain; 83% of cognitively intact and 76% of dementia patients did not receive a standing order for an analgesic medication⁹
- The majority of older adult pain sufferers never see a pain specialist. Therefore, it is important for the primary care clinician to be knowledgeable in the areas of pain assessment and management¹⁰

Slide 8

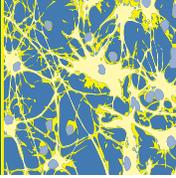
Intervention Can Significantly Improve Patient Care

- **Intervention in nursing homes for patients with moderate or severe pain**
- **Increased use of**
 - Appropriate pain assessments ($P<.001$)
 - Pain intensity scales ($P<.001$)
 - Nonpharmacologic treatments ($P<.001$)
 - WHO step II or III pain medications ($P=.057$)
- **Trends toward improvement (41% reduced pain prevalence, $P=.032$)**



WHO=World Health Organization.
Baier RR et al. *J Am Geriatr Soc*. 2004;52:1988-1995.

- A quasi-experimental, pretest/posttest study evaluated a multifaceted collaborative intervention to improve pain management processes of care and outcomes in 21 nursing homes, using audit and feedback of pain management, education, training, coaching using rapid-cycle quality improvement techniques, and inter-nursing home collaboration¹¹
- Postintervention, the 17 nursing homes that completed the study increased the use of appropriate pain assessments (from 3.9% to 43.8%, $P<.001$), pain intensity scales (from 15.6% to 73.9%, $P<.001$), and nonpharmacologic treatments (from 40.5% to 81.9%, $P<.001$)¹¹
- Prescriptions of WHO step II or III pain medications for patients with daily moderate to severe pain showed trends towards improvement (from 40.8% to 50.6%; $P=.057$). Prevalence of pain was reduced by 41% ($P=.032$) compared with 12.1% in facilities that did not participate in the study ($P=.286$)¹¹



Slide 9

Pain Assessment in Older Adults

- Always assess older patients for pain
- Thorough initial assessment is crucial
- Use simple questions/screening tools
- Older patients may be reluctant to report pain
- Identify and treat conditions that require a specific intervention
- Treat all patients with diminished quality of life from chronic pain
- Assess for depression when patient presents with pain



AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc.* 2002;50(6 suppl):S205-S224.

- Understanding that chronic pain is common in older people, the American Geriatric Society has issued specific recommendations and general principles to improve clinical practice with regard to the assessment and treatment of chronic pain in older adults
- Every older person who presents for examination by a healthcare professional should be assessed for pain. A thorough initial assessment using simple questions and screening tools is crucial to understanding the causes and pathophysiology of the patient's pain¹²
- Many older adults are reluctant to report pain despite what might be considerable physical or psychologic impairment. Proactive assessment for pain will help the clinician identify and treat those conditions that require specific interventions¹²
- All patients who experience a diminished quality of life as a result of their pain should be considered candidates for pain treatment¹²
- Initial evaluation should include psychosocial functions, including mood, especially depression¹²

Slide 10

Pain Management in Older Adults: Pharmacotherapy

- Most effective when combined with nonpharmacologic strategies
- Rational polypharmacy may minimize dose-limiting adverse events
 - Smaller, effective doses of differing medication classes
 - Close monitoring
 - Select agents with favorable therapeutic ratio (eg, low risk of drug interactions)
- Opioid, corticosteroid, or other adjunctive therapy may have fewer life-threatening risks than long-term, daily use of high-dose nonselective nonsteroidal anti-inflammatory drugs
- Opioid medications are probably underutilized

AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc.* 2002;50(6 suppl):S205-S224.

- Pharmacotherapy for older adults is most effective when it is combined with nonpharmacologic strategies such as education, cognitive-behavior therapy, and exercise programs¹²
- Using smaller, effective doses of medications from different medication classes, polypharmacy, may minimize those adverse events that are dose limiting. Patients should be monitored closely¹²
- Opioid medications are probably underutilized. Yet, opioid, corticosteroid, or other adjunctive therapy may reduce the sometimes life-threatening risks associated with long-term, daily use of high-dose nonselective nonsteroidal anti-inflammatory drugs¹²

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Pain Management in Older Adults: Pharmacotherapy (cont)

- Most common treatment involves analgesic medications¹
- Most medications are safe and effective¹
- May experience more adverse reactions/increased risk for drug interactions²
- May have increased analgesic sensitivity¹
- Optimum dosage and side effects difficult to predict¹
 - Age-adjusted dosing differences in efficacy, sensitivity, and toxicity should be expected¹
 - “Start low and go slow”^{1,2}
- Balance needs to be achieved with safety, tolerability, and efficacy

1. AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc.* 2002;50(6 suppl):S205-S224. 2. Davis MP, Srivastava M. *Drugs Aging.* 2003;20:23-57.

- The most common treatment for older adults with chronic pain involves the use of analgesic medications. Although all pharmacologic interventions have both benefits and risks, most medications available for treatment of chronic pain are safe and effective.¹² However, some patients may experience adverse reactions²
- With some pain-relieving medications, such as opioids, older adults may experience increased analgesic sensitivity¹²
- Because of the heterogeneity of the older adult population, it is difficult to predict the optimal dosage or what, if any, side effects a particular patient will experience. As recommendations for age-adjusted dosing are not available for most analgesic medications, the most appropriate approach is to “start low and go slow.” In general, it is recommended that the lowest anticipated effective dose be given, the patient be frequently monitored, and the analgesic agent be titrated slowly to optimize therapy and minimize adverse effects¹²
- In this population in particular, it is important to balance tolerability and safety with efficacy

Slide 12

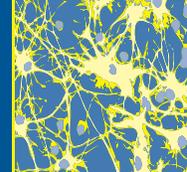
Pain Management in Older Adults: Pharmacotherapy (cont)

- Topical agents alone or in combination with other analgesics may provide relief for musculoskeletal and neuropathic pain
 - Capsaicin cream
 - Counterirritants (eg, menthol, methyl salicylate, tolamine salicylate)
 - Lidocaine patch 5%
- Topical agents are well suited to older patients
 - Low risk of systemic side effects
 - Low risk of drug interactions



American Medical Directors Association. *Pain Management in the Long-Term Care Setting: Clinical Practice Guidelines.* Columbia, Md: AMDA; 2004.

- Topical agents, such as capsaicin cream or the lidocaine patch 5%, either alone or in combination with other analgesics, may provide relief for patients with both musculoskeletal and neuropathic pain¹³
- These agents are well suited for older patients because of the reduced risk of systemic side effects and drug interactions¹³



Slide 13

Recommendations for Chronic Pain in Older Adults

- **Recommendations for the treatment of musculoskeletal pain are**
 - Exercise and physical activity
 - Topical analgesics
 - Combination therapy and opioids
 - Acetaminophen
 - Nonsteroidal anti-inflammatory drugs
- **For neuropathic pain**
 - Control of blood glucose levels
 - Topical analgesics
 - Acetaminophen
 - Anticonvulsants
 - Physical therapy
 - Nonsteroidal anti-inflammatory drugs
 - Combination therapy and opioids

American Medical Directors Association. *Pain Management in the Long-Term Care Setting: Clinical Practice Guidelines*. Columbia, Md: AMDA; 2004.

- The American Medical Directors Association recommendations for the treatment of musculoskeletal pain are¹³:
 - Exercise and physical activity
 - Topical analgesics
 - Combination therapy and opioids
 - Acetaminophen
 - Conventional nonsteroidal anti-inflammatory drugs
- For patients experiencing neuropathic pain¹³:
 - Control of blood glucose levels
 - Topical analgesics (eg, lidocaine patch 5%)
 - Acetaminophen
 - Anticonvulsants
 - Physical therapy
 - Nonsteroidal anti-inflammatory drugs
 - Combination therapy and opioids

Slide 14

Safety Considerations in Older Adults

Topical Analgesics/Other Peripherally Acting Treatments

Agent	Considerations
Capsaicin	<ul style="list-style-type: none"> • Repeated applications needed¹ • Apply to intact skin • Clinical effect generally not experienced until 2 to 4 weeks after initiating treatment¹ • Burning, sneezing, and coughing
Lidocaine patch 5%	<ul style="list-style-type: none"> • Localized skin reaction (eg, rash, pruritis) generally mild and transient² • Apply to intact skin • Use with caution in patients receiving class 1 antiarrhythmic drugs • No clinically significant drug interactions or systemic side effects in clinical trials^{2,3}

1. Attal N. *Clin J Pain*. 2000;16(3 suppl):S118-S130. 2. Burch F et al. *Osteoarthritis Cartilage*. 2004;12:253-255. 3. Galer BS et al. *Curr Med Res Opin*. 2004;20:1455-1458.

