OPIOIDS FOR CHRONIC PAIN: NEW EVIDENCE, NEW STRATEGIES

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Opioids for Chronic Non-Cancer Pain

Objectives:

- To describe the populations that may be candidates for opioid therapy in chronic non-cancer pain
- To discuss the potential indications for opioids in patients with osteoarthritis (OA) pain

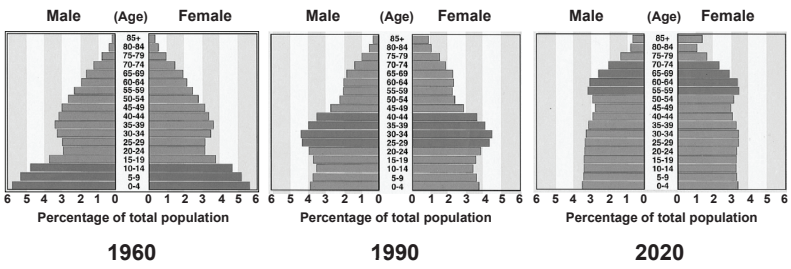
The Burden of Pain: Demographics

- US Population (2010 census): 308,746,000
- 100 million Americans seek treatment for chronic pain[1]
  - Annual cost is $560-$635 billion[2]
  - More than 4 of 10 patients do not get adequate relief[2]
  - Need for involvement of primary care and other healthcare professionals

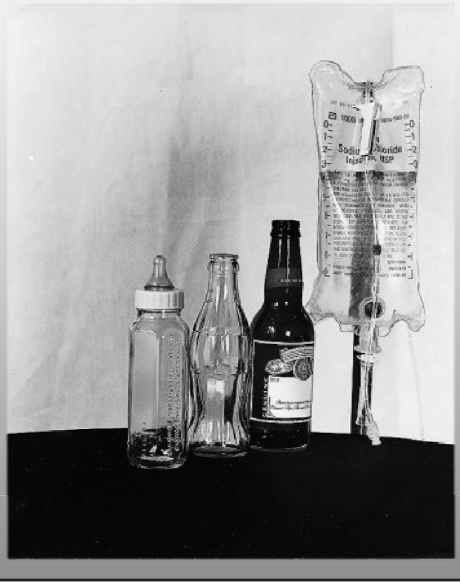
~38,666 patients—1 pain specialist[1,2]

1. Institute of Medicine Report – 2011. Available at : http://www.iom.edu/~/media/Files/Report%20Files/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research/Pain%20Research%202011%20Report%20Brief.pdf. Accessed May 1, 2012.
2. American Academy of Pain Management Website. Pain issues: pain is an epidemic. Available at: http://www.aapainmanage.org/literature/Articles/PainAnEpidemic.pdf. Accessed April 17, 2012.

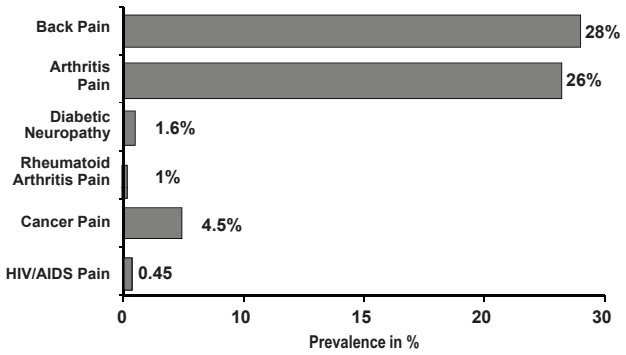
The Aging Population



Source: US Bureau of the Census. The older population: 2010. Available at: http://www.census.gov/prod/cen2010/briefs/c2010br-09.pdf. Accessed April 17, 2012.



Chronic Pain: Prevalence Across Conditions



Centers for Disease Control and Prevention (CDC) and National Center for Health Statistics (NCHS). Health, United States, 2010. Available at: http://www.cdc.gov/nchs/hus.htm. Accessed April 17, 2012.

