

Pharmacotherapeutic Update on Analgesics:

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

SAGE NSG-622 2008 Update

www.paindr.com

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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 20-64¹
- 6 million age >65¹
- Nearly 50% of adults report low back pain each year¹
- In 1998, incremental direct US medical costs from back pain ~\$26 billion²

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)

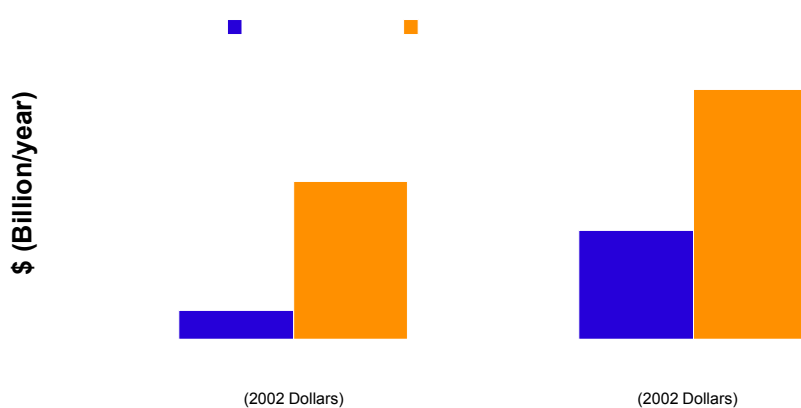
Osteoarthritis

- >20 million Americans currently have OA¹
 - 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^{2,3}
- In 1997, direct US medical costs from arthritis >\$50 billion⁴



1. NIAMS. At: <http://www.niams.nih.gov/hi/topics/arthritis/oahandout.htm>. Accessed March 2, 2006.
2. Roos. *Curr Opin Rheumatol*. 2005;17:195.
3. Gelber et al. *Ann Intern Med*. 2000;133:321.
4. Yeilin 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 life¹
- Sleep disturbance^{1,2}
- Impact on cognitive functions, activities of daily living, and productivity¹
- Depression and increased anxiety¹
- Interference with social relationships¹

1. American Pain Society. At: 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

Therapeutic Goal	Acute	Chronic
Sedation		
Rapid Onset		
Duration (T1/2)		
Timing		
Dose		
Route		

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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

Pharmacologic Treatment of Chronic Pain

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

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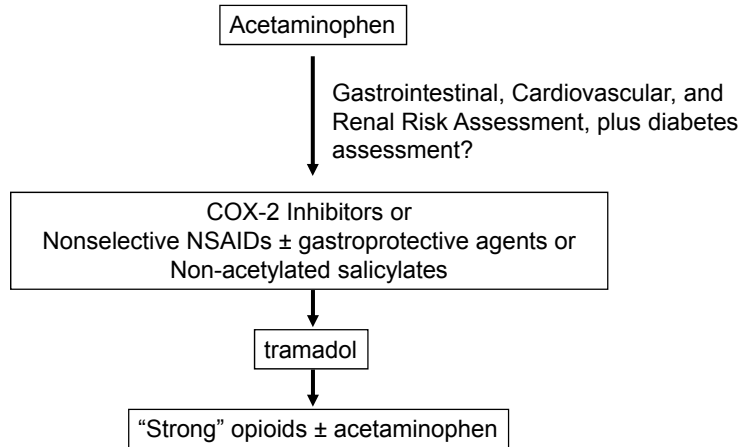
Limitations of Analgesic Therapies

- NSAIDs
 - Risk for GI toxicity¹
 - Recommended use of concomitant gastroprotective agents increases cost¹ What are they???
 - Risk for renal toxicity¹
 - Cardiovascular safety issues²
- COX-2 inhibitors
 - Risk for renal toxicity¹
 - Cardiovascular safety issues³
- Scheduled opioids associated with
 - Respiratory depression⁴ (???)
 - Fear of dependence/tolerance/abuse⁵
 - Stringent regulatory requirements and perceived potential for scrutiny may limit adequate prescribing⁵

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[®]

