

***Pharmacotherapeutic Considerations in the Treatment of Pain:  
Current Paradigms for NSAIDs/COX-2's, Anti-Convulsants, and Anti-Depressants***

**VA NEW ENGLAND HEALTH CARE SYSTEM**

November 14, 2008

**Jeffrey Fudin, Pharm.D., DAAPM**

Clinical Pharmacy Specialist-Pain Management

Dept. of Veterans Affairs Medical Center-Albany, NY

Adjunct Associate Professor of Pharmacy Practice, Albany College of Pharmacy

CEO, Nova Pain Associates

Please visit [www.NOVAPAIN.net](http://www.NOVAPAIN.net) or [www.PAINDR.com](http://www.PAINDR.com)

**LEARNING OBJECTIVES:**

Upon completion of this educational program, the participant should be able to:

1. Differentiate between Acute and Chronic Pain.
2. Compare and contrast various pharmacological classes of opioids.
3. Select appropriate medication options for various pain syndromes.
4. Understand the differences advantages, and disadvantages among and between opioids, NSAIDs, Anti-Convulsants, and Anti-Depressants

**SUGGESTED READINGS:**

Ballantyne Jane C. [Opioids for Chronic Nonterminal Pain.](#) South Med J. 2006;99(11):1245-1255.

[Fudin J, Levasseur DJ, Passik SD, Kirsh KL, Coleman J. Chronic pain management with opioids in patients with past or current substance abuse problems. Journal of Pharmacy Practice. 2003, 16;4:291-308.](#)

Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of Nonsteroidal [Antiinflammatory Drugs. An Update for Clinicians. A Scientific Statement From the American Heart Association.](#) Circulation. 2007;115.

Wilcox MC, Allison J, Benzuly K, Borum M, Cryer B, Tilo G, Hunt R, Ladabaum U, Lanus A, Paulus H, Regueiro C, Sandler RS, Simon L. [Consensus Development Conference on the Use of Nonsteroidal Anti-Inflammatory Agents, Including Cyclooxygenase-2 Enzyme Inhibitors and Aspirin.](#) CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2006;4:1082-1089.

Sumapa Chaiamnua, Jeroan J. Allison, and Jeffrey R. Curtis. [Risks versus benefits of cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs.](#) Am. J. Health Syst. Pharm., Oct 2006; 63: 1837 - 1851.

Cupp MJ, Tracy TS. [Cytochrome P450:new nomenclature and clinical applications.](#) American Family Physician. Jan. 1, 1998. Pages 107-116.

Virani A, Mailis A, Shapiro LE, Shear NH. [Drug interactions in human neuropathic pain pharmacology.](#) Pain. 73:1997:3-13.

## Pharmacotherapeutic Update on Analgesics:

*Focus on Opioids, NSAIDs/COX-2's,  
Anti-Convulsants, and Anti-Depressants*

**[www.paindr.com](http://www.paindr.com)**

Jeffrey Fudin, Pharm.D., DAAPM

*Clinical Pharmacy Specialist, VA Medical Center - Albany, NY  
Adjunct Associate Professor of Pharmacy Practice, Albany College of Pharmacy  
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## Education Objectives

- Chronic vs. Acute pain: significant and growing
  - Epidemiology
  - Economic Burden
- Met and Unmet Pharmacologic needs
  - NSAIDs
  - COX-II
  - Opioids
  - Neuropathy
- Summary

## Epidemiology and Economic Burden of Chronic Pain (cont'd, informational)



### Low Back Pain

- >26 million Americans age 20-64<sup>1</sup>
- 6 million age >65<sup>1</sup>
- Nearly 50% of adults report low back pain each year<sup>1</sup>
- In 1998, incremental direct US medical costs from back pain ~\$26 billion<sup>2</sup>

1. Lawrence et al. *Arthritis Rheumatism* 1998;41:778.  
 2. Luo et al. *Spine*. 2004;29:79.

## Epidemiology and Economic Burden of Chronic Pain (informational)

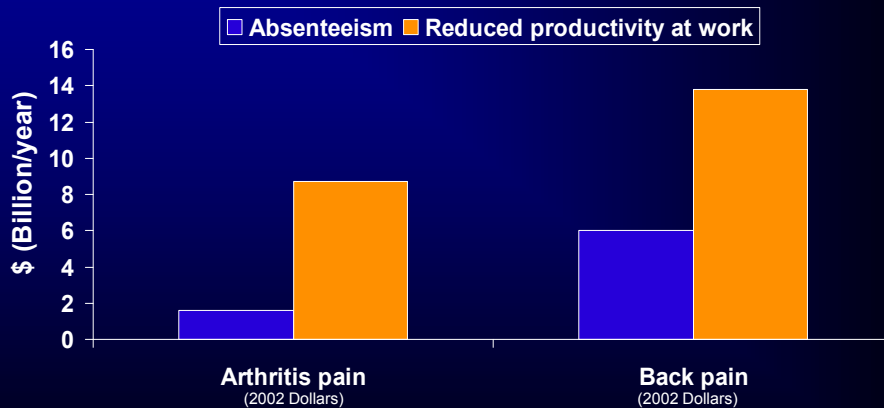
### Osteoarthritis

- >20 million Americans currently have OA<sup>1</sup>
  - 70 million will be age >65 and at risk for OA by 2030
- Early onset OA a common result of joint injury in individuals <65 years<sup>2,3</sup>
- In 1997, direct US medical costs from arthritis >\$50 billion<sup>4</sup>



1. NIAMS. At: [http://www.niams.nih.gov/hi\\_topics/arthritis/oaandout.htm](http://www.niams.nih.gov/hi_topics/arthritis/oaandout.htm). Accessed March 2, 2006.  
 2. Roos. *Curr Opin Rheumatol*. 2005;17:195.  
 3. Gelber et al. *Ann Intern Med*. 2000;133:321.  
 4. Yelin et al. At: <http://ihps.ucf.edu/ARG/1997CostOfMuscfinal.pdf>. Accessed March 2, 2006.

## Economic Burden of Arthritis and Back Pain: Lost Productivity Costs



Stewart et al. *JAMA* 2003;290:2443.