- Because of increased risk factors in older patients, it is important to balance the efficacy of a pharmacologic treatment against its potential adverse effects
- Capsaicin is a neurotoxin that displays analgesic properties when applied topically to intact skin¹⁴
 - Its mechanism of activity is probably related to its effect on C-nociceptive fibers¹⁴
- Capsaicin has been found to be effective when administered with other analgesic medications and should be used as adjuvant therapy^{14,15}
- The clinical effect of capsaicin generally is not experienced until 2 to 4 weeks after treatment initiation
 - Repeated applications (every 6 hours) are needed^{14,15}
- The commonly reported burning sensation may be reduced with the use of a topical anesthetic¹⁴
- The need for repeated applications combined with local treatment-related pain and burning limits its use in many patients¹⁴
- The lidocaine patch 5%, a topical analgesic patch, is applied directly to intact skin over the area of maximal pain
- Systemic absorption is minimal, resulting in clinically insignificant serum drug levels and a low potential for systemic side effects or drug interactions¹⁶
- Unlike other formulations of lidocaine, the lidocaine patch 5% is not associated with sensory loss¹⁷
- The most common adverse effects of the lidocaine patch 5% are localized skin reactions^{18,19}

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Safety Considerations in Older Adults (cont)

Oral Nonopioid Analgesics

Agent	Considerations
Acetaminophen ¹	<ul style="list-style-type: none"> • Relatively safe in this population • Lower gastrointestinal and renal toxicity compared with NSAIDs • Few associated drug interactions • No age-related differences in drug clearance • Caution is advised for use with other hepatically metabolized drugs and in concomitant liver disease, in those who are fasting, and with excessive alcohol consumption
Nonselective NSAIDs	<ul style="list-style-type: none"> • Gastrointestinal toxicity increases 3-fold² • Increase in risk of hemorrhagic peptic ulcer disease when administered concurrently with anticoagulants³ • Increased gastrointestinal bleeding • Drug-drug interactions • Cardiovascular issues: may cause hypertension and may increase risk of myocardial infarction
Selective COX-2 inhibitors	<ul style="list-style-type: none"> • Potential for adverse renal and increased cardiovascular effects^{4,5}

NSAIDs=nonsteroidal anti-inflammatory drugs; COX-2=cyclooxygenase 2.

1. Weiner DK, Hanlon JT. *Drugs Aging*. 2001;18:13-29. 2. Gabriel SE et al. *Ann Intern Med*. 1991;115:787-796. 3. Shorr RI et al. *Arch Intern Med*. 1993;153:1665-1670. 4. Komers R et al. *Am J Kidney Dis*. 2001;38:1145-1157. 5. Mamdani M et al. *Lancet*. 2004;363:1751-1756.

- Oral nonopioids are often used as first-line therapy for treatment of mild to moderate nociceptive pain
- Acetaminophen generally is the first-choice agent because of its relative safety in older persons¹²
- Compared with:
 - Nonsteroidal anti-inflammatory drugs, acetaminophen has lower gastrointestinal and renal toxicity, few associated drug interactions, and no age-related differences in drug clearance²⁰
 - Because it is metabolized in the liver, caution should be exercised when it is used with other hepatically metabolized drugs, with concomitant liver disease, when fasting, and with excessive alcohol consumption²¹⁻²³
 - There have been no reports of cardiovascular risks
- Because of their anti-inflammatory activity, nonsteroidal anti-inflammatory drugs are commonly used to treat inflammatory disorders such as rheumatoid arthritis, gout, pseudogout, and bursitis
- Risk of gastrointestinal toxicity is increased 3-fold in nonsteroidal anti-inflammatory drug users versus nonusers²³
- When nonsteroidal anti-inflammatory drugs are administered concurrently with anticoagulants, there is a nearly 13-fold increased risk of hemorrhagic peptic ulcer disease²⁴
- Other issues that need to be taken into consideration include other drug-drug interactions with concurrent usage
- The utility of cyclooxygenase-2 agents and nonsteroidal anti-inflammatory drugs has been questioned recently because of the withdrawal of rofecoxib and valdecoxib, cyclooxygenase-2-selective nonsteroidal anti-inflammatory drugs, from the market because of their adverse cardiovascular event profiles. Celecoxib also may be associated with negative cardiovascular effects
 - The Food and Drug Administration has asked manufacturers of all nonsteroidal anti-inflammatory drugs to include a boxed warning highlighting the potential for increased risk of cardiovascular and gastrointestinal events²⁵

Slide 16

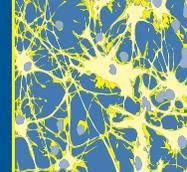
Safety Considerations in Older Adults (cont)

Adjunctive Agents/Anticonvulsants

Agent	Considerations
Gabapentin ¹	<ul style="list-style-type: none"> • Cognitive impairment, somnolence • Exacerbation of gait and balance problems, dizziness • Gastrointestinal symptoms • Mild peripheral edema
Pregabalin ²	<ul style="list-style-type: none"> • The relatively high frequency of central nervous system adverse events, particularly dizziness and somnolence, is a concern in the elderly • No geriatric-specific efficacy/tolerability data
Carbamazepine ³	<ul style="list-style-type: none"> • Somnolence, ataxia, dizziness, leukopenia, thrombocytopenia, and rarely aplastic anemia

1. Dworkin RH et al. *Arch Neurol*. 2003;60:1524-1534. 2. Guay DR. *Am J Geriatr Pharmacother*. 2005;3:274-287. 3. AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc*. 2002;50(6 suppl):S205-S224.

- The term "adjunctive agent" describes a medication with a primary indication that is not analgesic but that has demonstrated analgesic properties. Adjunctive agents can be used alone or in combination with analgesics to treat persistent pain conditions such as neuropathic pain. In general, these agents are characterized by a wide interindividual variability in therapeutic effects and inconsistent dose-response relationships²⁶
- Typically, lower doses are used for off-label pain relief than those for their primary indication.²⁰ Most require gradual, time-consuming titration and close monitoring for therapeutic and adverse effects^{12,27}
- Although gabapentin is generally well tolerated and lacks significant drug interactions, it is associated with several adverse effects²⁷
- To avoid side effects, it is suggested that gabapentin be started at a low dose and gradually titrated to achieve pain relief
- Patients should be told that it may take several weeks to achieve a therapeutic effect²⁷
- Pregabalin is approved for the management of pain associated with both painful diabetic peripheral neuropathy and postherpetic neuropathy; however, there has been little experience with this agent in older adults, and its place in the therapeutic cascade is unknown²⁸
- Carbamazepine is indicated only for lancinating pain (eg, trigeminal neuralgia). It may have more serious side effects than gabapentin¹²



Slide 17

Safety Considerations in Older Adults (cont)

Adjunctive Agents (cont)

Agent	Considerations
Tricyclic antidepressants ¹	<ul style="list-style-type: none"> • Potential drug-drug interactions • Caution should be exercised in patients with history of cardiovascular disease, glaucoma, urinary retention, or autonomic neuropathy • May cause balance disturbance and cognitive impairment
Systemic local anesthetics (eg, mexiletine, intravenous lidocaine) ^{2,3}	<ul style="list-style-type: none"> • Drowsiness, fatigue, nausea, and dizziness • Avoid use in patients with preexisting heart disease • Neuropathic doses not established

1. Dworkin RH et al. *Arch Neurol*. 2003;60:1524-1534. 2. Tremont-Lukats IW et al. *Anesth Analg*. 2005;101:1738-1749. 3. AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc*. 2002;50(6 suppl):S205-S224.