Opioids for Non-Cancer Pain

- Patients with chronic low back pain of somatic origin (mechanical) not responding to other agents or as third-line adjuvants when neuropathic pain is present
- **Patients with osteoarthritis not responding to acetaminophen who have a contraindication to receive NSAIDs, COX-2 inhibitors**
- Patients with neuropathic pain who have not achieved adequate analgesia despite treatment with maximum doses of first- and second-line anti-neuropathics

Opioids for Osteoarthritis (OA) Pain

Therapeutic recommendations for the management of hand, hip and knee OA pain:

- **European League Against Rheumatism (EULAR)**
  - Zhang W, et al. *Ann Rheum Dis.* 2007;66:377-388.
- **Osteoarthritis Research Society International**
  - Zhang W, et al. *Osteoarthritis Cartilage*. 2008;16:137-162.
- **American Academy of Orthopaedic Surgeons**
  - AAOS (2008). Available at: http://www.aaos.org/research/guidelines/OAKguideline.pdf.
- **American College of Rheumatology**
  - Hochberg MC, et al. *Arthritis Care Res*. 2012;64:465-472.

ACR 2012 Recommendations

SPECIAL ARTICLE

American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee

MARC C. HOCHBERG,[1] ROY D. ALTMAN,[2] KARINE TOUPIN APRIL,[3] MARIA BENKHALTI,[3] GORDON GUYATT,[4] JESSIE McGOWAN,[3] TANVEER TOWHEED,[5] VIVIAN WELCH,[3] GEORGE WELLS,[3] AND PETER TUGWELL[3]

Hochberg MC, et al. *Arthritis Care Res*. 2012;64:465-472.

ACR 2012 Recommendations: Initial Management of Hand OA

We conditionally recommend that health professionals should use one or more of the following:

- Topical capsaicin
- Topical NSAIDs, including trolamine salicylate
- Oral NSAIDs, including COX-2 selective inhibitors
- Tramadol

We conditionally recommend that health professionals should use one or more of the following:

- Intraarticular therapies
- Opioid analgesics

We conditionally recommend that persons age ≥75 years should use topical rather than oral NSAIDs. In persons age <75 years, the TEP expressed no preference for using topical rather than oral NSAIDs.

Hochberg MC, et al. *Arthritis Care Res*. 2012;64:465-472.

ACR 2012 Recommendations: Initial Management of Knee OA

We conditionally recommend that patients with knee OA should use one of the following:

- Acetaminophen
- Oral NSAIDs
- Topical NSAIDs
- Tramadol
- Intraarticular corticosteroid injections

We conditionally recommend that patients with knee OA should not use the following:

- Chondroitin sulfate
- Glucosamine
- Topical capsaicin

We have no recommendations regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics

Hochberg MC, et al. *Arthritis Care Res.* 2012;64:465-472.

ACR 2012 Recommendations: Initial Management of Hip OA

We conditionally recommend that patients with hip OA should use one of the following:

- Acetaminophen
- Oral NSAIDs
- Tramadol
- Intraarticular corticosteroid injections

We conditionally recommend that patients with hip OA should not use the following:

- Chondroitin sulfate
- Glucosamine

We have no recommendations regarding the use of the following:

- Topical NSAIDs
- Intraarticular hyaluronate injections
- Duloxetine
- Opioid analgesics

Hochberg MC, et al. *Arthritis Care Res.* 2012;64:465-472.

Management of Knee OA Following an Inadequate Response

Finally, for patients with symptomatic knee OA who have not had an adequate response to both nonpharmacologic and pharmacologic modalities and are either unwilling to undergo or are not candidates for total joint arthroplasty, the TEP strongly recommends the use of opioid analgesics and conditionally recommends the use of duloxetine. The authors suggest that practitioners follow the

Hochberg MC, et al. *Arthritis Care Res.* 2012;64:465-472.