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^{1,2}
- Risk for GI toxicity³
- Need for concomitant use of gastroprotective agents in some patients³
- Risk for renal toxicity³

COX-2s

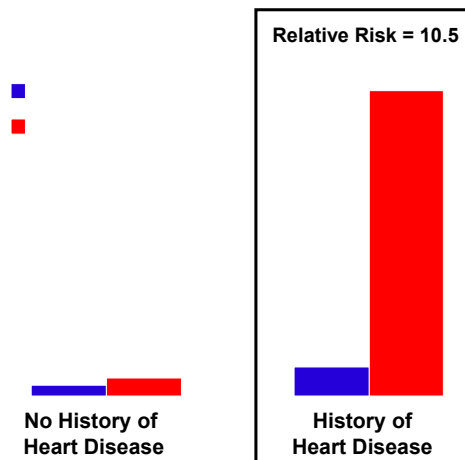
- Cardiovascular safety issues⁴
- Risk for renal toxicity³

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

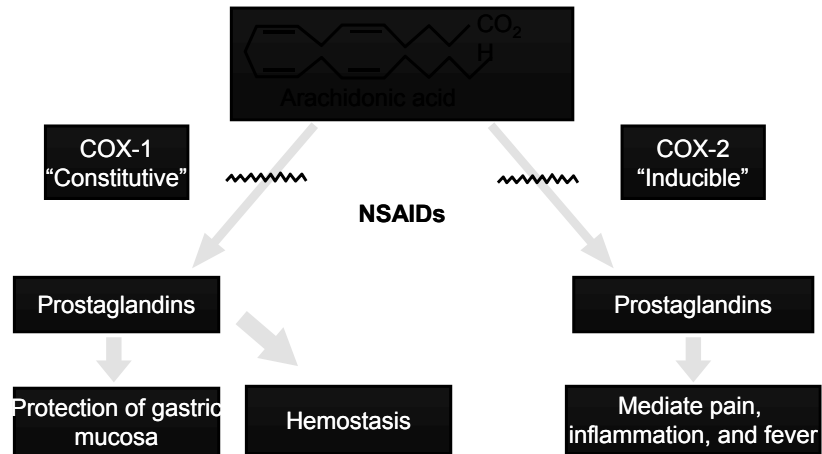
NSAID users with a history of heart disease had 10.5-fold greater incidence of CHF vs non-NSAID users



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

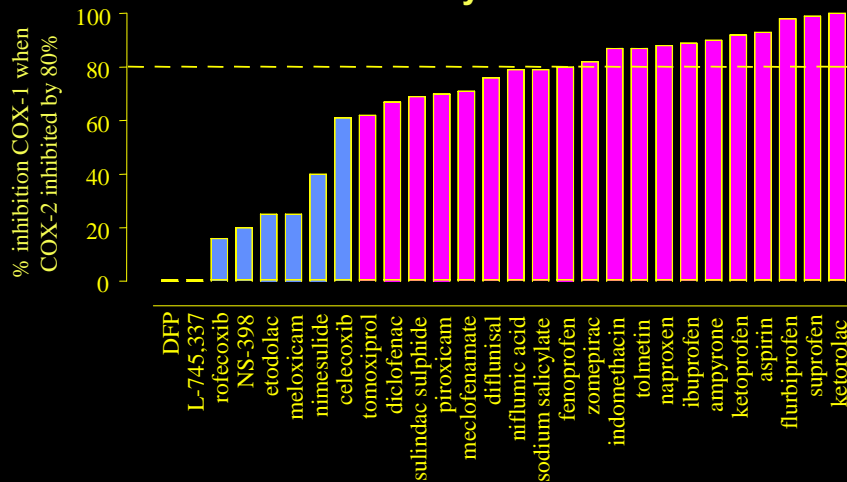
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Mechanism of Action of NSAIDs



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

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

Results of Case-Control and Cohort Studies Reporting on Cardiovascular Risks With NSAIDs and COX-2s

NSAIDs

	Naproxen	Diclofenac	Ibuprofen	Indo- methacin	Any/Other NSAIDs	Piroxicam

COX-2s

	All Celecoxib	All Rofecoxib	Rofecoxib ≤25mg/d	Rofecoxib ≥25mg/d	Meloxicam

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

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Barriers to Treatment of Chronic Pain

- **Drug-Related¹**
 - Currently recommended analgesics may provide inadequate efficacy and/or unacceptable tolerability/safety
- **Physician/Pharmacist-Related³**
 - Bias against opioid therapy and overestimation of risks
 - Fear of regulatory scrutiny/action
- **Patient-Related⁶**
 - 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. Accessed March 2, 2006.

