Applying New Concepts in The Management of Chronic Pain

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Disclosure

- There are no conflicts of interest regarding relevant financial interests in making this presentation and I have indicated that my presentation does not include discussion of an unlabeled use of a commercial product or an investigational use not yet approved for any purpose

LAKE WOBEGON GENERAL HOSPITAL

Problem of Pain and Barriers to Pain Management

CORE

Pain is the most common reason for patients to seek medical attention

- Acute pain (<1 wk) accounts for 1 out of every 6 visits to the PCP
- 35 million injury visits to ER/year in the United States
  - 4.3 million sports- and recreation-related injuries
  - Represent 16% of all unintentional injury-related ER visits
- 46 million surgeries/year in the United States
  - 60% to 65% performed on an outpatient basis
- Possibility of acute pain becoming chronic
- Emphasis on patient satisfaction
  - Pain is one of the primary concerns of patients facing procedures

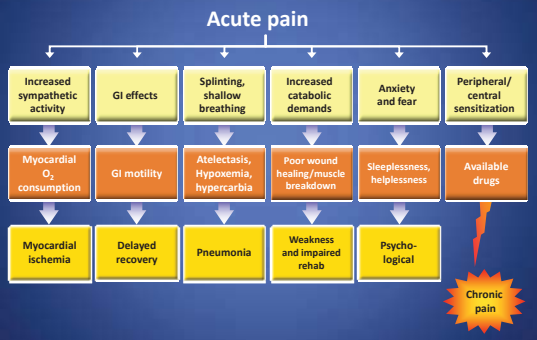
Coda et al. In: *Bonica's Management of Pain.* 2001:222-240; Mäntyselkä et al. *Pain.* 2001;89: 175-180.

Patients in Pain

- 97 NH patients[1]
  - 71% reported pain; only 15% of patients with pain received analgesics in past 24 h
- Over 13,000 NH patients with cancer[2]
  - 29% c/o daily pain; 26% of those received no analgesics
  - Those older than 85 years less likely to receive any analgesics
- Cognitively impaired NH residents[3]
  - 76% with at least 1 diagnosis known to cause pain
  - No pain medication in previous month
- Minimum Data Set 50 states; 2.2 million records[4]
  - 15% residents in daily pain
  - 41% residents with pain, still in pain 60 to 180 days later
  - Substantial statewide variation—41 states between 39% to 46%

1. Ferrell et al. *J Am Geriatr Soc.* 1990;38:409-414; 2. Bernabei et al. *JAMA.* 1998;279:1877-1882; 3. Feldt et al. *J Gerontol Nurs.* 1998;24:14-22; 4. Teno et al. *JAMA.* 2001;285:2081.

Consequences of Unrelieved Pain



Chronic Pain After Surgery

Surgical procedure	Chronic pain (%)
Limb amputation	30-83
Thoracotomy	22-67
Breast surgery	31-83
Gall bladder (LP)	3-56
Hernia surgery	4-37

Perkins et al. *Anesthesiology.* 2000;93:1123-1133.

Effects of Chronic Pain on the Patient

Physical Functioning
- Ability to perform activities of daily living
- Sleep disturbances

Psychological Morbidity
- Depression
- Anxiety
- Anger
- Loss of self-esteem

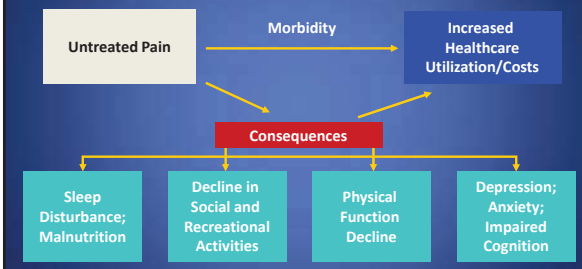
Social Consequences
- Relationships with family and friends
- Intimacy/sexual activity
- Social isolation

Societal Consequences
- Healthcare costs
- Disability
- Lost workdays

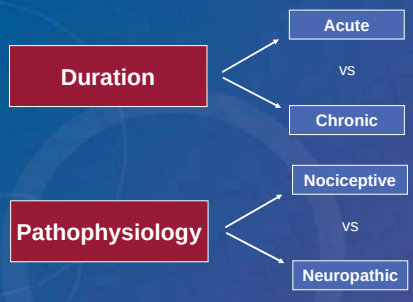
Galer et al. In: *A Clinical Guide to Neuropathic Pain.* 2000:15-19; Eisendrath. *Neurology.* 1995;45(suppl 9):S26-S34.

Physiology of Pain Perception

Patients in Pain



Classifying Pain

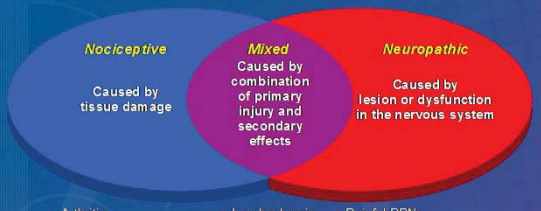


Nociceptive vs Neuropathic Pain States

Nociceptive	vs	Neuropathic
• Arises from stimulus outside of nervous system • Proportionate to receptor stimulation • When acute, serves protective function		• Arises from primary lesion or dysfunction in nervous system • No nociceptive stimulation required • Disproportionate to receptor stimulation • Other evidence of nerve damage

Serra. *Acta Neurol Scand.* 1999;173(suppl):7-11.