- The analgesic mechanism of actions in tricyclic antidepressants is unclear; however, it may be related to serotonin activity and receptor-reuptake blockade²⁹
- Although tricyclic antidepressants have demonstrated effectiveness in the treatment of neuropathic pain,³⁰ their clinical usefulness may be limited by their adverse-effect profile and associated drug interactions²⁷
- Caution should be exercised in patients with a history of cardiovascular disease, glaucoma, urinary retention, or autonomic neuropathy. An electrocardiogram is recommended before starting treatment in patients aged >40 years to check for cardiac condition abnormalities²⁷
- Tricyclic antidepressants may cause balance disturbances and cognitive impairments in older persons²⁷
- Local anesthetics have been used systemically for a number of neuropathic pain syndromes (eg, diabetic neuropathy, cancer-associated neuropathic pain)³¹
 - General adverse effects include dizziness, gastrointestinal upset, headaches, irritability, nervousness, tremors, and seizures^{12,31}
 - These agents should be used with caution in patients with or at risk for heart failure¹²

Slide 18

Safety Considerations in Older Adults (cont)

Adjunctive Agents (cont)

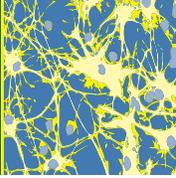
Agent	Considerations
Tramadol	<ul style="list-style-type: none"> • Low abuse potential • Most common adverse events are nausea and drowsiness • Caution should be used in patients with a seizure history
Pure opioid analgesics	<ul style="list-style-type: none"> • Common adverse effects include nausea, sedation, impaired concentration, and constipation • Other considerations include respiratory depression and falls/fractures • Potential for addiction

AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc*. 2002;50(6 suppl):S205-S224.

- Tramadol is effective for a number of musculoskeletal conditions, diabetic neuropathy, and fibromyalgia. Its primary benefit is a low abuse potential. The most common adverse effects include nausea and drowsiness, which are serious concerns in older patients. Tramadol should be used with caution in patients with a seizure history or in those taking medications that lower the seizure threshold¹²
- Opioids have an important role in the management of pain, particularly in cases where the pain responds poorly to other treatments. Opioids offer effective pain relief for moderate to severe pain. Common adverse effects include nausea, sedation, impaired concentration, and constipation. Other more serious but less common adverse effects include respiratory depression and falls/fractures¹²
- Specific opioid analgesics that should be avoided in older adults because of an increased incidence of adverse events include meperidine and the mixed agonist-antagonist agents (eg, pentazocine)²¹
- With the transdermal patch, clinicians must consider that the medication may be absorbed systemically, thereby having the potential for systemic drug reactions

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Slide 1



Opioid Therapy for Chronic Pain

Slide 2

Opioids: Definition

- **Opioids are morphine-like substances**
 - The term is derived from opium, an extract from the poppy plant
 - Opioids have been available for centuries to relieve pain
 - There are both naturally occurring and synthetic opioids
- **Opioid receptors in the body mediate analgesia**
- **The body generates internal or endogenous opioids called endorphins, enkephalins, and dynorphins**



American Chronic Pain Association. Medications & Chronic Pain; Supplement 2006. Available at: <http://www.theacpa.org/documents/ACPA%20Meds%202006.pdf>. Accessed March 25, 2006.

- Opioids are morphine-like substances¹
- Opium derivatives have been used throughout history for a variety of perception-altering purposes (eg, pain, relief-inducing sleep)¹
- Opioids fill a medical need to relieve moderate to severe pain that would be largely unmet without these drugs¹
- Their therapeutic effect as potent analgesics has made this class of medications clinically useful¹

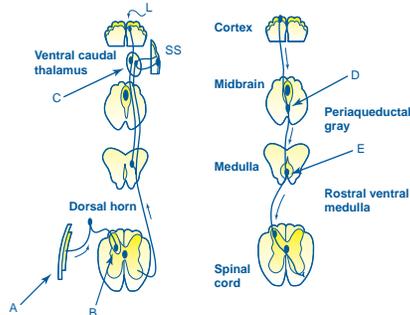
Slide 3

Opioids: Sites of Action

On the left, sites of action on the pain transmission pathway from the periphery to the higher centers are shown.

A: Direct action of opioids on inflamed peripheral tissues.
B: Inhibition occurs in the spinal cord.
C: Possible site of action in the thalamus. Different thalamic regions project to the somatosensory (SS) or limbic (L) cortex.

On the right, actions of opioids on pain-modulating neurons in the midbrain (D) and medulla (E) indirectly control pain transmission pathways.



Reprinted with permission from Schumacher MA, Basbaum AI, Way, WL. Opioid analgesics & antagonists. In: Katzung BG, ed. *Basic & Clinical Pharmacology*, 9th ed. New York, NY: The McGraw-Hill Companies; 2004:497-516.

- Opioid analgesia results from specific drug-receptor interactions in the spinal cord and brainstem that inhibit nociceptive transmission²
 - At both levels, analgesia is mediated by interactions between endogenous endorphinergic systems and subtypes of the μ -, κ -, and δ -receptors
 - Most commonly used opioid drugs are pure agonists that selectively bind to the μ -receptor
- Supraspinal sites of action of opioids include³:
 - Mesencephalic central gray
 - Mesencephalic reticular formation
 - Medulla
 - Substantia nigra
 - Nucleus accumbens/ventral forebrain
 - Amygdala

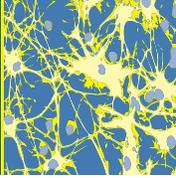
Slide 4

Opioids: Agonists, Antagonists, and Mixed Agonist-Antagonists

- **Drugs that bind to opioid receptors are classified as agonists, mixed agonist-antagonists, or antagonists**
 - Agonists initiate pharmacologic action
 - Antagonists block agonists from binding
 - Agonist-antagonists are μ -agonists with lower intrinsic efficacy (partial agonists) or agents that produce agonist effects at 1 receptor and antagonist effects at another
- **Opioid agonists bind to the μ -receptor and are called μ -agonists**
- **Pure μ -agonists are preferred clinically over agonist-antagonists**

Fine PG, Portenoy RK. *A Clinical Guide to Opioid Analgesia*. Minneapolis, Minn: McGraw-Hill; 2004.

- Drugs that bind to receptors are classified as agonists, antagonists, or agonist-antagonists (partial agonists)⁴
- Opioid analgesics, most commonly used in clinical practice, are agonists that bind selectively to the μ -receptor and are called μ -agonists⁴
- Morphine is the prototype μ -agonist
- Opioid antagonists exert their pharmacologic action by competing with endogenous and exogenous opioids and by preventing activation of the receptor^{2,4}
 - They are used to prevent or reverse opioid-induced adverse effects
 - In patients with physical dependence, displacement of an agonist drug by an antagonist is associated with abstinence or withdrawal symptoms
- Mixed agonist-antagonists are agonists that produce less-than-maximal response to these drugs⁴
 - They have antagonistic properties because they compete with pure agonists for occupancy of the receptor sites, blocking the action of the pure agonists
- Clinically, pure agonists are generally preferred over agonist-antagonists for management of moderate to severe pain, as agonist-antagonists have a ceiling effect (increasing doses have progressively smaller incremental analgesic effects)
 - Pure agonists have no ceiling effect for analgesia



Slide 5

Examples of Opioid Analgesics

Pure agonists

- Fentanyl, hydrocodone, hydromorphone, levorphanol, methadone, morphine, oxycodone, oxymorphone
- No ceiling effect; commonly used for moderate to severe pain

Agonist-antagonists

- Buprenorphine (partial agonist), butorphanol, dezocine, nalbuphine, pentazocine
- Ceiling effect; some produce psychotomimetic side effects

Pure antagonists

- Naloxone, naltrexone
- Administered for prevention or reversal of opioid effects

Other

- Tramadol
- μ -Agonist; also affects monoamines such as serotonin

Fine PG, Portenoy RK. A Clinical Guide to Opioid Analgesia. Minneapolis, Minn: McGraw-Hill; 2004.

- Opioids are classified as⁴:
 - Pure agonists
 - Agonist-antagonists (which include partial agonists)
 - Pure antagonists
- Tramadol, a pure μ -agonist, also affects monoamines such as serotonin⁴

Slide 6

Risks vs Benefits of Opioids

• Clinical benefits

- Demonstrated efficacy in numerous randomized clinical trials and chronic pain conditions
- Low risk for end-organ damage

• Risks

- Side effects (eg, constipation, nausea, sedation)
- Addiction
- Abuse potential, physical dependence, tolerance

Must evaluate risks versus benefits in each patient being considered for long-term treatment

Portenoy RK. Opioid analgesics. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Co; 1996:248-276.