## Patient Burden of Untreated Chronic Pain

- Overall decreased quality of life<sup>1</sup>
- Sleep disturbance<sup>1,2</sup>
- Impact on cognitive functions, activities of daily living, and productivity<sup>1</sup>
- Depression and increased anxiety<sup>1</sup>
- Interference with social relationships<sup>1</sup>

1. American Pain Society. At: [http://www.ampainsoc.org/whatsnew/conclude\\_road.htm](http://www.ampainsoc.org/whatsnew/conclude_road.htm). Accessed March 2, 2006.  
 2. Cohen et al. *Int Rev Psych*. 2000;12:115.

## Goals of Therapy for Acute Vs Chronic Pain Levy, 1985

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Therapeutic Goal	Acute	Chronic
Sedation	Often desirable	Generally not desired
Rapid Onset	Yes	Irrelevant
Duration (T1/2)	Short (IR)/parenteral	Extended activity
Timing	PRN	A-T-C
Dose	Generally fixed	Multiple RX/doses
Route	Parenteral/Oral/Trans mucosal/Effervesant	Transdermal/Oral

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- ## Chronic Pain: Definition
- Historically defined as pain extending 3 or 6 months beyond onset or expected period of healing
  - Now considered as pain that:
    - Extends beyond the healing period
    - May have low levels of identified pathology that inadequately explain the presence and/or extent of pain
    - Disrupts sleep or normal activities
- NPC and JCAHO. At: [http://www.jcaho.org/news+room/health+care+issues/pain\\_mono\\_npc.pdf](http://www.jcaho.org/news+room/health+care+issues/pain_mono_npc.pdf). Accessed March 2, 2006.

## Pharmacologic Treatment of Chronic Pain

- Acetaminophen
- NSAIDS
- Muscle relaxants
- Anticonvulsants
- Antidepressants
- Opioids
- Stimulants
- Sleeping aids
- Anxiolytics
- Glucocorticoids
- Anesthetics
- Topicals

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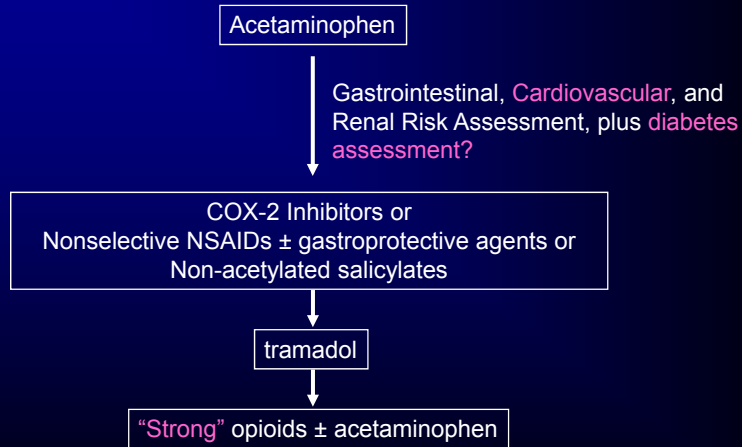
## Limitations of Analgesic Therapies

- NSAIDs
  - Risk for GI toxicity<sup>1</sup>
  - Recommended use of concomitant gastroprotective agents increases cost<sup>1</sup> What are they???
  - Risk for renal toxicity<sup>1</sup>
  - Cardiovascular safety issues<sup>2</sup>
- COX-2 inhibitors
  - Risk for renal toxicity<sup>1</sup>
  - Cardiovascular safety issues<sup>3</sup>
- Scheduled opioids associated with
  - Respiratory depression<sup>4</sup> (???)
  - Fear of dependence/tolerance/abuse<sup>5</sup>
  - Stringent regulatory requirements and perceived potential for scrutiny may limit adequate prescribing<sup>5</sup>

1. American College of Rheumatology *Arthritis Rheum.* 2000;43:1905. 2. Hudson. *BMJ.* 2005;330:1370.  
 3. Caldwell. *J R Soc Med.* 2006;99:132. 4. Stephens J. et al. *Rheumatology* 2003;42(Suppl. 3):iii40. 5. Weinstein et al. *South Med J.* 2000;93:479.

## Pharmacologic Management of OA Pain: 2000 ACR Treatment Guidelines

### Systemic Analgesics



American College of Rheumatology *Arthritis Rheum.* 2000;43:1905.

## Recently Published Review Highlighting Increased CV Risk With Selective and Nonselective Cyclooxygenase 2

**JAMA**<sup>®</sup>

### Cardiovascular Risk and Inhibition of Cyclooxygenase

A Systematic Review of the Observational Studies of Selective and Nonselective Inhibitors of Cyclooxygenase 2

McGettigan, P. et al. *JAMA.* 2006;296:1633-44.

**Context** Evidence that rofecoxib increases the risk of myocardial infarction has led to scrutiny of other nonsteroidal anti-inflammatory drugs (NSAIDs). Regulatory agencies have provided variable advice regarding the cardiovascular risks with older non-selective NSAIDs.

**Objective** To undertake a systematic review and meta-analysis of controlled observational studies to compare the risks of serious cardiovascular events with individual NSAIDs and cyclooxygenase 2 inhibitors.