Examples of Nociceptive and Neuropathic Pain

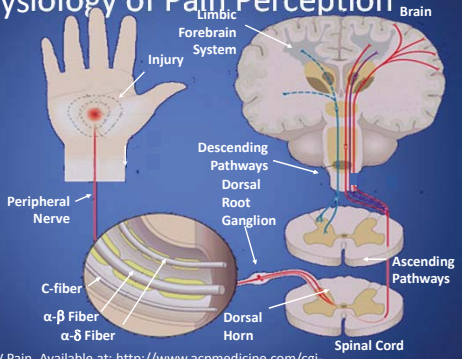


- Arthritis
- Mechanical low back pain
- Sports/exercise injuries
- Postoperative pain
- Low back pain
- Fibromyalgia
- Neck pain
- Cancer pain
- Painful DPN
- PHN
- Neuropathic low back pain
- Trigeminal neuralgia
- Central poststroke pain
- Complex regional pain syndrome
- Distal HIV polyneuropathy

Physiology of Pain Perception

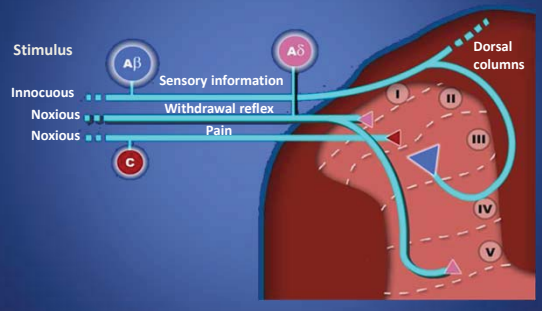
CORE

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



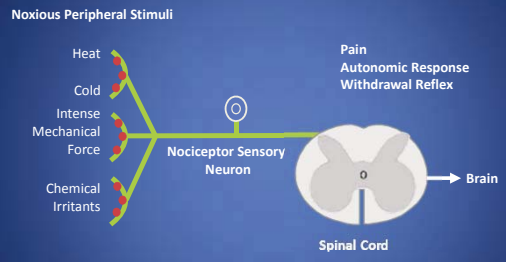
Carver et al. XIV Pain. Available at: http://www.acpmedicine.com/cgi-bin/publiccgi.pl?loginOP. Accessed March 29, 2006.

Normal Pain Pathways in the Dorsal Horn



Mannion et al. *Clin J Pain.* 2000;16(suppl 3):S144-S156.

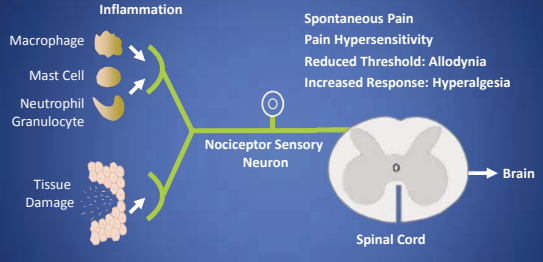
Nociceptive Pain



Transient pain in response to a noxious stimulus
High threshold, protective

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

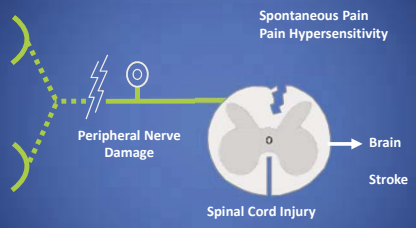
Inflammatory Pain



Spontaneous pain and hypersensitivity to pain in response to tissue damage and inflammation (postop pain, trauma, arthritis)—healing and repair

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

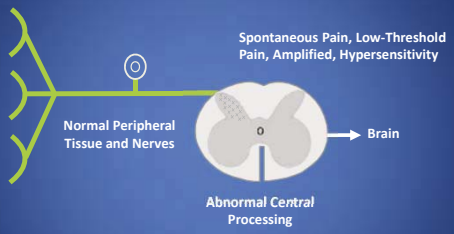
Neuropathic Pain



Spontaneous pain and hypersensitivity to pain in association with damage to or lesion of the nervous system—pathological pain

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

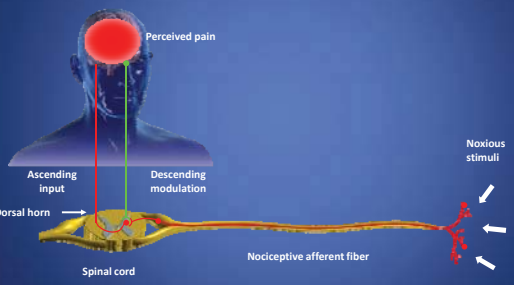
Functional Pain



Hypersensitivity to pain resulting from abnormal central processing of normal input—pathological IBS, fibromyalgia

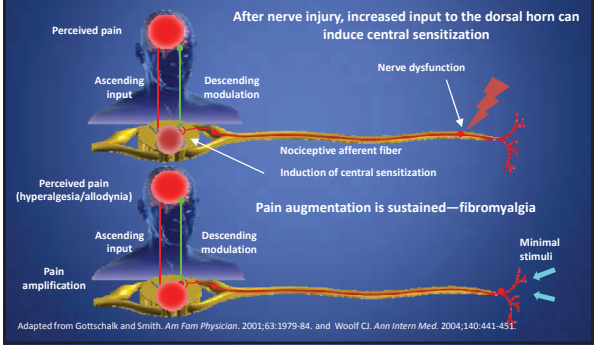
Woolf. *Ann Intern Med.* 2004;140:441-451.