- Opioids have an important role in the treatment of chronic pain⁴
 - Numerous randomized clinical trials have demonstrated their efficacy
- Opioid analgesics possess a low risk for end-organ damage^{2,4}
- Patients should be monitored for signs of addiction
- Common side effects of opioid usage include constipation, nausea, and sedation, which can be effectively managed in some patients^{2,4}
- The likelihood of a favorable balance between analgesia and side effects (ie, opioid responsiveness) varies among patients and pain syndromes⁴
- Clinicians must evaluate risks versus benefits in each patient being considered for long-term treatment

Slide 7

Opioids: Achieving Maximum Pain Relief

- **Select**
 - Appropriate opioid
 - Appropriate route of administration
 - Appropriate dosing
- **Anticipate potential side effects and treat accordingly**
- **Educate patient**
- **Monitor for aberrant medication-related behavior**

Fine PG, Portenoy RK. *A Clinical Guide to Opioid Analgesia*. Minneapolis, Minn: McGraw-Hill; 2004.

Slide 8

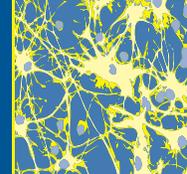
Opioid Rotation

- **Sequential trial of different opioids to obtain the most favorable balance between analgesia and adverse effects^{1,2}**
- **Reasons for opioid rotation³**
 - Substantial variability in patient response
 - Inadequate analgesia
 - Intolerable adverse effects
 - Chronic sedation

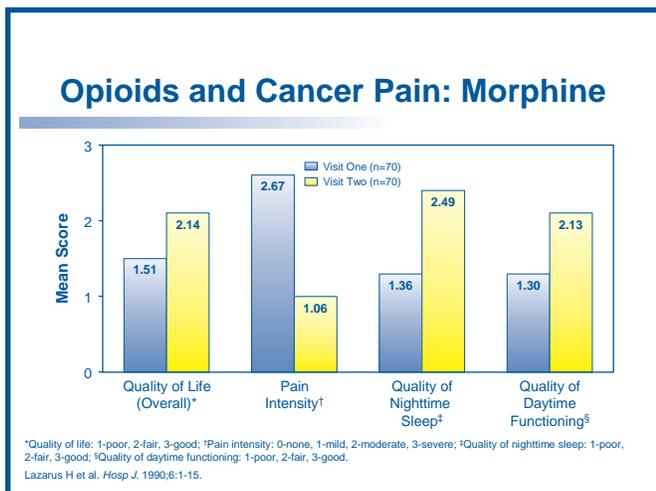


1. Fine PG. *J Pain Palliat Care Pharmacother*, 2004;18:75-79. 2. Bruera E, Kim HK. *JAMA*, 2003;290:2476-2479. 3. Fine PG, Portenoy RK. *A Clinical Guide to Opioid Analgesia*. Minneapolis, Minn: McGraw-Hill; 2004.

- Many options are available for opioid prescription, including immediate-release and modified-release forms⁴
- Single-entity pure μ -agonist opioids are preferred for management of severe pain⁴
 - There is no clinically relevant ceiling effect to analgesia; as the dose is raised, analgesic effects increase until analgesia is achieved or dose-limiting side effects occur
 - Sequential opioid trials (opioid rotation) may be needed to find the best balance between analgesia and side effects
 - This class of pure μ -agonists includes fentanyl, hydromorphone, levorphanol, methadone, morphine, oxycodone, and oxymorphone²
- Traditionally, short-acting, immediate-release combination products (eg, hydrocodone and acetaminophen) have been prescribed for patients with moderate pain
 - These medications have a short half-life and duration of action, typically 2 to 4 hours
 - They are taken on an as-needed basis for acute pain or breakthrough pain
- The least invasive and most convenient route of administration of opioids should be used⁴
 - Noninvasive routes include oral, transdermal, sublingual, rectal, oral transmucosal, intranasal, and inhaled
 - Invasive routes should be considered for patients who require a rapid onset of effect, have impaired swallowing or gastrointestinal obstruction, or require high doses. These include intramuscular injections and subcutaneous, intravenous, and intraspinal administration; repetitive intramuscular injections, however, are painful and offer no pharmacokinetic advantage
- Long-acting, modified-release opioids for moderate pain are also effective and improve the convenience and adherence of therapy in patients on long-term opioid treatment⁴
- Once dose and route of administration are chosen, the dose should be titrated until adequate analgesia occurs or side effects are intolerable⁴
- Treatment of opioid-related side effects is an integral part of effective administration⁴
- Patients should be monitored for aberrant medication-related behaviors such as abuse, addiction, and diversion⁴
- A technique called “opioid rotation” may be appropriate to optimize therapy⁴⁻⁶
- Opioid rotation usually involves abrupt discontinuation of the initial opioid and replacement with an equivalent dose of an alternative opioid⁶
- Based on factors such as genetics, demographic and disease-related variables, as well as comorbidities, there is substantial variation in how patients respond to opioids
 - In some patients, the opioid dose required to maintain analgesia also causes chronic sedation
 - Patients who become nauseated from oral therapy may benefit from transdermal administration
 - Responsiveness to opioid treatment may be impaired if the analgesic effect declines rapidly, resulting in the need to escalate the dose to an intolerable level
 - Metabolism of the drugs is variable. For example, codeine is metabolized to the active metabolite of morphine by the cytochrome P-450 hepatic enzyme system, where about 7% of the United States population are slow metabolizers; as a result, poor codeine responsiveness may occur⁴
- Poor responsiveness to one opioid does not predict response to another
- When switching from one opioid to another, calculated equianalgesic doses are used as a starting point to reduce the risk of overdosing or underdosing⁴

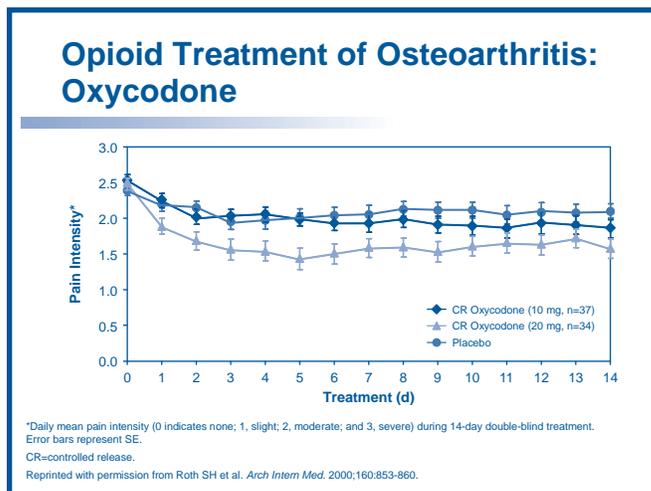


Slide 9



- The analgesic efficacy of oral controlled-release morphine sulfate tablets was evaluated in cancer patients⁷
 - 70 patients completed the sequential, crossover, open-label study
 - Evaluations were made at baseline (when patients received their previous analgesic medicine) and after at least 2 weeks on morphine sulfate tablets
 - Previous analgesics included hydromorphone, methadone, levorphanol, oxymorphone, hydrocodone, codeine, pentazocine, butorphanol, nalbuphine, buprenorphine, and morphine
 - Appropriate dose conversions were used when switching to morphine sulfate tablets
- Pain intensity was significantly decreased ($P < .0001$ vs baseline)⁷
- Patient overall quality of life also improved significantly ($P = .0001$ vs baseline)⁷