## Limitations of Therapy for Management of Persistent Pain: NSAIDs and COX-2s

### NSAIDs

- Cardiovascular safety issues<sup>1,2</sup>
- Risk for GI toxicity<sup>3</sup>
- Need for concomitant use of gastroprotective agents in some patients<sup>3</sup>
- Risk for renal toxicity<sup>3</sup>

### COX-2s

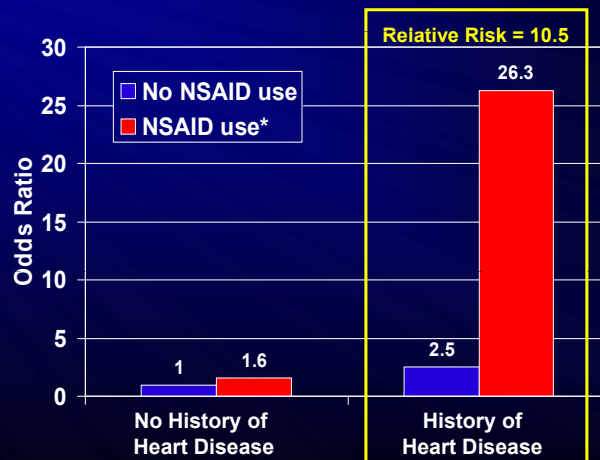
- Cardiovascular safety issues<sup>4</sup>
- Risk for renal toxicity<sup>3</sup>

1. Hudson. *BMJ*. 2005;330:1370; 2. McGettigan, P. et al. *JAMA*. 2006;296:1633-44; 3. American College of Rheumatology. *Arthritis Rheum*. 2000;43:1905; 4. Caldwell. *J R Soc Med*. 2006;99:132

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## Consumption of NSAIDs and the Development of Congestive Heart Failure in Elderly Patients

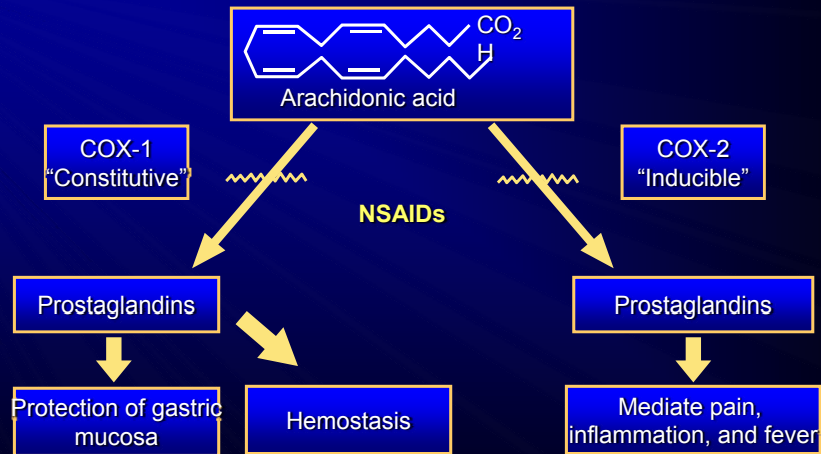
NSAID users with a history of heart disease had 10.5-fold greater incidence of CHF vs non-NSAID users



\*Exposure to any NSAID in the previous week.  
Page. *Arch Intern Med*. 2000;160:777-84.

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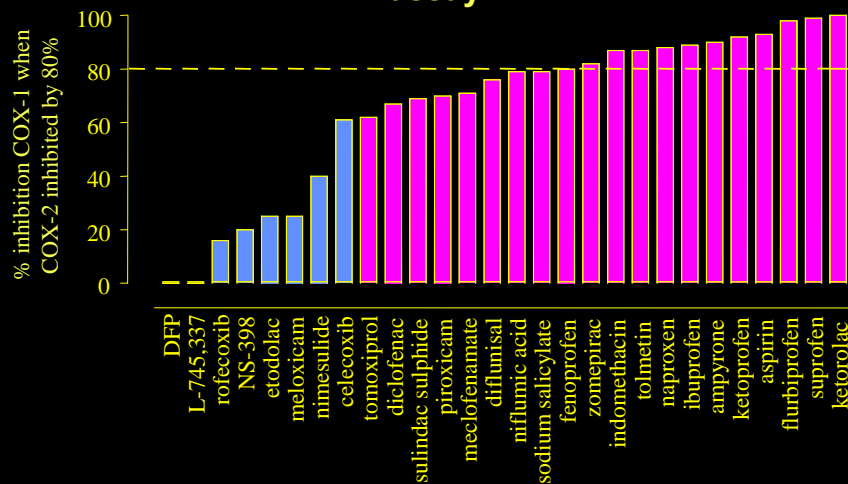
## Mechanism of Action of NSAIDs



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

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## Relationship between 80% ('therapeutic') inhibition of COX-2 and inhibition of COX-1 in an in vitro human whole blood assay



Warner et al, PNAS 1999; 96:7563-7568

## Barriers to Tx of Chronic Pain w/ Opioids

- Drug-Related<sup>1</sup>
  - Currently recommended analgesics may provide inadequate efficacy and/or unacceptable tolerability/safety
- Physician/*Pharmacist*-Related<sup>3</sup>
  - Bias against opioid therapy and overestimation of risks
  - Fear of regulatory scrutiny/action
- Patient-Related<sup>6</sup>
  - Reluctance to report pain
  - Concerns about “meaning” of pain (associate increased pain with worsening disease)
  - Low priority given to pain and symptom control
  - Regulatory and economic barriers
  - Exaggerated fear of addiction, tolerance, side effects

1. American College of Rheumatology *Arthritis Rheum.* 2000;43:1905; 2. Crichton. *Curr Med Res Opin* 2002;18:92.  
 3. Weinstein et al. *South Med J.* 2000;93:479. 4. NPC and JCAHO. At: [http://www.jcaho.org/news+room/health+care+issues/pain\\_mono\\_npc.pdf](http://www.jcaho.org/news+room/health+care+issues/pain_mono_npc.pdf). Accessed March 2, 2006.

## Opioid Receptors

- Mu (Endorphin)
  - Delta (Enkephalin)
  - Kappa (Dynorphin)
- Mu agonist: morphine, hydromorphone, fentanyl, oxycodone, hydrocodone, codeine, methadone, and meperidine
  - Mixed agonist-antagonist: butorphanol, nalbuphine, pentazocine
  - Partial agonist: buprenorphine

Brunton L, et al. *Goodman & Gillman's The Pharmacological Basis of Therapeutics.* 11th ed. New York: McGraw Hill; 1984.

## Street Value Perspective

- 120 Percocet 5/325 (brand name)
  - \$2400.00
- 120 Lortab 5/500 (any brand)
  - \$2000.00
- 60 Oxycontin 80mg
  - \$4800
- 120 Actiq Lollipop 200mcg
  - \$3240.00
- Knowing when your patient is diverting drug...
  - PRICELESS!