Normal Nerve Impulses Leading to Pain



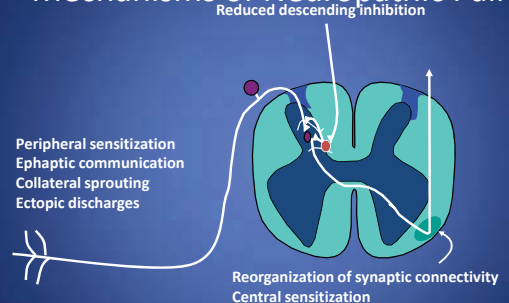
Adapted from Gottschalk and Smith. *Am Fam Physician.* 2001;63:1979-84 and Woolf. *Ann Intern Med.* 2004;140:441-451.

Theory of Central Sensitization



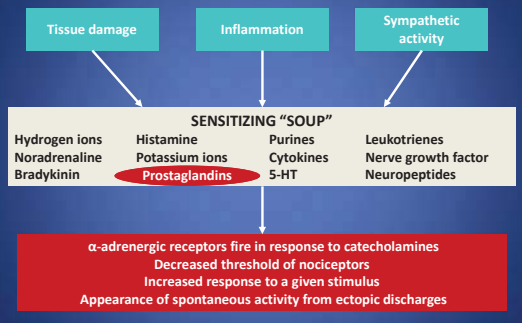
Adapted from Gottschalk and Smith. *Am Fam Physician.* 2001;63:1979-84. and Woolf CJ. *Ann Intern Med.* 2004;140:441-451.

Mechanisms of Neuropathic Pain



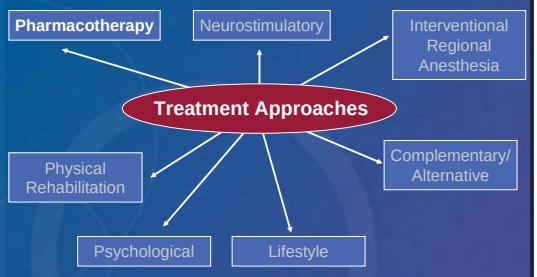
Dworkin. *Clin J Pain.* 2002;18:343-349.

Peripheral Sensitization



Woolf et al. *Anesth Analg.* 1993;77:362-379. Siddal et al. In: *Neural Blockade.* 1998:675-699.

Management of Neuropathic Pain Associated With DPN and PHN



Belgrade. *Postgrad Med.* 1999;106:127-132, 135-140; Ashburn, Staats. *Lancet.* 1999;353:1865-1869; Abuaisha et al. *Diabetes Res Clin Pract.* 1998;39:115-121.

Analgesic Options

- Acetaminophen
- NSAIDs/COX-2 inhibitors
- Local anesthetics
- Central analgesics (tramadol), tapentadol
- Opioids
  - Codeine, hydrocodone, oxycodone, propoxyphene
  - Morphine, hydromorphone, methadone, tapentadol

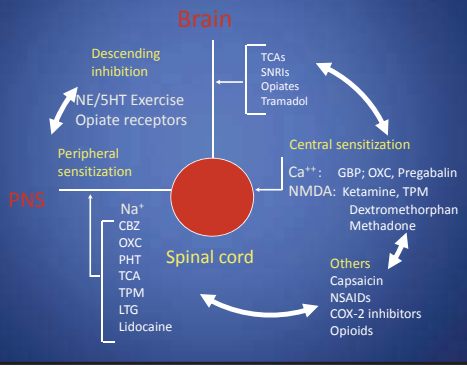
Adjunct Analgesics

- TCAs
  - Amitriptyline, nortriptyline, desipramine, trazodone, doxepin
- SNRIs
  - Duloxetine, milnacipran, venlafaxine
- Anticonvulsants
  - Gabapentin, pregabalin, carbamazepine, oxcarbazepine, topiramate, tiagabine, lacosamide, lamictal

Adjunct Analgesics

- Muscle relaxants
- NMDA antagonists
  - Ketamine, dextromethorphan
- α_2-agonists
  - Clonidine, tizanidine
- Sedative/anxiolysis
- Topical therapy
  - Capsaicin, lidocaine, NSAIDs
- Intra-articular therapy
  - Corticosteroids, hyaluronan

Mechanistic Approach to Treatment

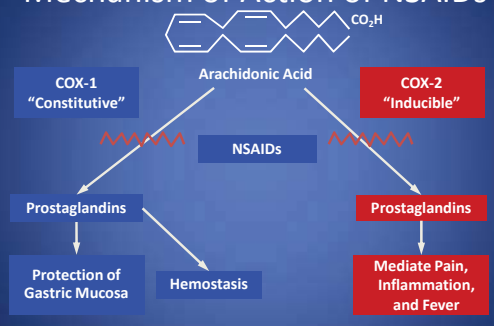


Acetaminophen

Acetaminophen: Mechanisms

- Mechanism of action unclear
- The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and substance P.
- It is probably both an isoform nonspecific and partial cyclooxygenase (COX) inhibitor in humans at doses commonly taken for mild pain and pyrexia, such as 1000 mg

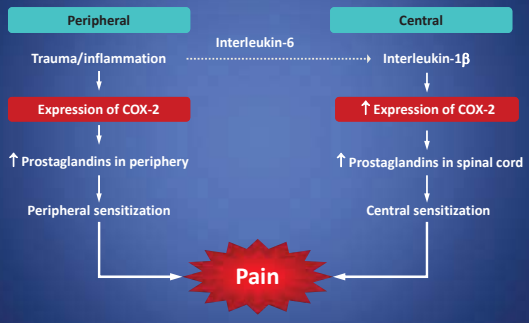
Mechanism of Action of NSAIDs



Bakhle et al. *Mediators Inflamm*. 1996;5:305-323; Vane et al. *Inflamm Res*. 1995;44:1-10.