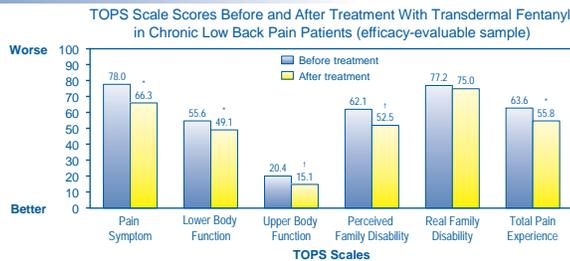
Slide 10



- The effects of controlled-release oxycodone treatment on pain and function and its safety versus placebo were studied in 133 patients with moderate to severe osteoarthritis pain for at least 1 month⁸
 - Patients were randomized to double-blind treatment with placebo or 10 mg or 20 mg of controlled-release oxycodone every 12 hours for 14 days
 - Most patients (73.7%) were women; the average age of the patients was 62 years
 - Patients with a history of drug or alcohol abuse were excluded
- In many analgesic trials, a 20% average reduction in baseline pain intensity is considered clinically meaningful. Based on the 4-point categorical scale, 20 mg of controlled-release oxycodone every 12 hours attained this goal within 1 day; the placebo group never achieved this reduction⁸
- The reduction in pain intensity with 20 mg of controlled-release oxycodone every 12 hours was sustained during the 14-day trial: 20 mg of controlled-release oxycodone was more effective ($P < .05$) in reducing mean pain intensity at weeks 1 and 2 and overall than was taking placebo or 10 mg of controlled-release oxycodone⁸
- Eighty-seven (65.4%) of 133 patients reported at least 1 treatment-related adverse experience during the study; the most common were known opioid-related side effects (nausea, constipation, somnolence, vomiting, dizziness, pruritus, headache)⁸

Slide 11

Opioid Treatment Improved Health-Related Quality of Life: Fentanyl and Chronic Low Back Pain



* $P < .001$; † $P < .01$. TOPS=Treatment Outcomes in Pain Survey.
Reprinted with permission from Kosinski MR et al. *Curr Med Res Opin.* 2005;21:849-862.

- Kosinski et al examined the effect of long-acting transdermal fentanyl on patient health-related quality of life⁹
 - An observational study was conducted at 17 clinical centers in the United States
 - Eligible patients had chronic low back pain for at least 3 months and were taking short-acting opioids chronically (ie, opioid tolerant)
 - 358 patients were recruited; 251 patients completed baseline and follow-up data; 131 patients comprised the efficacy-evaluable sample
- Patients were evaluated on a range of health-related quality of life variables⁹
 - Patients completed the Treatment Outcomes in Pain Survey, which included the SF-36 Health Survey, at baseline and at ≥ 9 weeks of treatment
- At follow-up, significant improvement ($P < .05$) was observed on 6 of the SF-36 scales and on both SF-36 summary measures, and on 5 of the 6 Treatment Outcomes in Pain Survey scales⁹
- Thirty percent of patients experienced adverse events. The most common adverse events were skin irritation (9.5%), nausea (6.4%), and vomiting (6.4%)⁹

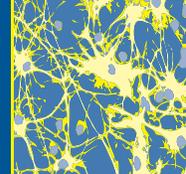
Slide 12

Management of Opioid Side Effects

Side Effects	Amelioration
Constipation	Treat prophylactically with stool softeners, bowel stimulants; nonpharmacologic measures; switch opioids
Nausea and vomiting	Switch opioids; antiemetics
Sedation	Lower doses (if possible); add coanalgesics; add stimulants
Itching	Switch opioids; add antihistamines
Endocrine dysfunction/ reduced libido	Switch opioids; endocrine monitoring; testosterone replacement; endocrine consultation
Edema and sweating	Switch opioids
Dizziness	Antivertiginous agents (eg, scopolamine)
Confusion	Titrate dose; switch opioids

McNicol E et al. *J Pain.* 2003;4:231-256.

- The major side effects of opioid analgesics are well known and include constipation, nausea, vomiting, dizziness, sedation, cognitive dysfunction, itching, sweating, and respiratory depression¹⁰
- Clinical experience suggests that many of these effects resolve over time, although this has not been carefully studied. However, side effects are the reason that many patients discontinue therapy^{10,11}
- Patients who continue opioid therapy and are affected by these side effects may be suffering needlessly. Many of these side effects can be prevented and treated, which will optimize therapy¹⁰
- The best approach to prevent opioid-related side effects is to gradually titrate the dose and to consider prophylaxis (eg, constipation)¹⁰
- Finally, because the side effects of opioids are idiosyncratic, switching opioids can eliminate or improve side effects in any given patient¹⁰



Slide 13

Opioid Dependence, Tolerance, Pseudoaddiction, and Addiction

What are the differences?

- **Physical dependence:** Withdrawal syndrome would occur if the medication is discontinued abruptly, dose is reduced rapidly, or an antagonist is administered^{1,2}
- **Tolerance:** A greater amount of medication is needed to maintain therapeutic effect, or loss of effect over time²
- **Pseudoaddiction:** Behavior suggestive of addiction caused by undertreatment of pain²; can be a major barrier to appropriate treatment of patients in pain
- **Addiction (psychologic dependence):** A biopsychosocial disorder characterized by continued compulsive use of a substance despite harm^{2,3}

1. APS. *Guideline for the Management of Cancer Pain in Adults and Children*. Glenview, Ill: American Pain Society; 2005.
2. Savage SR et al. *APS Consensus Statement*. Glenview, Ill: American Pain Society; 2001. 3. Fishbain DA et al. *Clin J Pain*. 1992;8:77-85.

- Opioid tolerance and physical dependence are expected physiologic adaptations to long-term opioid treatment and should not be confused with addiction (psychological dependence)
 - Misunderstanding these terms often leads to undertreatment of patients with chronic pain^{11,12}
- Physical dependence is expected in all patients who receive opioids for more than a few days¹¹
- Physical dependence is manifested by a drug-class-specific withdrawal syndrome when the medication is stopped abruptly, the dose is reduced rapidly, the blood level of the medication drops, or an antagonist (eg, naloxone) is administered
 - Withdrawal can be avoided by tapering the dose of the opioid when therapy is discontinued^{11,12}
- Pseudoaddiction is a response to the patient's need for appropriate pain management
 - Pseudoaddiction may occur when a patient with severe pain that has not been managed effectively seems preoccupied with potent analgesics or is engaged in other drug-seeking behaviors.¹² When the patient receives adequate medication, the behavior stops and the patient uses the medication as prescribed^{11,12}
- Addiction is a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors characterized by impaired control over medication use, compulsive use, continued use despite harm, and craving^{11,12}
- Physical dependence is not the same as addiction^{11,13}

Slide 14

Opioid Analgesics and Iatrogenic Addiction

- **Few systematic studies on long-term medical use of opioids and associated addiction have been conducted¹**
 - Earlier studies found that addiction is rare in patients without a history of substance/drug abuse^{2,3}
 - However, a recent study of patients with intractable headache found that problem drug behavior occurred in 50% of patients, usually involving dose violations⁴

1. Portenoy RK. Opioid analgesics. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Co; 1996:248-276. 2. Perry S, Heidrich G. *Pain*. 1982;13:267-280. 3. Medina JL, Diamond S. *Headache*. 1977;17:12-14. 4. Saper JR et al. *Neurology*. 2004;62:1687-1694.

- The true incidence of iatrogenic addiction related to the medical use of opioids in patients with pain is unknown
- Early published reports suggest it is very low
 - A national survey of >10,000 burn patients who received opioids revealed that drug addiction was rare in patients without history of substance/drug abuse¹⁴
 - A study of 2369 patients with chronic headache, most of whom had access to opioids, revealed that only 5 abused the analgesics¹⁵
- A recent examination of patients receiving daily scheduled opioids to remediate intractable headache found much greater cause for concern of addiction, diversion, or misuse (aberrant medication behaviors)¹⁶
 - 160 patients completed structured questionnaires at each medical visit as part of routine clinical care
 - Medical records were assessed during treatment and during the 2 years before starting daily scheduled opioids
 - Aberrant medication-related behavior (dose violations, lost prescriptions, multisourcing) occurred in 50% of patients, usually involving dose violations
- Given the lack of existing data regarding iatrogenic addiction, clinicians should ensure that assessment of the patient for chronic pain includes a variety of factors related to the relative risk of abuse and addiction⁴
- A patient's relative risk could then be determined, and if the clinician determines that the patient is an appropriate candidate for opioid therapy, an individual treatment regimen can be developed

Slide 15

Assessing Relative Risk for Aberrant Behavior

- Document patient's personal history to determine present or past substance abuse or psychiatric disorders¹
 - Consider screening tools to augment clinical judgment
- Screener and Opioid Assessment for Patients With Pain²
 - Brief screening tool completed by patient
 - Helps assess relative risk of misuse of opioid analgesics
 - Intended only for patients considered for long-term opioid treatment
 - Study in 175 patients showed reliability and predictive validity of scale