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## Urine Tox Screen Algorithm

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## Analgesic Choices

### ● Extended Release Products:

- Transdermal Fentanyl Patch
- Morphine-ER (several products available)
- Oxycodone-ER
- Oxymorphone-ER
- Hydromorphone-ER (not available in US)

### ● Synthetic Atypical

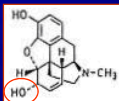
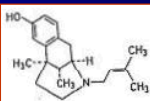
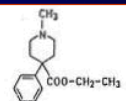
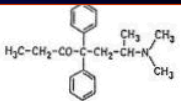
- Long Biological half-lives / intermediate analgesic half-lives
  - Levorphanol
  - Methadone
  - Tramadol (does this belong here?)

### ● Poor Choices for Chronic Pain

- short-acting, higher peaks, higher toxicity profiles
  - Propoxyphene
  - Meperidine
  - Other short acting combination products

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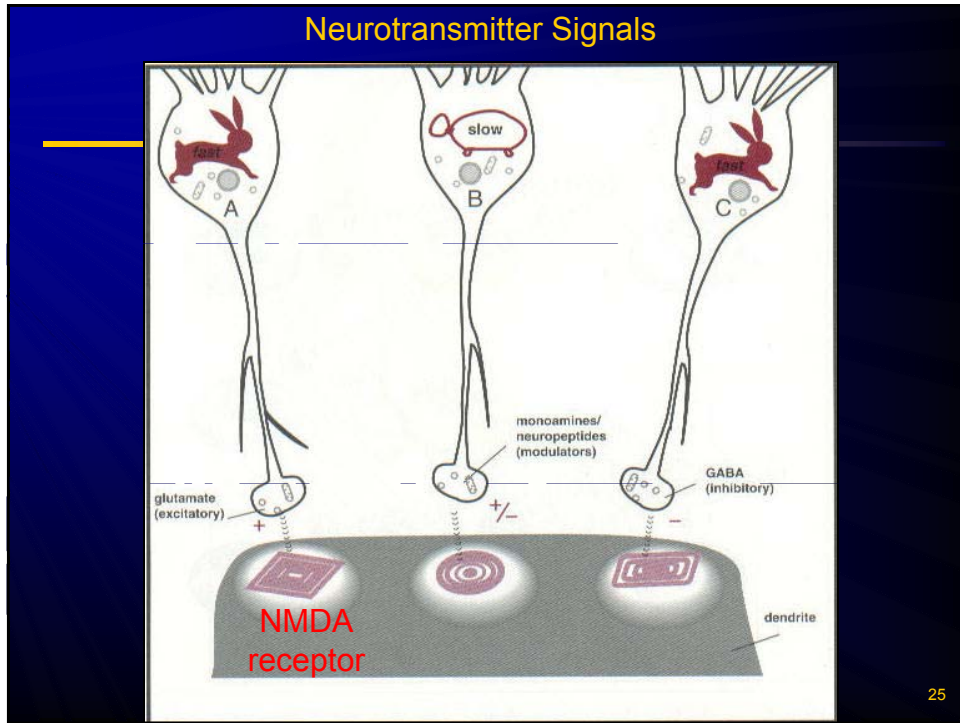
## Chemical Classes of Opioids

	PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES
				
Rx EXAMPLES >	MORPHINE morphine codeine hydrocodone* hydromorphone* levorphanol* oxycodone* oxymorphone* buprenorphine* nalbuphine butorphanol* naloxone* heroin (diacetyl-morphine)	PENTAZOCINE pentazocine diphenoxylate loperamide	MEPERIDINE meperidine fentanyl sufentanil alfentanil remifentanil	METHADONE methadone propoxyphene
X-SENSITIVITY >	PROBABLE	POSSIBLE	LOW RISK	LOW RISK

\*These agents lack the 6-OH group of morphine, possibly decreasing cross-sensitivity within the phenanthrene group.  
 Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill Companies; 1996:521-555.

Willette RE. Analgesic Agents. In: Delgado JN, Remers WA, eds. Wilson and Grisvold's Textbook of Organic Medicinal Chemistry. 9th ed. JB Lippincott Company, Philadelphia, Pa. 1991:629-654.  
 Courtesy of Dr. J. Fudin 2003

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## Opioid Analgesic P-Kinetics

Agent	Time to Peak (hr)	Half-life (hr)	Analgesic Onset (min)	Analgesic Duration (hr)
Morphine (IM)	0.5-1	2	10-20	3-5
Hydromorphone (IM)	0.5-1	2-3	10-20	3-5
<b>Levorphanol (IM)</b>	<b>0.5-1</b>	<b>12-16</b>	<b>10-20</b>	<b>5-8</b>
Hydrocodone (PO)	1	4	30-60	4-6
Codeine (IM)	0.5-1	3	10-20	4-6
Oxycodone (PO)	0.5-1	2-3	30-60	4-6
Meperidine (IM)	0.5-1	3-4	10-20	2-5
Fentanyl (IM)	10-20	3-4	7-15	1-2
<b>Methadone (IM)</b>	<b>0.5-1</b>	<b>15-30</b>	<b>10-20</b>	<b>&gt;8 (chronic)</b>
Propoxyphene (PO)	2-2.5	6-12	30-60	4-6

## Metabolic Pathway from Drug Elimination

DRUG	OPIOID CLASS	MAJOR METABOLIC PATHWAY
Morphine	Phenanthrene (w/-OH)	Glucuronidation
Hydromorphone	Phenanthrene	Glucuronidation
Codeine	Phenanthrene (w/ -OH)	Demethylation, glucuronidation
Levorphanol	Phenanthrene	Glucuronidation
Oxycodone	Phenanthrene	Demethylation, glucuronidation, keto-reduction
Oxymorphone	Phenanthrene	Glucuronidation, minor 3A4
Meperidine	Phenylpiperidine	Oxidation, hydrolysis, demethylation, glucuronidation
Fentanyl	Phenylpiperidine	Oxidation, hydrolysis, minor 3A4
Alfentanil	Phenylpiperidine	Oxidation
Sufentanil	Phenylpiperidine	Dealkylation, demethylation
Methadone	Diphenylheptane	Demethylation, 3A4 substrate (significant)

Volles DF, McGory R. Pharmacokinetic considerations, 15:5:Jan 1999.