Peripheral and Central Prostaglandins and COX-2

CORE



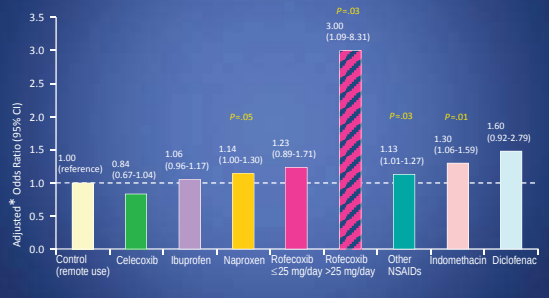
Ek et al. *Nature*. 2001;410:430-431.

NSAID Analgesic Properties

- Target peripheral pain pathways (peripheral sensitization)
- Anti-inflammatory and analgesic effects
- Selectively inhibit C-fiber ("second pain") and not A-δ fiber ("first pain")
- Analgesic ceiling effect
- Reversibly inactivate the COX enzyme (except aspirin)

Retrospective Observational Study

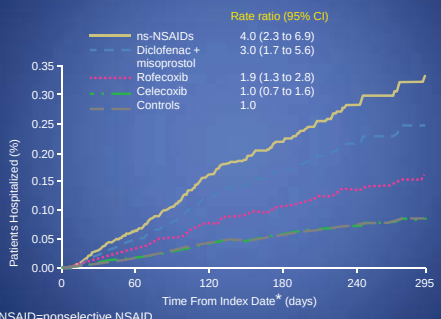
Risk of Acute MI and Sudden Cardiac Death With Current Use of COX-2–Selective Inhibitors and ns-NSAIDs



*Adjusted for age, gender, health plan region, medical history, and medication use.
Graham et al. *Lancet*. 2005.

Retrospective Observational Study

Adjusted Hazard Estimates for Hospitalization for Upper GI Hemorrhage Among Elderly Patients Using Prescribed NSAIDs



ns-NSAID=nonselective NSAID.
*Index date was first coxib or ns-NSAID prescription after a patient's 66th birthday.
Mamdani et al. *BMJ*. 2002.

CORE

NSAIDs

Benefits
- No addiction
- Decrease or eliminate opioid use
- Lower side-effect profile than opioids

Risks
- Bleeding
- PUD
- Renal impairment
- Wound/bone healing
- Analgesic ceiling effect

Tramadol

Tramadol: Dosing and Administration

- In RCTs the optimum dosage self-selected by patients was 250 mg/d
- Initiate at low dosages 50 mg/d or bid
- Titrate every 3 to 7 d by 50 to 100 mg/d in divided doses as tolerated
- An adequate trial requires 4 wk at maximum dosage
- Initiate tramadol ER at 100 mg/d and increase every 5 days to maximum of 300 mg/d

Harati et al. *Neurology*. 1998;50:1842-1846; Sindrup et al. *Pain*. 1999;83:389-400. ULTRAM ER (tramadol HCl) Extended-Reliease Tablets [package insert]. Raritan, NJ: PriCara Unit of Ortho-McNeil, Inc. 2005.

Tramadol: AE

- Nausea
- In polypharmacy, increased risk with rapid dose escalation
  - Dizziness
  - Somnolence
  - Orthostatic hypotension
  - Serotonin syndrome with MAOIs or SSRIs
- Dosage adjustment required for renal/hepatic disease
- Lowers the seizure threshold
- Increased risk of addiction in patients with history of substance abuse

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

Tramadol ER

- Extended-release formulation created to help moderate-to-moderately severe chronic pain in adults who need round-the-clock pain treatment for extended periods of time
- Lag in drug absorption; reaches peak in 12 to 15 hours; steady state in 4 days
- As yet unstudied adverse event profile in patient population over 65 years of age; not to be used in severe renal or hepatic disease

ULTRAM ER (tramadol HCl) Extended-Reliease Tablets [package insert]. Raritan, NJ: PriCara Unit of Ortho-McNeil, Inc. 2005.

Mechanism of Action of Opioids

Opioids: Mechanisms of Action

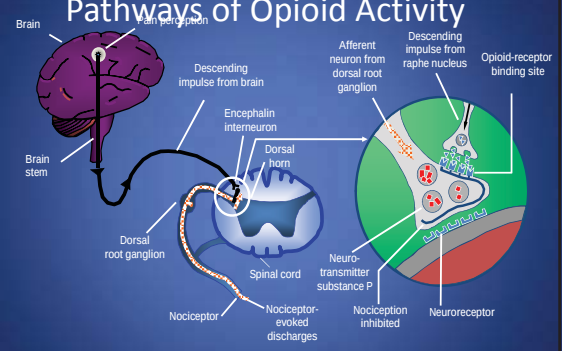
- Act on peripheral and central μ, κ, and δ opioid receptors
- Inhibit the transmission of nociceptive input from the periphery to the spinal cord (presynaptic and postsynaptic)
- Activate descending inhibitory pathways that modulate transmission in the spinal cord
- Alter limbic system activity

Duggan et al. *Pharmacol Rev.* 1983;35:219-281; Stein. *N Engl J Med.* 1995;332:1685-1690; Benedetti. In: *Advances in Pain Research and Therapy.* Vol 2. 1979:31-44.