Management of Hip OA Following an Inadequate Response

Pharmacologic modalities. The approach to pharmacologic therapy for the patient with hip OA is similar to that for the patient with knee OA except that no recommendations were made for intraarticular hyaluronates, duloxetine, or topical NSAIDs because of the lack of data from RCTs on either benefit or safety at the time of the TEP meeting in December 2008 (Table 6). Again, opioid analgesics are strongly recommended only for patients with symptomatic hip OA who have not had an adequate response to both nonpharmacologic and pharmacologic modalities and are either unwilling to undergo or are not candidates for total joint arthroplasty.

Hochberg MC, et al. *Arthritis Care Res.* 2012;64:465-472.

NSAIDs and Adverse Events in the Elderly

SPECIAL ARTICLE

Pharmacological Management of Persistent Pain in Older Persons[1]

American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons

…the evidence that the use of NSAIDs and COX-2 inhibitors may result in serious and life-threatening gastrointestinal and cardiovascular adverse events or gastrointestinal bleeding has shifted attention to opioids, especially for older patients who may be at particular risk for NSAID-related adverse effects.

1. American Geriatrics Society. *JAGS.* 2009;57:1331-1346.
2. Singh G, et al. *Arthritis Res Ther.* 2006;8:R153.

My View of NSAIDs and COXIB Therapy *(today)*

Significant renal disease? → **yes** → **Avoid NSAIDs** **Avoid COXIBs**

American Geriatrics Society. *JAGS.* 2009;57:1331-1346.
Hochberg MC, et al. *Arthritis Care Res.* 2012;64:465-472.

My View of NSAIDs and COXIB Therapy *(today)*

Impaired heart function? → **yes** → **Avoid NSAIDs**

American Geriatrics Society. *JAGS.* 2009;57:1331-1346.

NSAID-Associated Adverse Events

Number of AEs each year in a population of 100,000 patients where 3,800 over 65 years take NSAIDs

Event	Cases per year
Upper GI bleed	18
Congestive heart failure	22
Acute renal failure	10

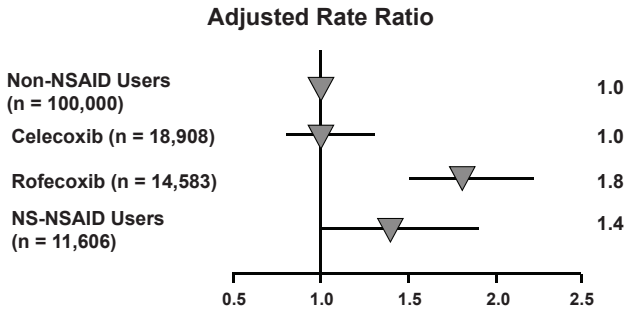
Bandolier 79. 2000;7:6-8. Available at: http://www.medicine.ox.ac.uk/bandolier/painres/download/bando079.pdf.
Page J, Henry D. *Arch Intern Med.* 2000;160:777-784.
Merlo J, et al. *Eur J Clin Pharmacol.* 2001;57:71-75.

NSAIDs and Congestive Heart Failure

- Highest incidence in older people
- Higher risk with piroxicam, naproxen, or tenoxicam
- Pre-existing heart disease increases risk
- Heart disease + NSAIDs: Odds Ratio ~25

Page J, Henry D. *Arch Intern Med.* 2000;160:777-784.

CHF Outcomes With COX-2–Specific Inhibitors and NS-NSAIDs Compared With Nonusers



NS-NSAIDs, non-selective NSAIDs
Mamdani M, et al. *Lancet.* 2004;363:1751-1756.

My View of NSAIDs and COXIB Therapy *(today)*

Significant renal disease?
Impaired heart function?

yes

Topical NSAIDs ± Duloxetine/Tramadol/Opioids

American Geriatrics Society. *JAGS.* 2009;57:1331-1346.