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!

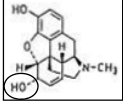
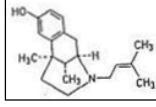
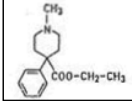
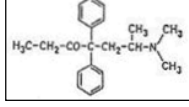
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Analgesic Choices

- **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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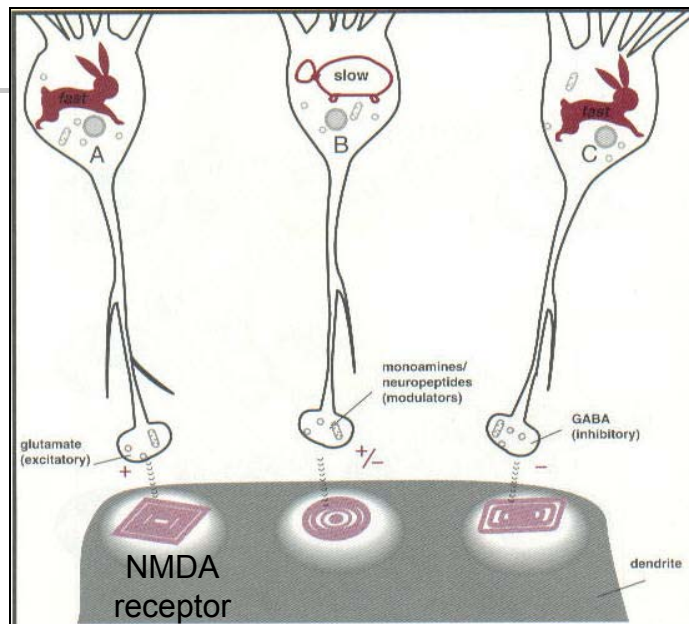
Chemical Classes of Opioids

	PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES
				
Rx EXAMPLES >	<p>MORPHINE morphine codeine hydrocodone* hydromorphone* levorphanol* oxycodone* oxymorphone* buprenorphine* nalbuphine butorphanol* naloxone* heroin (diacetyl-morphine)</p>	<p>PENTAZOCINE pentazocine diphenoxylate loperamide</p>	<p>MEPERIDINE meperidine fentanyl sufentanil alfentanil remifentanil</p>	<p>METHADONE methadone propoxyphene</p>
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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Neurotransmitter Signals



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Opioid Analgesic P-Kinetics

Drug	Half-life (hr)	Duration of Action (hr)	Onset of Action (hr)	Elimination Half-life (hr)
Levorphanol (IM)	0.5-1	12-16	10-20	5-8
Methadone (IM)	0.5-1	15-30	10-20	~8 (chronic)

Combined data from: Reisine T, Paternak G 1995 and Pasero C, Portenoy RK, McCaffery M. 1999

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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)