Mu-1 Mu2 and kappa

- Mu 1=Analgesia
- Mu 2 = Analgesia, respiratory depression, euphoria, GI dysmotility, physical dependence.
- Kappa= Analgesia and dysphoria

Pathways of Opioid Activity



Adapted from Goldstein. *Hospital Pract.* 1978;1:32.

Opioid Action and Descending Modulating System

- Supraspinal opioids cause release of norepinephrine and serotonin
- Direct adrenergic application inhibits dorsal horn discharge
  - Sympathetically mediated pain: α-adrenergic receptors, expressed on injured neurons, fire in response to local and systemic catecholamines
- Reproduced with clonidine
- Yohimbine reverses opioid analgesia

Opioids: Studies in PHN

- Controlled-release oxycodone hydrochloride titrated to a maximum dosage of 60 mg/d significantly relieved PHN pain compared with placebo[1]
- In a comparison with TCAs and placebo, controlled-release MS titrated to a maximum dosage of 240 mg/d provided statistically significant benefits for pain and sleep, but not for physical function and mood[2]

1. Watson et al. *Neurology*. 1998;50:1837-1841; 2. Raja et al. *Neurology*. 2002;59:1015-1021.

Opioids: Studies in PHN

- High-dose levorphanol is superior to low-dose levorphanol
  in treating chronic neuropathic pain, including PHN resistant to other therapies[1]
- Other studies have shown a lack of response in up to 37%
  of patients despite liberal use of opioids[2,3,4]

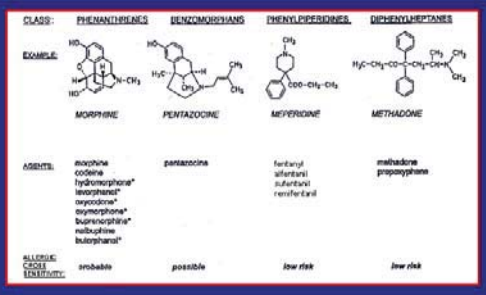
1. Rowbotham et al. *N Engl J Med.* 2003;348:1223-1232; 2. Becker et al. *Pain.* 2000;84:203-211; 3. Portenoy et al. *Pain.* 1986;25:171-186; 4. Zenz et al. *J Pain Symptom Manage.* 1992;7:69-77.

Opioids: AEs

- Constipation
- Sedation
- Nausea
- Neurotoxic effects
  - Delirium
  - Hyperalgesia
- Respiratory depression
  - Low risk in ambulatory patients taking opioids at recommended starting doses
- Other effects
  - Decreased testosterone
  - Decreased immunity

Dworkin et al. *Arch Neurol.* 2003;60:1524-1534; Ballantyne et al. *N Engl J Med.* 2003;349:1943-1953.

Urine Toxicology Screen by Chemical Class



*These agents lack the 6-OH group of morphine, possibly decreasing cross-sensitivity within the phenanthrene group.

(Jaffe, 1996; courtesy J Fudin, 2003)

Physical Dependence

- Abstinence syndrome induced by administration of an antagonist or by dose reduction
- Usually unimportant if abstinence is avoided
- Assumed to exist after few days' dosing, but actually highly variable

(Passik, 2000; Portenoy, 1997)

Addiction

- Disease with pharmacologic, genetic, psychosocial elements
- Fundamental features: loss of control, compulsive use, use despite harm
- Diagnosed by observation of aberrant drug-related behavior

(Passik, 2000; Portenoy, 1997)

Tolerance

- Diminished drug effect from drug exposure
- Tolerance develops to both analgesic effects and to unwanted side effects
- Tolerance to analgesia is seldom a problem in the clinical setting

(Passik, 2000; Portenoy, 1997)

Drug-Related Behavior Predictive of Addiction

Probably More Predictive

- Selling prescription drugs
- Prescription forgery
- Stealing or "borrowing" drug from another person
- Injecting oral formulation
- Obtaining prescription drugs from nonmedical source
- Multiple episodes of prescription "loss"
- Concurrent abuse of related illicit drugs
- Multiple dose escalations despite warnings
- Repeated episodes of gross impairment or dishevelment

Probably Less Predictive

- Aggressive complaining
- Drug hoarding when symptoms milder
- Requesting specific drugs
- Acquisition of drugs from other medical sources
- Unsanctioned dose escalation once or twice
- Unapproved use of the drug to treat another symptom
- Reporting psychic effects not intended by the clinician
- Occasional impairment

(Portenoy, 1997)

- Many patients currently receiving long-term opioids were started when opioids were still considered a viable treatment option and if satisfied with their pain control and using their medications appropriately should not be unilaterally compelled to wean off opioids," Kurt Kroenke, MD, and co-author Andrea Cheville, MD, recently wrote in *JAMA*

- "Before launching into hysteria that the recent, small drops in opioid prescribing reflect a 'war on pain patients,' we should recognize that U.S. consumption dwarfs that of other developed countries," Keith Humphreys, PhD, a professor of psychiatry at Stanford University, wrote in *The Washington Post.*
- But the focus should not be on overall consumption. It should be on whether opioid medications for chronic pain actually work. And they do, for many patients

Tapentadol

- New opioid with dual action
- Mu agonist central acting opioid
- Norepinephrine reuptake inhibitor
- Works on ascending and descending pathways

  Good data noted and excellent results in our clinic.
- Less constipation and sedation noted

TAPENTADOL ER

- Same ingredients of Tapentadol IR, in a q 12 hours dosing scheme.
- Decreased nausea, vomiting and constipation.
- Very low withdrawal symptoms if abruptly stopped.
- Cost and availability could be an issue.
- High patient satisfaction in my practice

BUTRANS

- First 7 day pain patch in USA
- Excellent data from Europe with many years of use there.
- Single agent buprenorphine product.
- Partial agonist.
- Very different molecule than other typical opioids.