My View of NSAIDs and COXIB Therapy *(today)*

Significant renal disease?
Impaired heart function?

no

On low dose aspirin? → **yes** → **NSAIDs + ASA?** **COX-2 + ASA?**

ASA, aspirin (acetylsalicylic acid)
American Geriatrics Society. *JAGS.* 2009;57:1331-1346.

NSAIDs and Potential Interaction with Aspirin

Ibuprofen + ASA issue (acetylation of the serine 529 residue results in >95% inhibition of TXA_2 production)

Catella-Lawson F, et al. *N Eng J Med.* 2001;345:1809-1817
Ellison J, Dager W. *Prev Cardiol.* 2007;10:61-63.
FDA. Concomitant use of ibuprofen and aspirin. Available at:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125222.htm.

NSAIDs and Potential Interaction with Aspirin

This interaction does NOT appear to occur between ASA and diclofenac or ASA and celecoxib

Schuijt MP, et al. *Br J Pharmacol.* 2009;157:931-934.
Wilner KD, et al. *J Clin Pharmacol.* 2002;42:1027-1030.

My View of NSAIDs and COXIB Therapy *(today)*

Significant renal disease?

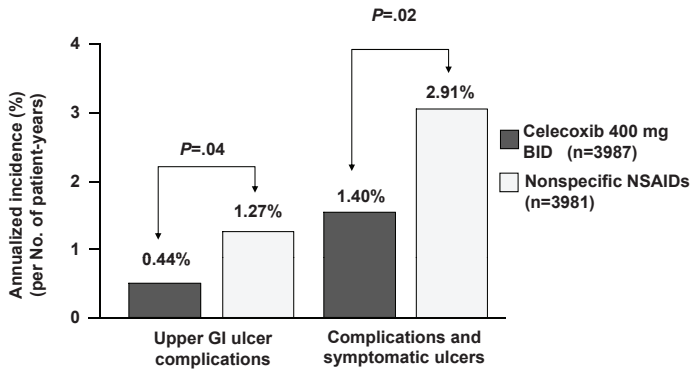
Impaired heart function?

no

On low dose aspirin? → **yes** → ***COX-2 + ASA?***

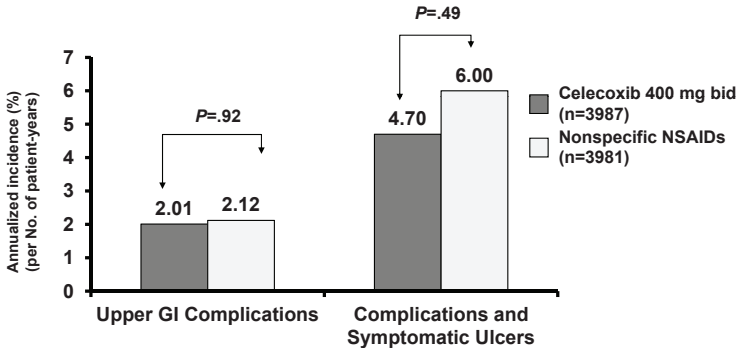
American Geriatrics Society. *JAGS.* 2009;57:1331-1346.

CLASS: Ulcer Complications and Symptomatic Ulcers at 6 Months Nonusers of ASA



Silverstein FE, et al. *JAMA*. 2000;284:1247-1255.

CLASS: Ulcer Complications and Symptomatic Ulcers at 6 Months ASA Users



Silverstein, FE et al. *JAMA*. 2000;284:1247-1255.

My View of NSAIDs and COXIB Therapy *(today)*

Significant renal disease?
Impaired heart function?

yes → **Avoid NSAIDs**
Avoid COXIBs

no

On low dose aspirin?

yes → ***COX-2 + ASA***

Topical NSAIDs ± Duloxetine/Tramadol/Opioids

American Geriatrics Society. *JAGS*. 2009;57:1331-1346.

Opioids in OA Pain

- **Two additional groups:**
  - Patients with history of
    - Diabetes mellitus and evidence of proteinuria
    - Treatment with ACE Inhibitors for afterload reducing purposes
  - The use of NSAIDs or COXIBs may very quickly result in the deterioration of renal function

American Geriatrics Society. *JAGS*. 2009;57:1331-1346.