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## Methadone Conversion Study

- Ripamonti, et al 1998
  - Cross-sectional
  - Morphine to methadone
  - 38 patients

- Dose Ranges

<u>Morphine (mg)</u>	<u>Morphine to Methadone Ratio</u>
30-90	3.70 to 1
91-300	7.75 to 1
301 and higher	12.25 to 1

J Clin Oncol 1998;16:3216-3221

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**“Fudin Factor”**

**A Methadone Conversion Formula**

Most exact to data from Ripamonti, et al 1998; less flowing and unlikely in real life

$$\text{Methadone (mg)} = \frac{X}{21} \left\{ 5.7 - 3 \sin \left( \frac{90}{\frac{100}{X} + 1} \right) - \sin \left( \frac{90}{\frac{310}{X} + 1} \right) \right\}$$

Let X= Morphine (mg)

Relation Between Daily Morphine and Methadone Dosages

Relation Between Daily Morphine and Methadone Dosages

**Formula derived by Jason Fudin (Engineering Student, McGill University) in collaboration with Dr. Jeffrey Fudin**

**“Fudin Factor”**

**A Methadone Conversion Formula**

Less exact to data from Ripamonti, et al 1998; more flowing and more likely in real life

$$\text{Methadone (mg)} = \frac{X}{21} \left\{ 5.7 - 3 \sin \left( \frac{90}{\frac{110}{X} + 1} \right) - \sin \left( \frac{90}{\frac{320}{X} + 1} \right) \right\}$$

Let X= Morphine (mg)

Relation Between Daily Morphine and Methadone Dosages

Relation Between Daily Morphine and Methadone Dosages

**Formula derived by Jason Fudin (Engineering Student, McGill University) in collaboration with Dr. Jeffrey Fudin**

## Potentially Clinically Relevant Methadone-Drug Interactions

- Agents That May **DECREASE** Serum Methadone Concentrations
  - Antiepileptics: carbamazepine, Phenobarbital, phenytoin
  - Antipsychotics: risperidone
  - Antiretrovirals: nevirapine, ritonavir
  - Antitubercular: rifampin
- Agents That May **INCREASE** Serum Methadone Concentrations
  - Antidepressants: SSRIs (venlafaxine is least likely), amitriptyline
  - Antifungals: fluconazole, Ketoconazole
- Agents That May Significant Increase Adverse Effects of Methadone
  - Benzodiazepines
  - St. John's Wort

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## NEUROPATHIC PAIN AND PHARMACOLOGY

- Tricyclic Antidepressants-enhancement of inhibitory pathway
- Anticonvulsants-sodium channel blockade
- Antiarrhythmics/Anesthetics-sodium channel blockade
- Clonidine-decrease sympathetic tone
- Capsaicin-substance P depletion
- Ketamine/Amantadine-NMDA receptor blockade
- Baclofen-enhance inhibitory blockade

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## Anti-depressants

	Dose [mg]	Amine Effects	Sedation	Anticholinergic
<i>3<sup>o</sup> Amine TCA</i>				
Amitriptyline [Elavil]	25-300	NE > 5HT	3	3
Clomipramine [Anafranil]	25-300	5HT	2	3
Doxepin [Sinequan]	25-300	NE > 5HT	3	2
Imipramine [Tofranil]	25-300	NE > 5HT	2	2
Trimipramine [Surmontil]	25-300	NE > 5HT	3	3
<i>2<sup>o</sup> Amine TCA</i>				
Amoxapine [Asendin]	50-600	NE	1	1
Desipramine [Norpramin]	25-300	NE	0.5	1
Maprotiline [Ludiomil]	25-225	NE	2	2
Protriptyline [Vivactil]	10-60	NE	0.5	2
Nortriptyline [Pamelor]	25-250	NE	1	1

<i>Serotonin Reuptake Inhibitors</i>				
Fluoxetine [Prozac]	5-80	5HT	0.5	0
Fluvoxamine [Luvox]	50-300	5HT	0.5	0
Paroxetine [Paxil]	10-50	5HT	0.5	0.5
Citalopram [Celexa]	10-60	5HT	0.5	0
Sertraline [Zoloft]	50-200	5HT	0.5	0
Escitalopram [Lexapro]	10-20	5HT	0.5	0
<i>Atypical Antidepressants</i>				
Venlafaxine [Effexor]	25-375	5HT > NE	0	0
Duloxetine [Cymbalta]	20-120	5HT > NE	0	0
Bupropion [Wellbutrin]	100-450	NE, DA	0	0
Nefazodone [Serzone]	100-600	5HT > NE	3	0
Trazodone [Desyre]	50-600	5HT > NE	3	0
Mirtazapine [Remeron]	15-45	NE [?]	3	0
<i>MAOIs</i>				
Nardil (phenelzine)	45-90mg	NE, DA, 5-HT	1	0
Selegiline (Eldepryl)	5-20mg	NE?, DA?, 5-HT	0	0
Parnate (Tranylcypromine)	30-60mg	NE, DA, 5-HT	1	0

## Anti-depressants, continued

## Tricyclic Antidepressants: Positive Controlled Trials

Study	Agent (mg/d)	N	Weeks	Primary End Point
<b>Painful DPN</b>				
Max	Amitriptyline (25-150, PBO)	29	12	Pain relief
Max	Desipramine (12.5-150, PBO), Amitriptyline (12.5-150, PBO)	108	14	Pain relief
Sindrup	Desipramine (50 or 200, PBO), Clomipramine (50 or 75, PBO)	26	6	Neuropathy symptoms
Max	Desipramine (12.5-250, PBO)	20	12	Pain relief
<b>PHN</b>				
Watson	Amitriptyline ( $\geq 12.5$ , PBO)	24	8	Pain relief
Max	Amitriptyline (12.5-150, PBO)	58	12	Pain relief
Graff-Radford	Amitriptyline (12.5-200, PBO)	49	8	Pain intensity
Kishore-Kumar	Desipramine (12.5-250, PBO)	26	12	Pain relief
Raja	Nortriptyline (10-160, PBO)	76	24	Pain intensity, relief; cognitive function

Max et al. *Neurology*. 1987;37:589-596; Max et al. *N Engl J Med*. 1992;326:1250-1256; Sindrup et al. *Br J Clin Pharmacol*. 1990;30:683-691; Max et al. *Pain*. 1991;45:3-9; Watson et al. *Neurology*. 1982;32:671-673; Max et al. *Neurology*. 1988;38:1427-1432; Graff-Radford et al. *Clin J Pain*. 2000;16:188-192; Kishore-Kumar et al. *Clin Pharmacol Ther*. 1990;47:305-312; Raja et al. *Neurology*. 2002;59:1015-1021.