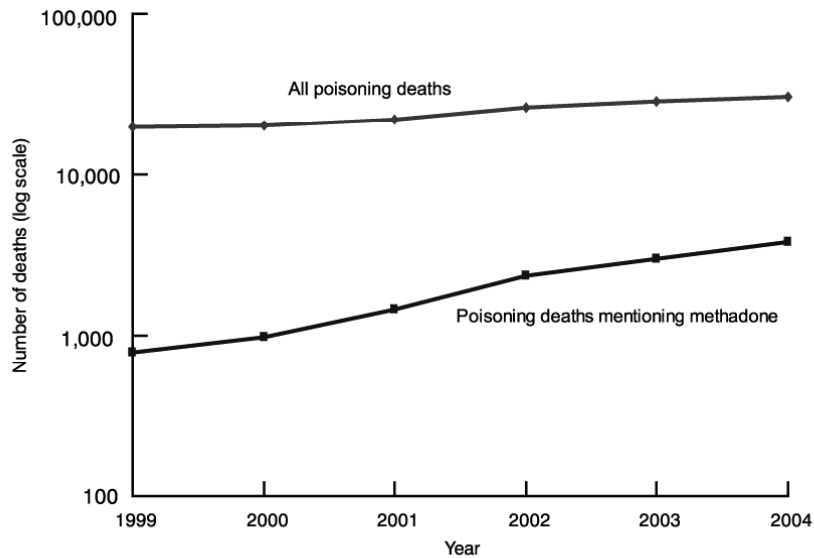
Volles DF, McGory R. Pharmacokinetic considerations, 15:5:Jan 1999.

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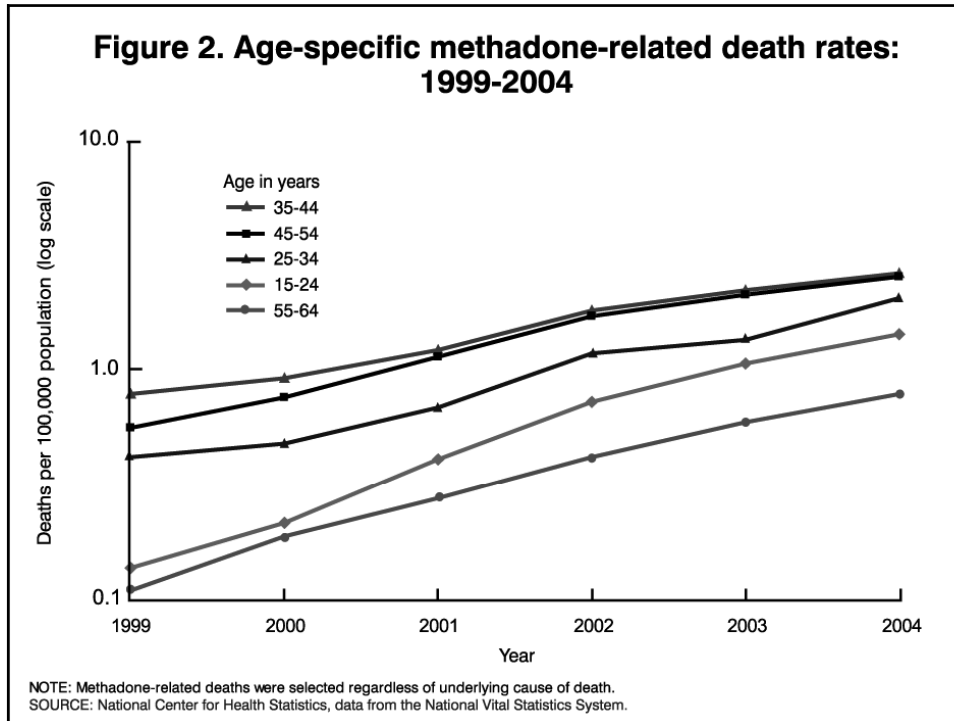
<http://www.fda.gov/cder/drug/infopage/methadone/default.htm>

The screenshot shows the FDA website interface. At the top, the URL is displayed. Below the navigation bar, a search box contains the text "Methadone Hydrochloride (marketed as Dolophine) Information". Below the search results, an "FDA ALERT [11/2006]: Death, Narcotic Overdose, and Serious Cardiac Arrhythmias" is highlighted with an arrow. The alert text states: "FDA has reviewed reports of death and life-threatening side effects such as slowed or stopped breathing, and dangerous changes in heart beat in patients receiving methadone. These serious side effects may occur because methadone may build up in the body to a toxic level if it is taken too often, if the amount taken is too high, or if it is taken with certain other medicines or supplements. Methadone has specific toxic effects on the heart (QT prolongation and Torsades de Pointes). Physicians prescribing methadone should be familiar with methadone's toxicities and unique pharmacologic properties. Methadone's elimination half-life (8-59 hours) is longer than its duration of analgesic action (4-8 hours). Methadone doses for pain should be carefully selected and slowly titrated to analgesic effect even in patients who are opioid-tolerant. Physicians should closely monitor patients when converting them from other opioids and changing the methadone dose, and thoroughly instruct patients how to take methadone. Healthcare professionals should tell patients to take no more methadone than has been prescribed without first talking to their physician." Below the alert, a note reads: "This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available."