Opioids for Chronic Pain: Dose Escalation

CONCLUSIONS

Although opioid drugs have been used in the treatment of pain for thousands of years, it is only in the past 60 years that they have been regulated, with legitimate use placed entirely in the hands of licensed practitioners. Also during this period, scientific research has led to a better understanding of the actions of opioids. Physicians are in a better position now to control opioid use so that it helps, rather than harms, patients. Current guidelines recommend a cautious approach to dose escalation and the discontinuation of opioids if treatment goals are not met. However, in busy practice settings, the reality of dealing with patients who have complex problems often forces physicians to compromise. As a consequence, very large doses of opioids are prescribed for patients with chronic pain that is not associated with terminal disease, often in the absence of any real improvement in the patient's pain or level of functioning. Whereas it was previously thought that unlimited dose escalation was at least safe, evidence now suggests that prolonged, high-dose opioid therapy may be neither safe nor effective. It is therefore important that physicians make every effort to control indiscriminate prescribing, even when they are under pressure by patients to increase the dose of opioids.

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MEDICAL PROGRESS

Opioid Therapy for Chronic Pain

Jane C. Ballantyne, M.D., and Jianren Mao, M.D., Ph.D.

Ballantyne JC, Mao J. *N Engl J Med*. 2003;349:1943-1953.

Opioids for Chronic Pain: Stable vs. Escalating Doses

American Pain Society RESEARCH EDUCATION TREATMENT ADVOCACY

PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 12, No 2 (February), 2011: pp 288-296
Available online at www.sciencedirect.com

A Randomized Trial of 2 Prescription Strategies for Opioid Treatment of Chronic Nonmalignant Pain

Bruce D. Naliboff,*,†,‡ Stephen M. Wu,*,† Beatrix Schieffer,* Roger Bolus,† Quynh Pham,*,§ Ariel Baria,* Dixie Aragaki,*,§ Walter Van Vort,* Frederick Davis,* and Paul Shekelle*,§

abuse, and proper prescribing guidelines. The current study directly compares for the first time in a randomized trial the effectiveness of a conservative, hold the line (Stable Dose) prescribing strategy for opioid medications with a more liberal dose escalation (Escalating Dose) approach. This 2-arm,

No group differences were found for primary outcomes of usual pain or functional disability although the Escalating Dose group did show a small but significantly larger increase in self-rated pain relief from medications. About 27% of patients were discharged over the course of the study due to opioid misuse/noncompliance, but there were no group differences in rate of opioid misuse.

Naliboff BD, et al. *J Pain*. 2011;12:288-296.

Opioids for Non-Cancer Pain

Conclusions:

- Opioids are a viable alternative in patients with non-cancer pain
- Recent data suggest that opioids may be useful in the treatment OA pain as third-line agents when surgery is not an option
- However, one must be aware of the pitfalls in their use
- An exit strategy, if no success is achieved, should always be part of the treatment strategy


PATIENT-
CENTERED
CLINICAL CASE
WITH
TAKE-AWAY
MESSAGES

Case Study: Cindy

- A **72-year-old female** presents with **severe right knee joint pain** that is **not responding** to **acetaminophen** therapy
- **Height**: 5 ft, 7 in
- **Weight:** 120 kg
- Vital signs stable other than **high pain scores** based on VAS

Case Study: History

- Reports worsening pain over the last 6 months with no history of injury
- History of knee joint pain related to use, short-lasting inactivity stiffness, pain on movement, cracking (crepitus)
- VAS on exam: 7/10
  - Worse VAS during previous week: 8/10
  - Lower VAS during week prior to that: 5/10
- Reports pain also in hands, shoulders
- Poor psychosocial function (ADL, sleep, ability to socialize)

Case Study: History (cont'd)