## Tricyclic Antidepressants: Adverse Effects

- Most common adverse effects
  - Sedation
  - Anticholinergic effects
    - Dry mouth
    - Blurred vision
    - Increased intraocular pressure
    - Mydriasis (pupil dilation)
    - Constipation
    - Paralytic ileus
    - Urinary retention
    - Delayed micturition
    - Urinary tract dilation
    - Hyperpyrexia
    - Sinus tachycardia
- Often have unacceptable side effects in the elderly

Drug Facts & Comparisons. 2004; AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc*. 2002;50(suppl):S205-S224.

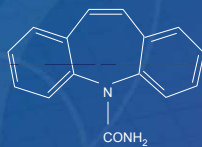
## Tramadol: Important Safety Information

- Tramadol M/A versus SNRIs?
  - What's coming? Tapentadol
- Is tramadol abusable?
  - Cicero TJ, Adams EH. et al. A postmarketing surveillance program to monitor ultram (tramadol hcl) abuse in the united states. Drug and Alcohol Dependence 57 (1999) 7-22.
- What is the seizure risk with anti-depressants?
  - Gassa C, Derby L, Vasilakis-Scaramozza C, Jick H. Incidence of first-time idiopathic seizures in users of tramadol. Pharmacotherapy 2000;20 (6):629-634.

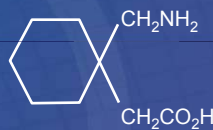
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## Anticonvulsants

- First generation
  - Phenytoin
  - Phenobarbital
  - Primidone
  - Ethosuximide
  - Carbamazepine
  - Valproic acid
- Second generation
  - Gabapentin
  - Lamotrigine
  - Topiramate
  - Tiagabine
  - Levetiracetam
  - Oxcarbazepine
  - Zonisamide
  - Felbamate



Carbamazepine



Gabapentin

McNamara. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. 2001; *Physicians' Desk Reference*. 59th ed. 2005; Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc; 2004.

## Anticonvulsants: Positive Controlled Trials

Study	Agent (mg/d)	N	Weeks	Primary End Point
<i>Painful DPN</i>				
Wilton	Carbamazepine (600, PBO)	40	4	Pain relief
Rull	Carbamazepine (600, PBO)	30	6	Neuropathy symptoms
Backonja	Gabapentin (900-3600, PBO)	165	8	Daily pain severity
Eisenberg	Lamotrigine (25-400, PBO)	59	6	Pain intensity
<i>PHN</i>				
Rice	Gabapentin (1800 or 2400, PBO)	334	7	Mean daily pain
Rowbotham	Gabapentin (300-3600, PBO)	229	8	Mean daily pain

Wilton. *S Afr Med J.* 1974;48:869-872; Rull et al. *Diabetologia.* 1969;5:215-218; Backonja et al. *JAMA.* 1998;280:1831-1836; Eisenberg et al. *Neurology.* 2001;57:505-509; Rice, Maton. *Pain.* 2001;94:215-224; Rowbotham et al. *JAMA.* 1998;280:1837-1842.

## General Considerations

### Autoinduction

carbamazepine

phenytoin

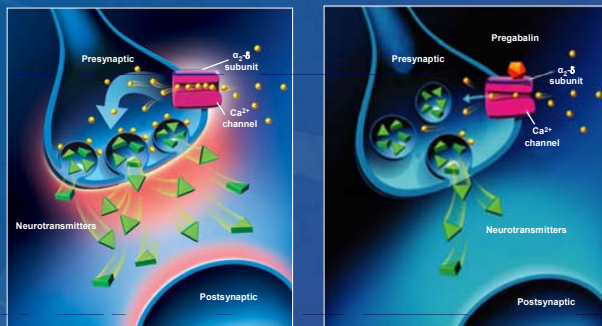
### Plasma Protein Displacement

phenytoin

valproate

carbamazepine

## Pharmacology: Gabapentin & Pregabalin Binds to the $\alpha_2$ - $\delta$ Subunit of Voltage-Gated $\text{Ca}^{2+}$ Channels in the Central Nervous System

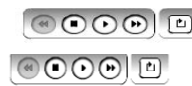
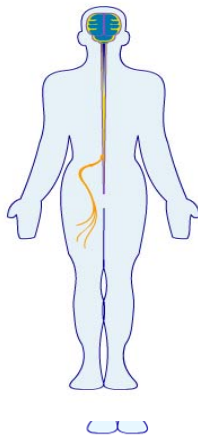


Schematic representation of pregabalin's proposed mechanism of action

- Pregabalin selectively binds to  $\alpha_2$ - $\delta$  subunit of calcium channels
  - Modulates calcium influx in hyperexcited neurons
  - Reduces neurotransmitter release
  - Pharmacologic effect requires binding at this site
  - The clinical significance of these observations in humans is currently unknown

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

## Gabapentin and Pregabalin Mechanism of Action are identical.

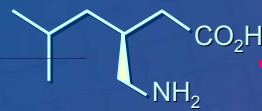
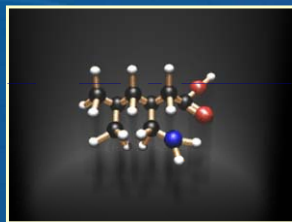


## Gabapentin: Mechanism of Action

- Interacts with  $\alpha_2\text{-}\delta$  subunit of voltage-gated  $\text{Ca}^{2+}$  channels
- In animal models
  - Prevents allodynia and hyperalgesia
  - Prevents pain-related responses in models of neuropathic pain
  - Decreases pain-related responses after peripheral inflammation
- Relevance of these models to human pain is not known

Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc; 2004.