1. Nedejkovic SS et al. *Clin J Pain*. 2002;18(4 suppl):S39-S51. 2. Butler SF et al. *Pain*. 2004;112:65-75.

- Prior to prescribing opioid analgesics, it is important to assess the patient's personal history to determine present or past history of substance abuse or other psychiatric disorders that might preclude the use of opioids¹⁷
 - There are several screening tools that can be used; some are reviewed on the next slide
- The Screener and Opioid Assessment for Patients With Pain is a screening tool to help assess the relative risk of misuse of opioid analgesics¹⁸
 - The initial validation study of the Screener and Opioid Assessment for Patients With Pain demonstrated its reliability and predictive validity
 - A randomized study is currently being conducted by the National Institute on Drug Abuse
 - Screener and Opioid Assessment for Patients With Pain is available at: <http://www.painedu.org>
- Screening tools such as the Screener and Opioid Assessment for Patients With Pain are not intended to "screen in" or "screen out" patients but rather to provide information to the clinician that can supplement clinical judgment

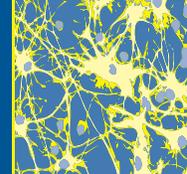
Slide 16

Predictors of Aberrant Behavior

Predictive of Aberrant Behavior	Use Caution With These Patients
How many alcoholic drinks on a typical day?	Men who drink more than 4 alcoholic beverages per day or 16 per week
How many drinks in a typical week?	Women who drink more than 3 alcoholic beverages per day or 12 per week
Have you used marijuana or hashish in the past year?	Persons who admit to recreational use of marijuana or hashish in the last year
Have you ever smoked cigarettes? What is your age?	Persons who are younger than 40 years and smoke

Fine PG, Portenoy RK. *A Clinical Guide to Opioid Analgesia*. Minneapolis, Minn: McGraw-Hill; 2004.

- There is currently no standard approach to the prediction of risk
- Several questionnaires have been developed for assessing the potential for opioid abuse in patients
- The Screening Instrument for Substance Abuse Potential was designed to determine the potential for patient abuse of opioids⁴
 - Use when a physician already knows the patient or has sufficient other information to confirm the patient's responses
 - This test has a low false-negative rate, but it results in a fairly high percentage of patients who are falsely labeled as being at higher risk
- Other tools include the Cut down, Annoyed, Guilt, and Eye-opener questionnaire⁴
- Clinicians should ensure that assessment of the patient with chronic pain includes a variety of items related to the risk of abuse and addiction
 - Patients can then be classified as being at relatively low versus relatively high risk of developing aberrant behaviors. This classification can be used to determine the approach to therapy monitoring and administration over time



Slide 17

Risk-Management Principles

Thorough Assessment and Appropriate Level of Monitoring

• PROACTIVE STRATEGIES	• REACTIVE STRATEGIES
<ul style="list-style-type: none"> - Written agreement - Long-acting drug without rescue dose - Frequent visits/limited prescription quantities/count pills at appointment - 1 pharmacy/no early refills or replacements - Require prior records/permission to contact prior providers - Referral for substance-abuse assessment for at-risk patients - Permission to get feedback from family members - Database query for electronic prescriptions 	<ul style="list-style-type: none"> - All proactive strategies - More specific written agreement - Discontinue rescue dose - Urine drug screens - Referral for substance-abuse assessment with follow-up treatment for problematic behaviors

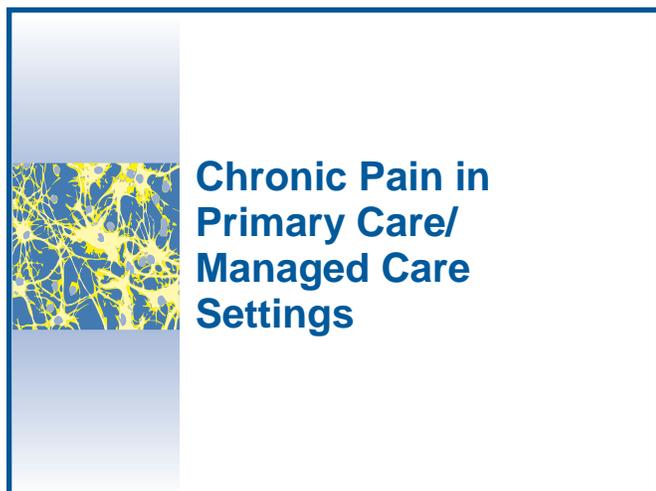
Fine PG, Portenoy RK. *A Clinical Guide to Opioid Analgesia*. Minneapolis, Minn: McGraw-Hill; 2004.

- Treatment strategies should be individualized to minimize the likelihood of misuse, abuse, addiction, or diversion; thorough assessment and an appropriate level of monitoring should reduce such outcomes⁴
- The clinician needs to assess the patient's relative risk of abuse and use proactive strategies; all patients taking opioids should be monitored for development of aberrant drug-related behaviors
- If a patient engages in problematic behavior, it is important to reassess the patient to clarify the meaning of the behavior and distinguish among addiction, pseudoaddiction, family problems, or criminal activity
- Proactive and reactive strategies include⁴:
 - A written agreement, which is more specific when assessing aberrant drug-related behaviors
 - Prescribing a long-acting drug without a rescue dose
 - Frequent visits, small prescription quantities, asking the patient to bring the pill bottle to appointments for a pill count
 - Using one pharmacy and allowing no early refills and no replacements without a police report documenting the loss of medication
 - Requiring all prior records and permission to contact the patient's healthcare providers
 - Mandatory referral to an addiction specialist when a patient is assessed to be at risk for substance abuse or behaviors suggest a potential problem
 - Mandatory permission to get feedback from spouse or family members
 - Communicating the intention of the clinician to perform a database query when using electronic prescription forms

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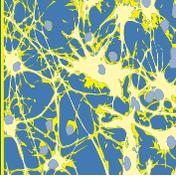
Slide 2

Current Practices of Chronic Pain Management: Need for Improvement

- **Chronic pain is often unrelieved and undertreated**
 - It is estimated that 4 out of 10 people with moderate to severe pain do not get adequate relief
 - Advances in pain management have not translated into standard-of-care practices in the clinical setting
- **A significant portion of patients**
 - Are not routinely asked about pain
 - Are reluctant to report pain
 - Are unaware of available management treatments
 - Do not adhere to pain treatments
 - Are sometimes not offered treatments when pain is reported

NIH/DHHS: An update on NIH pain research and related program initiatives, December 2005. Available at: http://www.theacpa.org/documents/2005_12_08%20An%20Update%20of%20NIH%20Pain%20Research%20and%20Related%20Program%20Initiatives.pdf Accessed May 17, 2006.

- More than 50 million Americans experience chronic pain and more than half of dying patients experience moderate to severe pain during the last days of their lives¹
 - About 45% of the population seek medical help for pain sometime during their lives
- Often patients are not aware of advances in pain management. A large number of patients¹:
 - Are not routinely asked about pain
 - Are reluctant to report pain
 - Are unaware of available management treatments
 - Do not adhere to pain treatments
 - Are sometimes not offered treatments when pain is reported
- Clinicians should assess patients for pain at routine office visits



Slide 3

Goals of Chronic Pain Management in Primary Care

- **Diminish suffering**
 - Pain and emotional stress
- **Increase/restore function**
 - Physical
 - Social
 - Vocational
 - Recreational
- **Optimize health**
 - Including psychological well-being
- **Improve coping ability and relationships with others**



NPC/JCAHO. Pain: Current Understanding of Assessment, Management, and Treatments. December 2001.

- Chronic pain is often associated with significant physical, emotional, and social disability
- The primary goals in chronic pain management include²:
 - Diminish patient suffering, both physical and psychological
 - Increase/restore function
 - Optimize health and well-being
 - Improve the ability to cope with pain and restore relationships with others

Slide 4

Therapeutic Strategies for Management of Chronic Pain in the Primary Care Setting

- **Multimodal therapy¹**

- "Concomitant use of separate therapeutic interventions under the direction of a single practitioner"²



- **Interdisciplinary approach to rehabilitation¹**

- Healthcare professionals with disparate training collaborate to diagnose and treat patients

1. NPC/JCAHO. Pain: Current Understanding of Assessment, Management, and Treatments. December 2001. 2. American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section. Anesthesiology, 1997;86:995-1004.