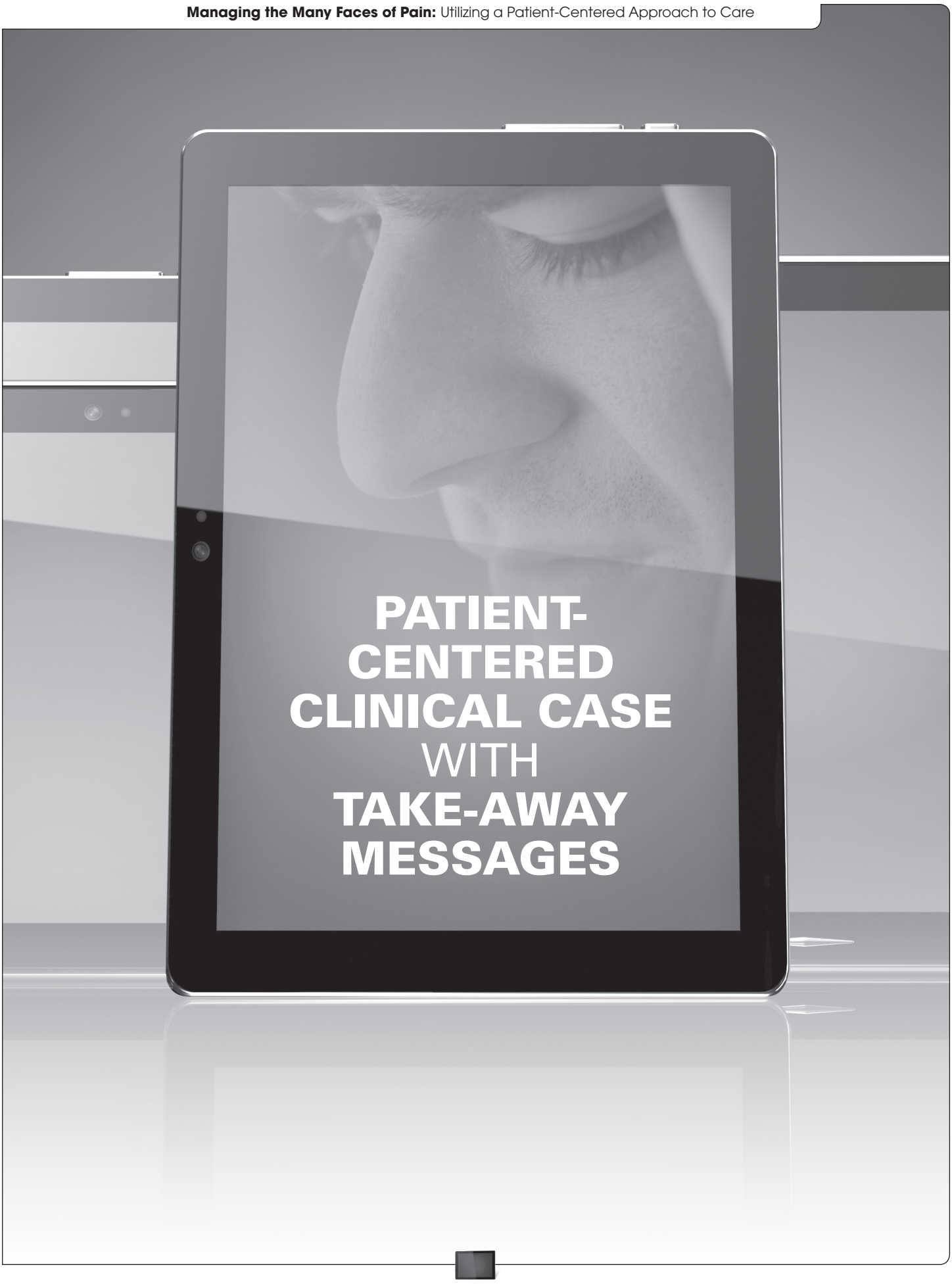
- **Medical:** OA, hypercholesterolemia, controlled angina, arterial hypertension
- **Surgical:** Negative
- **Social:** Cigarettes (1 pack per day); has worked at family farm all her life
- **Family:** Mother, 2 sisters have OA
- **Medications:** Acetaminophen 1 g every 6 hours, aspirin 81 mg daily, simvastatin 40 mg daily, diltiazem ER 120 mg daily

Case Study: Physical Findings

- No inflammatory signs in the right knee
- Restricted range of motion during flexion with severe pain with flexion beyond 90 degrees

What would NOT be appropriate to prescribe next?