Figure 1. Poisoning and methadone-related poisoning deaths: 1999-2004



SOURCE: National Center for Health Statistics, data from the National Vital Statistics System.



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

“Fudin Factor”

A Methadone Conversion Formula

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

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

Let X= Morphine (mg)

Relation Between Daily Morphine and Methadone Dosages

Methadone vs Morphine

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

$$\text{Methadone (mg)} = \frac{X}{21} \left\{ 5.7 - 3 \sin \left(\frac{90}{\left(\frac{110}{X} \right)^5 + 1} \right) - \sin \left(\frac{90}{\left(\frac{320}{X} \right)^7 + 1} \right) \right\}$$

Let X= Morphine (mg)

Relation Between Daily Morphine and Methadone Dosages

Methadone vs Morphine

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

<i>3° Amine TCA</i>				
<i>2° Amine TCA</i>				

<i>Serotonin Reuptake Inhibitors</i>				
<i>Atypical Antidepressants</i>				
<i>MAOIs</i>				

Anti-depressants, continued

Tricyclic Antidepressants: Positive Controlled Trials

Study	Agent (mg/d)	N	Weeks	Primary End Point
Painful DPN				
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
PHN				
Watson	Amitriptyline (≥ 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.

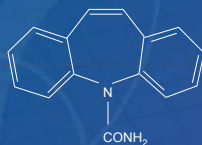
Tramadol: Important Safety Information

- 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.

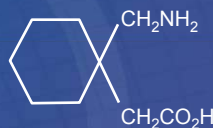
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Anticonvulsants

- 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

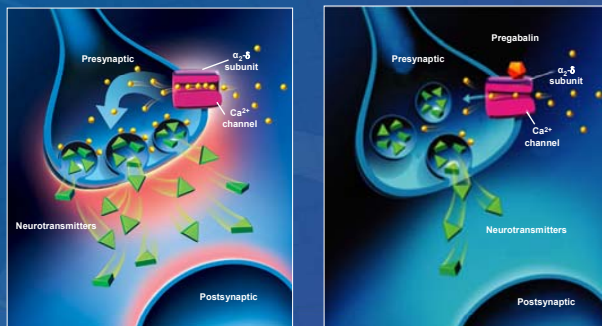
Plasma Protein Displacement

phenytoin

valproate

carbamazepine

Pharmacology: Gabapentin & Pregabalin Binds to the α_2 - δ Subunit of Voltage-Gated Ca^{2+} Channels in the Central Nervous System

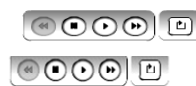
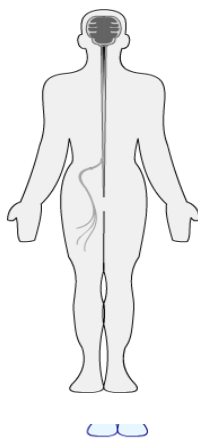


Schematic representation of pregabalin's proposed mechanism of action

- Pregabalin selectively binds to α_2 - δ 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.

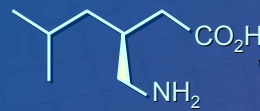
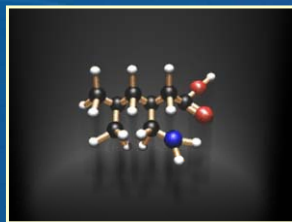


Gabapentin: Mechanism of Action

- Interacts with $\alpha_2\text{-}\delta$ subunit of voltage-gated 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.