BUTRANS

- Very long history of use in Europe
- Relatively low rate of side effects.
- Skin rash has been noted with 7 day patch
- Schedule III in USA, can do refills.
- Overall same precautions of all opioids.
- Only 4 patches needed
- per month.

ANTICONVULSANTS "Neuromodulators"

- Pregabalin
- Topiramate
- Oxcarbazepine
- Gabapentin
- Lamotrigine
- Tiagabine
- Lacosamide
- Sodium and/or calcium channel modulators
- Some have FDA pain approval indications.

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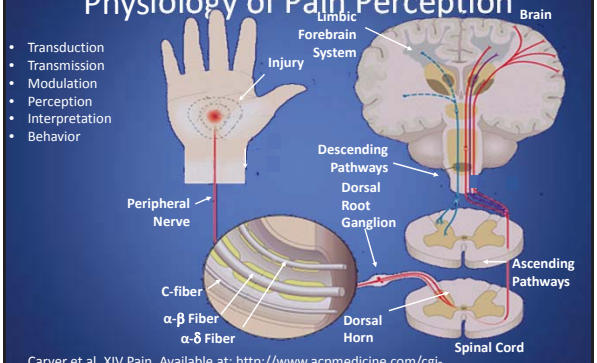


Carver et al. XIV Pain. Available at: http://www.acpmedicine.com/cgi-bin/publiccgi.pl?loginOP. Accessed March 29, 2006.

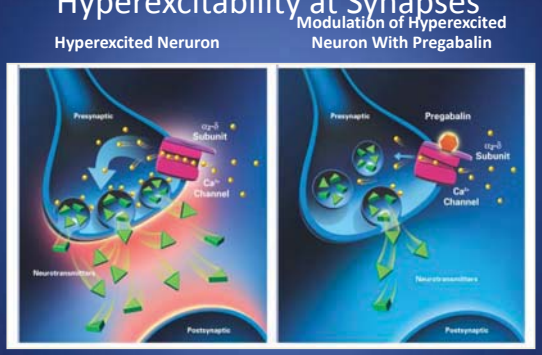
Gabapentin and Pregabalin

CORE

Gabapentin and Pregabalin: Mechanism of Action

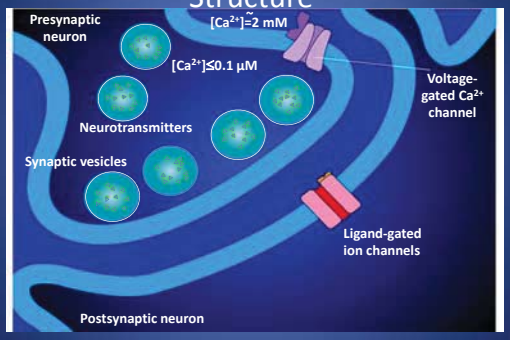
- Binds to α_2-δ subunit of voltage-gated calcium channels
  - Reduces Ca^{2+} influx during depolarization
  - Binding required for analgesic, anxiolytic, and anticonvulsant activity
- Reduces release of neurotransmitters, eg, glutamate, norepinephrine, substance P
- Effective in trials of epilepsy, neuropathic pain, and generalized anxiety

Hyperexcitability at Synapses



Taylor. *CNS Drug Rev.* 2004;10:183-188.

Voltage-Gated Calcium Channel Structure



Preoperative Gabapentin Reduced Postop Pain and Morphine Consumption in Mastectomy Patients

- The effects of a single dose of 1200 mg oral gabapentin on morphine consumption and immediate postop pain were evaluated
- Gabapentin reduced total morphine consumption from a median of 29 mg to 15 mg (*P*<.0001)
- Pain during movement, as assessed on VAS, was reduced from 41 mm to 22 mm at 2 hours postop (*P*<.0001)
- At 4 hours postop, pain was decreased from mean of 31 mm to 9 mm on VAS (*P*<.018)
- No significant differences were found between the groups with regard to pain at rest or side effects

Dirks et al. *Anesthesiology*. 2002;97:560-564 (A).

Gabapentin and Pregabalin Can Interact Synergistically With Naproxen to Produce Antihyperalgesia

- In a rat model either gabapentin, pregabalin, naproxen, or a fixed dose of gabapentin + naproxen or pregabalin + naproxen was administered orally to rats after the induction of inflammation by intraplantar injection of lambda-carrageenan in 1 hind paw
- The mixture of gabapentin + naproxen in fixed doses 50:1,10:1,1:1, and pregabalin + naproxen 10:1 interacted synergistically to reverse thermal hyperalgesia
- However 1:50 gabapentin + naproxen and pregabalin + naproxen 1:1 or 1:10 produced only additive effects
- The use of gabapentin or pregabalin in low-dose combinations with naproxen may afford therapeutic advantages for clinical treatment of persistent inflammatory pain

Hurley et al. *Anesthesiology.* 2002;92:1363-1373.