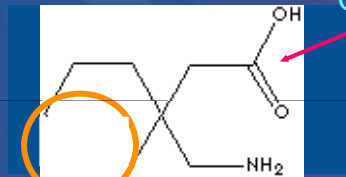
## Pregabalin Has a Different Chemical Structure



Pregabalin



GABA



Gabapentin

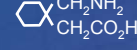
Lyrica® (pregabalin) Capsules CV [package insert]. New York, NY: Pfizer Inc; 2005;  
 Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc; 2004.

## Pregabalin and Gabapentin Pharmacology Facts

Pregabalin



Gabapentin



<b>FDA-approved pain indication</b>	Neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia	Postherpetic neuralgia
<b>Mechanism of action</b>	$\alpha_2$ - $\delta$ ligand • Selectively binds to the $\alpha_2$ - $\delta$ site in CNS tissues	$\alpha_2$ - $\delta$ ligand • Selectively binds to the $\alpha_2$ - $\delta$ site in CNS tissues
<b>Pharmacokinetic profile</b>	Linear • Plasma concentration is dose proportionate	Nonlinear • Plasma concentration increases disproportionately to dose
<b>Oral bioavailability</b>	$\geq 90\%$ all doses	60% 900 mg 47% 1200 mg 34% 2400 mg 33% 3600 mg
<b>Dose potency for PHN</b>	Effective at 150 mg/d • Dose range from 150 mg/d to 600 mg/d*	Effective at 1800 mg/d • No additional benefit at higher doses
<b>Dosing (PHN)</b>	BID or TID	TID
<b>Time to effective dose (PHN)</b>	1 day • Effective starting dose of 150 mg/d	9 or more days • Titrate to effective dose of 1800 mg/d

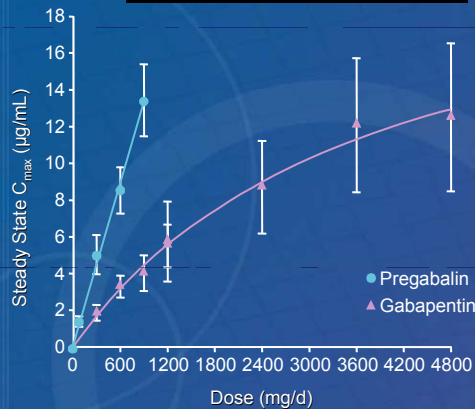
\*Some patients with PHN may benefit from up to 600 mg/d given after 2 to 4 weeks of treatment with 300 mg/d. Adverse events may increase with dose. CNS = central nervous system.

Lyrica® (pregabalin) Capsules CV [package insert], New York, NY: Pfizer Inc; 2005; Neurontin® (gabapentin) [package insert], New York, NY: Pfizer Inc; 2004.

## Pregabalin: Predictable Response Versus Gabapentin

**Linear PK Profile**

**High Bioavailability**



**Pregabalin**

**Gabapentin**

	900 mg, 60%
<b>All doses</b>	1200 mg, 47%
<b><math>\geq 90\%</math></b>	2400 mg, 34%
	3600 mg, 33%

**1800 mg Recommended dose**

Lyrica® (pregabalin) Capsules CV [package insert], New York, NY: Pfizer Inc; 2005; Neurontin® (gabapentin) [package insert], New York, NY: Pfizer Inc; 2004; Wesche, Bockbrader. Presented at: 24th Annual Scientific Meeting of the American Pain Society; 2005.

## Antiarrhythmic Agents

- Lidocaine
- Mexiletine:
  - Kastrup et al. Pain 1987.
  - Dejgard et al. Lancet 1988.
  - Strack et al. Diabetes Care 1992.

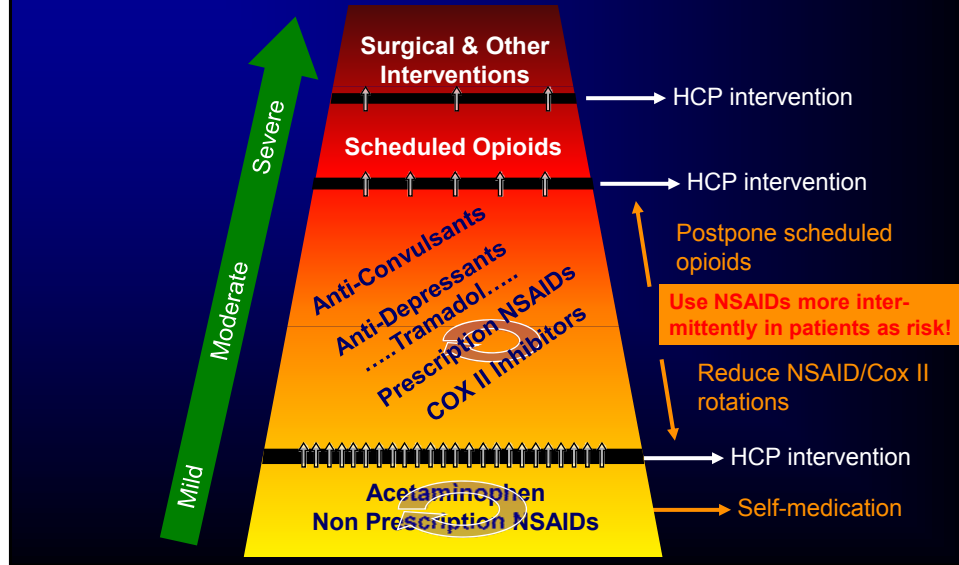
50

## My Recommendations

1. TCA's (amitriptyline)- **first line???**
2. Elderly (frail) patients TCA vs. SNRIs
3. Tramadol (Ultram®)
4. Gabapentin (Neurontin®)
5. Other Anti-convulsants
6. Anti-arrhythmics: Mexiletine (Mexitil®)-ECG

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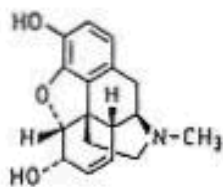
## Summary Pain Treatment Ladder



Questions?