- Therapeutic strategies for management of chronic pain include multimodal therapy and an interdisciplinary approach to rehabilitation²
- Multimodal therapy was defined by the American Society of Anesthesiologists as the concomitant use of separate therapeutic interventions under the direction of a single practitioner to obtain additive beneficial effects or reduction of adverse effects³
- An interdisciplinary approach refers to the process in which healthcare professionals with disparate areas of expertise cooperate to diagnose and treat the patient with chronic pain
- This will provide coordinated team services to reduce pain, improve function, and decrease dependence on the healthcare system

Slide 5

Challenges in Managing Chronic Pain in the Managed Care Setting

- Lack of consensus regarding treatment goals
- Lack of robust and generalized outcomes studies
- Need to understand pain as a chronic disease
- Insufficient reimbursement for physical therapy, behavioral intervention, or medication management
- Lack of focus on physical rehabilitation or long-term strategies

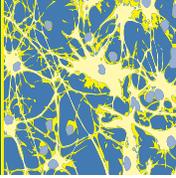
- Managed care organizations may benefit from implementing guidelines from the American Pain Society Position Statement on Pain Assessment and Treatment in the Managed Care Environment, which stresses education and accreditation of providers, recognition of the unique nature of chronic pain, and the need for case coordination and communication with patients' disability carriers and employers⁴
- Treating chronic pain in the managed care setting is challenging. There remains a need for consensus regarding treatment goals, outcome measurements, and generalized outcomes studies
- Managed care organizations need to become familiar with the variety of chronic pain conditions and new developments in the field so they do not unwittingly deny services to patients because they do not understand their utility
- Because procedural-based interventions are easier to understand and conceptualize, insurers often reimburse for such procedures but do not consider payment for longer-term interventions such as physical therapy, rehabilitation, or cognitive-behavioral therapy
- Long-term strategies for chronic pain need to be considered as well as, or instead of, more temporary interventions

Slide 6

Potential Solutions for the Management of Chronic Pain With Managed Care

- Protocol for measuring patients' baseline pain and responses to treatment
- Lexicon for common understanding of pain terminology
- Patient-clinician feedback mechanisms
- Multimodal, stepped-care plan spearheaded by primary care clinician

- Increasingly, managed care organizations are attempting to understand chronic pain prevalence, pathophysiology, management standards, and cost implications. Vital first steps are to:
 - Standardize tools for initial pain assessment and reassessment
 - Standardize pain terminology to prevent misunderstanding among clinicians and between the treating clinician and the patient
 - Develop patient-clinician feedback mechanisms regarding pain treatment to address and minimize ineffective treatment
 - Develop a stepped-care plan that is spearheaded by the primary care clinician



Slide 7

US Pain Management Standards: Requirements for Healthcare Organizations

- Recognize the right of patients to appropriate assessment and management of pain
- Identify patients with pain in an initial screening assessment
- Perform a more comprehensive pain assessment when pain is identified
- Record the results of the assessment in a way that facilitates regular reassessment and follow-up
- Educate relevant providers in pain assessment and management
- Determine and ensure staff competency in pain assessment and management

JCAHO. US pain management standards. Available at: http://www.whocancerpain.wisc.edu/eng/14_2/requirements.html. Accessed May 17, 2006.

- To address some of the problems noted by the American Pain Society, the Joint Commission on Accreditation of Healthcare Organizations in 2001 established standards for chronic pain management⁵
- The new pain standards do not specify how pain should be managed, just that it must be done

Slide 8

US Pain Management Standards: Requirements for Healthcare Organizations (cont)

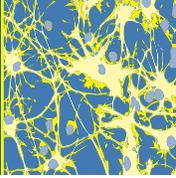
- Address pain assessment and management in the orientation of all new staff
- Establish policies and procedures that support appropriate prescription or ordering of effective pain medications
- Ensure that pain does not interfere with participation in rehabilitation
- Educate patients and their families about the importance of effective pain management
- Address patient needs for symptom management in the discharge planning process
- Collect data to monitor the appropriateness and effectiveness of pain management

JCAHO. US pain management standards. Available at: http://www.whocancerpain.wisc.edu/eng/14_2/requirements.html. Accessed May 17, 2006.

- Guidelines issued by the Joint Commission on Accreditation of Healthcare Organizations have increased the role for primary care clinicians in managing chronic nonmalignant pain.⁵ However, no specific treatment program is endorsed by guideline-issuing organizations
- Individual primary care clinicians, therefore, must establish their own guidelines and identify circumstances when subspecialty referral is indicated based on pain severity, associated comorbidity, disability, or increased risk of medication abuse or misuse⁶
- Most importantly, primary care clinicians need to create individualized treatment plans to suit their patients' needs

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1. National Institutes of Health, US Department of Health and Human Services. An update on NIH pain research and related program initiatives, December 2005. Available at: http://www.theacpa.org/documents/2005_12_08%20An%20Update%20of%20NIH%20Pain%20Research%20and%20Related%20Program%20Initiatives.pdf. Accessed May 17, 2006.
2. National Pharmaceutical Council, Inc, Joint Commission on Accreditation of Healthcare Organizations. *Pain: Current Understanding of Assessment, Management, and Treatments*. December 2001.
3. American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section. Practice guidelines for chronic pain management. *Anesthesiology*. 1997;86:995-1004.
4. American Pain Society. Pain assessment and treatment in the managed care environment. A position statement from the American Pain Society. © 2000 American Pain Society.
5. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO). US pain management standards. Available at: http://www.whocancerpain.wisc.edu/eng/14_2/requirements.html. Accessed May 17, 2006.
6. Marcus DA. Managing chronic pain in the primary care setting. Available at: <http://www.aafp.org/afp/20020701/editorials.html>. Accessed May 17, 2006.



Slide 1

Breakthroughs and Challenges in the Management of Chronic Pain: Summary

- **Chronic pain is**
 - Common, underassessed, and undertreated
 - Manifested in various conditions, including PDN, PHN, cancer, migraine, low back pain, and osteoarthritis
- **Assessing pain appropriately will help clinicians determine a treatment approach that considers:**
 - Unique patient characteristics
 - Behavioral and psychosocial issues
 - Mechanism of action of therapeutic agents
 - Rational polypharmacy
 - Safety, tolerability, and efficacy of pharmacotherapy
 - Nonpharmacologic alternatives

PDN=peripheral diabetic neuropathy; PHN=postherpetic neuralgia.

Obtaining Continuing Medical Education Credit

Breakthroughs and Challenges in the Management of Common Chronic Pain Conditions is a self-study educational slide kit designed for physicians, nurses, and other healthcare professionals who treat patients with chronic pain. Continuing medical education credit will be awarded to participants who successfully complete this activity. Participation should take approximately 4 hours. To complete this activity and receive credit, the participant should:

- Read and review the educational objectives included in this slide kit
- Review the slide kit and accompanying notes
- Complete the posttest and evaluation form online at: <http://www.hmc.psu.edu/ce/PainSlides>, or mail or fax them to:

Enduring Materials Coordinator
Continuing Education, G220
Penn State College of Medicine
PO Box 851
Hershey, PA 17033-0851
Fax: (717) 531-5604

Participants must receive a score of 80% or higher to receive credit.

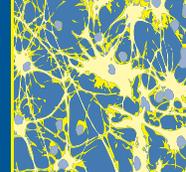
Be sure to submit the posttest and the evaluation form on or before July 31, 2007. After that date, the slide kit will no longer be designated for credit.

A certificate will be mailed within 6 to 8 weeks. It is recommended that participants keep a copy of their completed materials until they receive their certificate.

For questions regarding credit, the posttest, or evaluation form, please call Penn State Continuing Education at (717) 531-6483 or email continuinged@hmc.psu.edu. Please reference activity code **PSU# I3243-06-R**.