TCAs

TCAs: Mechanisms

- Relief of pain through serotonin and norepinephrine reuptake blockade[1]
- Blockade of α-adrenergic receptors[2]
- Sodium and potassium channel modulation[1,2]
- Modulation of monoamine neurotransmitters[1]
- ? NMDA-receptor antagonism[1]

1. Lawson. *Expert Opin Investig Drugs*. 2002;11:1437-1445; 2. Sindrup et al. *Pain*. 1999;83: 389-400.

CORE

TCAs

- Amitriptyline studied most extensively
  - Limitations due to anticholinergic AEs
    - Constipation and pseudodementia
  - Potential cardiac conduction abnormalities[1]
- Nortriptyline and desipramine
  - Better AE profiles
  - High doses cause anticholinergic AEs
    - Affect cardiac conduction
  - Desipramine an alternative to amitriptyline intolerance[2]

1. Max et al. *Pain*. 1991;45:3-9; 2. Duby et al. *Am J Health Syst Pharm*. 2004;61:160-176.

CORE

TCAs: AEs

- Commonly reported AEs (generally anticholinergic)
  - Blurred vision
  - Cognitive changes
  - Constipation
  - Dry mouth
  - Orthostatic hypotension
  - Sedation
  - Sexual dysfunction
  - Tachycardia
  - Urinary retention

- Desipramine
- Nortriptyline
- Imipramine
- Doxepin
- Amitriptyline

SNRIs

SNRIs

CORE

Venlafaxine, duloxetine and milnacipran

- Inhibit norepinephrine and serotonin reuptake and increase synaptic availability
- Preliminary results suggest safety, tolerability, and effectiveness in patients with painful DPN with duloxtene and fibromyalgia for both duloxetine and milnacipran
- Minimal anticholinergic Aes
- Venlafaxine has NO pain indications, much more serotonergic

Effexor® (venlafaxine hydrochloride) [package insert]. Philadelphia, Pa: Wyeth Pharmaceuticals; 2004; Sindrup et al. *Neurology.* 2003;60:1284-1289; Wernicke et al. Poster presented at: 56th Annual Meeting of the American Academy of Neurology; April 24-May 1, 2004; San Francisco, Calif; Raskin et al. Poster presented at: 23rd Annual Meeting of the American Pain Society; May 6-9, 2004; Vancouver, British Columbia, Canada; Wernicke et al. Poster presented at: 23rd Annual Meeting of the American Pain Society; May 6-9, 2004; Vancouver, British Columbia, Canada.

Emerging Treatment for Painful DPN: Duloxetine

- Balanced SNRI[1,2,3]
- Lacks significant affinity for anticholinergic, antihistamine, α_1-adrenergic, dopamine, and opioid receptors
- Relieves symptoms of major depressive disorder[1,2]
- Preliminary results suggest 60 mg qd and 60 mg bid safe and effective in patients with painful DPN[3,4]

1. Detke et al. *J Clin Psychiatry*. 2002;63:308-315; 2. Detke et al. *J Psychiatr Res*. 2002;36: 383-390; 3. Raskin et al. *J Palliat Med*. 2006;9:29-40; 4. Goldstein et al. *Pain*. 2005;116: 109-118.

Milnacipran

- New agent from Europe (France) 2009
- 3 to 1 Norepinephrine VS Serotonin
- SNRI
- FDA approved in USA for chronic pain due to Fibromyalgia
- Fast onset, good cost.
- 12 years of experience in Europe

SSRI's

Other Antidepressant Medications

- SSRIs have fewer adverse side effects and are better tolerated than TCAs[1]
- Unlike TCAs, SSRIs treat the depression and not pain[1,2]
- Most antidepressants that relieve chronic pain block reuptake of norepinephrine[1]
- No pain indications for any SSRI's

1. Atkinson et al. *Pain*. 1999;83:137-145; 2. Dickens et al. *Psychosomatics*. 2000;41:490-499.

5% Lidocaine Patch

5% Lidocaine Patch: Mechanism

- An amide-type local anesthetic
- Stabilizes neuronal membranes
- Inhibits ionic fluxes required for the initiation and conduction of impulses
- Penetration of lidocaine into the skin after application of the patch produces an analgesic effect
  - A topical, not transdermal, therapy
- A complete sensory block is not produced, eg, analgesia,
  but not anesthesia, is produced

Physicians' Desk Reference. 2005.

5% Lidocaine Patch: Studies in PHN

- Superior to both no treatment and vehicle patches in averaged category pain relief scores[1]
- Reduces intensity of all common neuropathic pain qualities and may be of potential benefit in nonallodynic neuropathic pain states[2]
- As add-on therapy, the patch was effective in[3]
  - Reducing ongoing pain
  - Reducing allodynia during the first 8 hours after application
  - Consistent pain relief over period of 7 days

1. Rowbotham et al. *Pain.* 1996;65:39-44; 2. Galer et al. *Clin J Pain.* 2002;18:297-301;
3. Meier et al. *Pain.* 2003;106:151-158.

COMPOUNDED CREAMS

- Very popular in Europe
- Can have good efficacy
- Lower total overall dose of medication
- Can be a way to use ketamine
- Obviously off label
- Can be cost effective

COMPOUNDED CREAMS

- Have had good success in RSD/CRPS, PHN and some neuropathies with PLO Ketamine 6%, Gabapentin 4 to 6 % and Lidocaine 2.5% applied up to qid.
- Only use a directed, patient's wife used one month supply on entire body in one day for fibromyalgia pain and hallucinated

, only major problem for me in 6 years of using.