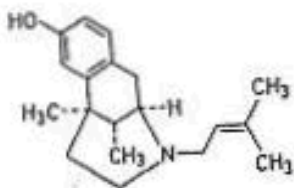
## Chemical Classes of Opioids

### PHENANTHRENES



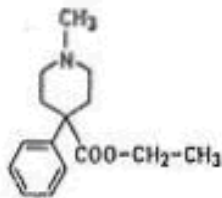
#### MORPHINE

### BENZOMORPHANS



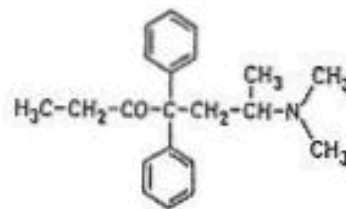
#### PENTAZOCINE

### PHENYLPYPERIDINES



#### MEPERIDINE

### DIPHENYLHEPTANES



#### METHADONE

Rx EXAMPLES > morphine  
codeine  
hydrocodone\*  
hydromorphone\*  
levorphanol\*  
oxycodone\*  
oxymorphone\*  
buprenorphine\*  
nalbuphine  
butorphanol\*  
naloxone\*  
heroin (diacetyl-morphine)

pentazocine  
diphenoxylate  
loperamide

meperidine  
fentanyl  
sufentanil  
alfentanil  
remifentanil

methadone  
propoxyphene

X-SENSATIVITY > PROBABLE

POSSIBLE

LOW RISK

LOW RISK

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

Courtesy of Dr. Jeffrey Fudin (FudinJ@gmail.com)

### References:

Fudin J, Levasseur DJ, Passik SD, Kirsh KL, Coleman J. Chronic pain management with opioids in patients with past or current substance abuse problems. *Journal of Pharmacy Practice*. 2003, 16;4:291-308

Reisine T, Pasternak G. Opioid analgesics and antagonists. In Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 9<sup>th</sup> ed. New York, NY: McGraw-Hill Companies; 1996:521-555.

Willette RE. Analgesic Agents. In: Wilson and Grisvold's *Textbook of Organic Medicinal Chemistry*. Ninth Edition, Editors: Delgado JN, Remers WA. JB Lippincott Company, Philadelphia, PA. 1991:629-654.

	Dose [mg]	Amine Effects	Sedation	Anticholinergic
<b>3° Amine TCA</b>				
Amitriptyline [Elavil]	25-300	NE > 5HT	3	3
Clomipramine [Anafranil]	25-300	5HT	2	3
Doxepin [Sinequan]	25-300	NE > 5HT	3	2
Imipramine [Tofranil]	25-300	NE > 5HT	2	2
Trimipramine [Surmontil]	25-300	NE > 5HT	3	3
<b>2° Amine TCA</b>				
Amoxapine [Asendin]	50-600	NE	1	1
Desipramine [Norpramin]	25-300	NE	0.5	1
Maprotiline [Ludiomil]	25-225	NE	2	2
Protriptyline [Vivactil]	10-60	NE	0.5	2
Nortriptyline [Pamelor]	25-250	NE	1	1
<b>Serotonin Reuptake Inhibitors</b>				
Fluoxetine [Prozac]	5-80	5HT	0.5	0
Fluvoxamine [Luvox]	50-300	5HT	0.5	0
Paroxetine [Paxil]	10-50	5HT	0.5	0.5
Citalopram [Celexa]	10-60	5HT	0.5	0
Sertraline [Zoloft]	50-200	5HT	0.5	0
Escitalopram [Lexapro]	10-20	5HT	0.5	0
<b>Atypical Antidepressants</b>				
Duloxetine (Cymbalta)	40-60	5HT > NE	0	0.5
Venlafaxine [Effexor]	25-375	5HT > NE	0	0.5
Bupropion [Wellbutrin]	100-450	NE, DA	0	0
Nefazodone [Serzone]	100-600	5HT > NE	3	0
Trazodone [Desyrel]	50-600	5HT > NE	3	0
Mirtazapine [Remeron]	15-45	NE [?]	3	0

**Courtesy of Jeffrey Fudin, Pharm.D., DAAPM**

Updates on Analgesics  
November 14, 2008 (Fudin Post-test)

1. Consider the following statements, and choose the best answer below.
  - a. Chronic pain may be pharmacologically and therapeutically treated identical to acute pain.
  - b. Chronic pain medications should be dosed in an “around-the-clock” fashion.
  - c. If a patient is properly titrated upwards with PURE opioids narcotics (ie. No combination drugs with acetaminophen), there is no maximum safe dose.
  - d. B and C above are both true.
  - e. Opiate addiction is always present with chronic narcotic use, and therefore opiates should only be used as a last resort, especially morphine.
  
2. In general, the dehydroxylated phenanthrenes...
  - a. are poorly tolerated.
  - b. are more well-tolerated than their hydroxylated counterparts.
  - c. have toxic metabolites.
  - d. are converted to nor-meperidine.
  
3. Polypharmacy is often necessary because of the cyclical nature of chronic pain, which often involves...
  - a. depression
  - b. sleep deprivation
  - c. loneliness
  - d. anxiety
  - e. all of the above
  
4. Medications used for neuropathic pain that don't interfere affect Cytochrome P450 Iso-enzymes are good choices for...
  - a. Chemistry buffs
  - b. Patient's with kidney dysfunction
  - c. HIV+ patients receiving anti-retrovirals
  - d. Nobody
  
5. The most important pharmacological mechanism of anti-depressants to treat neuropathy is...
  - a. blockade of the reuptake of serotonin.
  - b. blockade of the reuptake of dopamine
  - c. blockade of the reuptake of nor-epinephrine
  - d. all of the above
  
6. True or False?  
NSAIDs and COX-2's are superior analgesics for arthritic type-2 diabetics receiving ACEIs.