Posttest Assessment (Please record your answers in the space provided on page 110)

1. Which of the following is the "gold standard" for pain assessment?
 - a. Patient's medical history
 - b. Functional assessment including limits to range of motion and daily activities
 - c. Patient's self-report
 - d. Psychosocial assessment that addresses the patient's mood, level of emotional stress, and psychological state
2. The most common etiology of neuropathic pain is:
 - a. Low back pain
 - b. Diabetes
 - c. Postherpetic neuralgia
 - d. Cancer
3. Which of the following agents is NOT approved for postherpetic neuralgia?
 - a. Gabapentin
 - b. Lidocaine patch 5%
 - c. Pregabalin
 - d. Tramadol
4. A randomized, double-blind clinical trial found that patients with postherpetic neuralgia who received gabapentin had significantly better improvement than did patients who received placebo in:
 - a. Short Form-36 (SF-36) indicator: physical functioning only
 - b. SF-36 indicator: bodily pain and mental health, but not physical functioning
 - c. The Profile of Mood States (POMS) measure of total mood disturbance, but not SF-36 indicator: physical functioning or bodily pain
 - d. Three of the SF-36 indicators: physical functioning, bodily pain, and mental health, and in the POMS measure of total mood disturbance
5. In a randomized, placebo-controlled clinical trial of the lidocaine patch 5% in patients with postherpetic neuropathy and in other peripheral neuropathic pain syndromes (PNPS):
 - a. Decrease in ongoing pain intensity and allodynia was not significantly different from pretreatment (basal) values with lidocaine treatment ($P<.07$) at the first (2 hours) time point.
 - b. Decrease in ongoing pain intensity and allodynia was not significantly different from pretreatment (basal) values with placebo treatment ($P<.07$) at the first (2 hours) time point.
 - c. Study results demonstrated nonsignificant reductions in ongoing pain ($P=.07$) and allodynia ($P=.06$) during the first 8 hours of application of the lidocaine patch 5%.
 - d. The lidocaine patch 5% significantly reduced pain over a period of 7 days ($P=.018$) in diverse focal PNPS.
6. Back pain is the most common reason for workers' compensation claims, accounting for about:
 - a. One eighth of total compensation costs
 - b. One fifth of total compensation costs
 - c. One fourth of total compensation costs
 - d. One third of total compensation costs
7. Low back pain is most often related to:
 - a. Mechanical causes
 - b. Systemic causes
 - c. Pathophysiologic causes
 - d. Other causes
8. Which of the following treatments of low back pain is without significant scientific merit?
 - a. Physical therapy
 - b. Exercise
 - c. Weight control
 - d. Prolonged bed rest



9. Emerging treatments that have shown promise in clinical trials for low back pain include all of the following EXCEPT:
 - a. Combinations of opioids with other analgesics
 - b. Lidocaine patch 5% as add-on therapy
 - c. Botulinum toxin type A
 - d. All of the above have shown promise in clinical trials.
10. In a prospective cohort study of analgesic administration for hip fracture, what fraction of the cognitively intact patients who had moderate to very severe pain received inadequate analgesia for their level of pain?
 - a. One fifth
 - b. One fourth
 - c. One third
 - d. One half
 - e. Two thirds
11. Pain management in older adults:
 - a. Is most effective when pharmacotherapy is combined with nonpharmacologic interventions
 - b. Should include the daily use of high-dose nonsteroidal anti-inflammatory agents rather than opioids
 - c. Should avoid the use of polypharmacy to minimize dose-limiting adverse events
 - d. Should avoid the use of opioids
12. Pain results in lost US workforce productivity of \$61.2 billion per year. This figure represents what percentage of the total estimated work-related cost of pain?
 - a. 27%
 - b. 42%
 - c. 63%
 - d. 83%
13. Chronic pain differs from acute pain in all of the following EXCEPT:
 - a. In chronic pain, neural pathways undergo physiochemical changes that make them hypersensitive to pain signals.
 - b. In chronic pain, neural pathways undergo physiochemical changes that make them resistant to antinociceptive input.
 - c. Chronic pain acts as a warning system indicating tissue damage.
 - d. Chronic pain results from a pathological process that can recur at intervals.
14. All of the following statements are true about osteoarthritis EXCEPT:
 - a. It is the leading cause of work disability in people 16 to 72 years of age.
 - b. It accounts for more than 7 million ambulatory care visits per year.
 - c. It affects 80% of people over the age of 75 years.
 - d. All of the above are true.
15. Which of the following factors DOES NOT contribute to the development of osteoarthritis?
 - a. Obesity
 - b. Vitamin D deficiency
 - c. Low-impact aerobic exercise
 - d. Trauma
16. Which of the following agents is indicated for first-line management of mild osteoarthritis pain?
 - a. Cyclooxygenase-2 inhibitors
 - b. Capsaicin patch
 - c. Lidocaine 5% patch
 - d. Acetaminophen
17. Which of the following is not an opioid?
 - a. Fentanyl
 - b. Hydromorphone
 - c. Levorphanol
 - d. Methadone
 - e. Lidocaine
18. Variability in patient response, inadequate analgesia, and chronic sedation are common reasons for opioid rotation.
 - a. True
 - b. False
19. Pseudoaddiction is defined as behavior suggestive of addiction that results from:
 - a. Severe pain that has not been managed effectively
 - b. Adaptation to long-term opioid treatment
 - c. Need for greater amount of medication to maintain therapeutic effect
 - d. Abrupt discontinuation of medication
20. The Screener and Opioid Assessment for Patients with Pain (SOAPP) is a validated screening tool to help the clinician assess:
 - a. The risk of misuse of opioid analgesics
 - b. The efficacy of treatment
 - c. Development of treatment-related adverse events
 - d. Patient compliance with therapy
21. Which of the following statements is true about transdermal delivery systems?
 - a. They are associated with minimal systemic absorption.
 - b. They can be placed anywhere on the body to which a patch will adhere.
 - c. They are associated with a lower potential for systemic effects than are topical delivery systems.
 - d. They generally do not increase blood levels of the agent being delivered.
22. Which of the following statements is true about migraine prophylaxis?
 - a. Magnesium has received Food and Drug Administration (FDA) approval for migraine prophylaxis.
 - b. Naproxen sodium has received FDA approval for migraine prophylaxis.
 - c. Both a and b are true.
 - d. No agent has received FDA approval for migraine prophylaxis.
23. Which of the following is NOT a characteristic of menstrual migraine?
 - a. Migraine without aura
 - b. Severe intensity
 - c. Short duration (48 hours)
 - d. All of the above are characteristics of menstrual migraine.
24. Opioid rotation may be appropriate to optimize therapy:
 - a. When responsiveness to the initial opioid is poor
 - b. When the opioid dose required to maintain analgesia also causes chronic sedation
 - c. When nausea from oral therapy can be eliminated by transdermal administration.
 - d. All of the above

Obtaining Continuing Medical Education Credit

Posttest Answers

Expiration Date: July 31, 2007

1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____ 7. _____ 8. _____ 9. _____ 10. _____
 11. _____ 12. _____ 13. _____ 14. _____ 15. _____ 16. _____ 17. _____ 18. _____ 19. _____ 20. _____
 21. _____ 22. _____ 23. _____ 24. _____ 25. _____

Registration Form

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Actual time spent on the activity (up to 4 hours) _____

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Please fill in the circles completely using a dark pen or pencil.

OVERALL EVALUATION

	Very High	High	Moderate	Low	Very Low
1. To what extent were the overall objectives achieved?	<input type="radio"/>				
2. To what extent are you satisfied with the overall quality of the slide kit?	<input type="radio"/>				
3. To what extent did the slide kit present scientifically rigorous, unbiased, and balanced information?	<input type="radio"/>				
4. To what extent was the slide kit free of commercial bias?	<input type="radio"/>				
5. To what extent did this slide kit change your knowledge/attitudes?	<input type="radio"/>				
6. To what extent did this slide kit change your skills?	<input type="radio"/>				
7. To what extent will you make a change in your practice as a result of your participation in this slide kit?	<input type="radio"/>				
8. Which of the following statements best describes the impact of this activity on your performance? (choose one)					
<input type="radio"/> This activity will not change my behavior because my current practice is consistent with what was taught.					
<input type="radio"/> This activity will not change my behavior because I do not agree with the information presented.					
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9. May we contact you regarding similar CME activities on this subject?					
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<input type="radio"/> No					