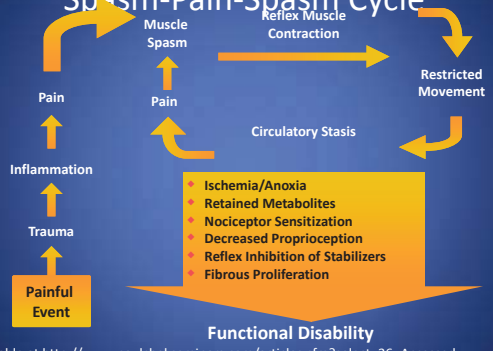
Muscle Relaxants

Centrally Acting Muscle Relaxants: Mechanisms

- Indirectly relax skeletal muscles by blocking polysynaptic neurons in the spinal cord[1]
- Block polysynaptic neurons in the descending reticular formation of the brain[1]
- Modest analgesic activity may be derived from suppression of nociceptive input[2]
- The antinociceptive mechanisms are unknown

1. Waldman. *J Pain Symptom Manage.* 1994;9:434-441; 2. Hunskaar et al. *J Int Med Res.* 1991;19:71-87.

Spasm-Pain-Spasm Cycle



Available at http://www.paulchekseminars.com/articles.cfm?select=36. Accessed February 15, 2006.

Muscle Relaxants: AEs

- CNS side effects
  - Sedation
  - Dizziness
  - Confusion
  - Blurred vision
- Potential for abuse with carisoprodol (Schedule IV*)
- GI AEs
  - Nausea, epigastric distress, vomiting
- Anticholinergic properties: dry mouth, urinary retention

*In Tennessee

Waldman. *J Pain Symptom Manage.* 1994;9:434-441 (B); Toth et al. *Clin Ther.* 2004;26:1355-1367 (A); van Tulder et al. *Spine.* 2003;28:1978-1992 (A).

Mechanism of Action of NMDA Antagonists

NMDA Receptor

- Opioid receptor and COX-2 activation stimulates protein kinase C, an enzyme that phosphorylates several target proteins (eg, NMDA receptor)
- Phosphorylation of the NMDA receptor results in release of Mg^{++} block and Ca^{++} entry into the cell resulting in series of cascades
- NMDA receptor antagonists (eg, ketamine) may prevent activation of excitatory glutamate receptors and thus prevent central sensitization

Mao et al: Pain 1995; 62: 259-274

α-$_2$ Adrenergic Agonists

Adrenergic Action and Descending Modulating System

- Direct adrenergic application inhibits dorsal horn discharge
  - Sympathetically mediated pain: α-adrenergic receptors, expressed on injured neurons, fire in response to local and systemic catecholamines
- Reproduced with clonidine

Epidural Steroid Injections
Facet joint Injections
SI joint Injections
Trigger point Injections
Spinal Cord Stimulators
Radiofrequency Techniques
Sympathetic Block

Nonpharmacologic Options CORE

- TENS: electrical stimulation of the skin to relieve pain by interfering with the neural transmission of signals from underlying pain receptors
  - 3 controlled studies
  - 66% experienced immediate symptomatic improvement and 44% maintained improvement for 1 year[1]
- Acupuncture: specific body areas associated with peripheral nerves are pierced with fine needles to produce anesthesia, relieve pain, and promote therapy
  - 10-week randomized study
  - Relieved pain and primary and secondary symptoms in 77% of the patients[2]

1. Alvaro et al. *Diabetes Technol Ther.* 1999;1:77-80; 2. Abuaisha et al. *Diabetes Res Clin Pract.* 1998;39:115-121.

Nonpharmacologic Options (cont'd)

- PT/massage/desensitization[1]
- Ice[1]
- Biofeedback: the technique of using monitoring devices to furnish information regarding an autonomic bodily function, such as heart rate or blood pressure, in an attempt to gain some voluntary control over that function[2]
- Relaxation techniques[2]
- Cognitive behavioral therapy[2]

1. Abuaisha et al. *Diabetes Res Clin Pract.* 1998;39:115-121; 2. Alvaro et al. *Diabetes Technol Ther.* 1999;1:77-80.

Practical Considerations: Acute Pain Treatment Recommendations CORE

- Use regional analgesic techniques whenever possible
- To that add a COX-2 inhibitor
- Use opioids as a rescue if nonopioids are not adequate
- Use of pregabalin and ketamine remains investigational and may be used for surgical procedures that have a reported high incidence of persistent postoperative pain
- Routine use of pregabalin and ketamine drugs cannot be recommended at this time

Practical Considerations: Chronic Pain Treatment Recommendations CORE

- In addition to the nonpharmacologic therapy, start with pregabalin
- If that is not adequate add lidocaine patch
- Also can add SNRI or TCA
- To this add opioids
- Consider interventional procedures at any time in point
- Therapy does not have to be in a "step fashion" it could be parallel

Summary

- Pain is mediated through both central and peripheral mechanisms
- Chronic pain has multifactorial effects on the continuum
  of depression/anxiety, functional impairment, and sleep disturbances
- Recent evidence supports multimodal analgesia techniques for management of both acute as well as chronic pain
- Better understanding of pain mechanisms allow a rational choice of analgesics and their combinations

- Serious, chronic pain affects at least 116 million Americans each year, many of whom are inadequately treated by the health-care system, according to a new report by the Institute of Medicine (IOM). The report offers a blueprint for addressing what it calls a "public health crisis" of pain.