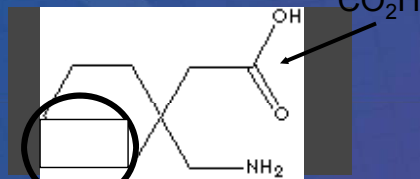
Pregabalin Has a Different Chemical Structure



Pregabalin



GABA



Gabapentin

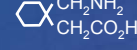
Lyrica® (pregabalin) Capsules CV [package insert]. New York, NY: Pfizer Inc; 2005;
 Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc; 2004.

Pregabalin and Gabapentin Pharmacology Facts

Pregabalin



Gabapentin



FDA-approved pain indication	Neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia	Postherpetic neuralgia
Mechanism of action	α_2 - δ ligand • Selectively binds to the α_2 - δ site in CNS tissues	α_2 - δ ligand • Selectively binds to the α_2 - δ site in CNS tissues
Pharmacokinetic profile	Linear • Plasma concentration is dose proportionate	Nonlinear • Plasma concentration increases disproportionately to dose
Oral bioavailability	$\geq 90\%$ all doses	60% 900 mg 47% 1200 mg 34% 2400 mg 33% 3600 mg
Dose potency for PHN	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
Dosing (PHN)	BID or TID	TID
Time to effective dose (PHN)	1 day • Effective starting dose of 150 mg/d	9 or more days • Titrate to effective dose of 1800 mg/d

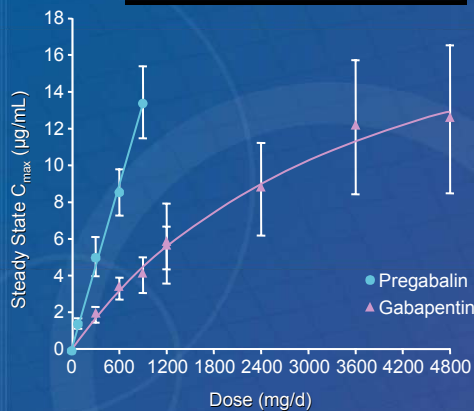
*Some patients with PHN may benefit from up to 600 mg/d given after 2 to 4 weeks of treatment with 300 mg/d. Adverse events may increase with dose. CNS = central nervous system.

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%
All doses	1200 mg, 47%
$\geq 90\%$	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.

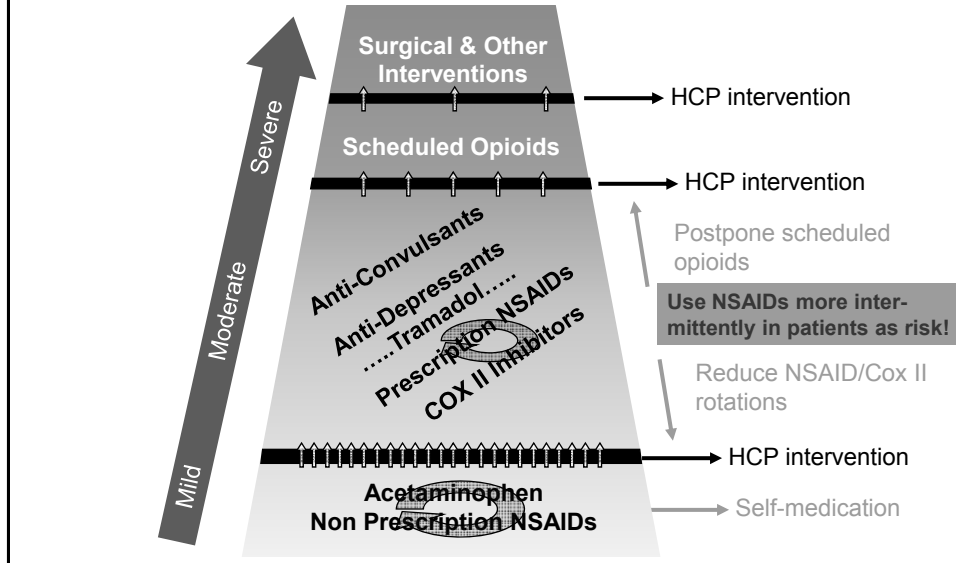
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My Recommendations

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?