The patient is taking 81 mg of aspirin every day. Is the risk of upper GI bleeding and gastric ulcer complication the same if she takes either an NSAID or a COX-2 inhibitor?



PATIENT-CENTERED CLINICAL CASE WITH TAKE-AWAY MESSAGES

Case Study: Ray

- **66 year-old male** with **chronic intractable pain** due to failed back surgical syndrome
  - 3 previous fusions
  - Concomitant cervical spine issues
- On **stable doses of opioids**, **neuropathic** and **adjunctive analgesics**
  - Methadone 40 mg q8h, gabapentin 600 mg q8h, venlafaxine 150 mg qd

Case Study: Failed Back

- **PMH:** HTN, hyperlipidemia, atrial fibrillation
- **Rx:** Simvastatin, metoprolol, digoxin
- **Social:** Smokes 1 ppd, "social" EtOH use
- **Physical Examination:**
  - Diffuse tenderness
  - Chronic stable neurologic sensory deficits

Reports :

- somnolence
- generalized fatigue
- depression
- loss of libido and almost complete loss of erectile function
- Constipation
- Poor pain control

This patient was almost functionless. He was recommended to our pain management center by his primary care physician.

Which aspect of Ray's status would you consider to be the highest priority?

Hypogonadism

Opioids diminish testosterone levels by inhibiting:

- Hypothalamic gonadotropin-releasing hormone production
- Testicular testosterone synthesis

Do you discuss sexual dysfunction as a consequence of your patient's pain or medication regimen?

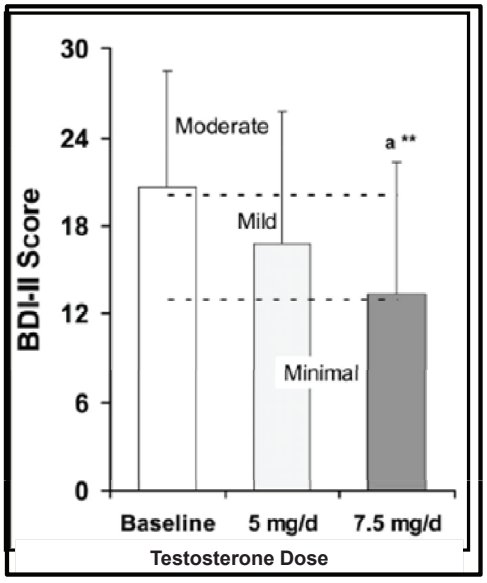
Hypogonadism in Men Using Daily Opioid Therapy for Chronic Noncancer Pain is Associated with Duration of Action of Opioid

- 81 men between 18 and 80 years of age on stable dose of an opioid used daily for at least three months
- None of them had previous diagnosis of hypogonadism
  - long-acting opioids, 34/46 (74%) were hypogonadal.
  - short-acting opioids, 12/43 (34%) were hypogonadal.
  - statistically significant difference at $p<0.001$
- When controlling for dosage and BMI, patients on long-acting opioids had 4.78 times greater odds of becoming hypogonadal (95% CI: 1.51–15.07; p=0.008).
- In the multivariate analysis, dose wasn't significantly associated with hypogonadism

Rubinstein AL, Kaiser Permanente. Presented at 2012 AAPM Annual Meeting.

Testosterone Replacement in Opioid-Induced Androgen Deficiency

- Effect of testosterone replacement on depression score
- Note: no study on therapy in women yet, although more often on birth control pill



Daniell HW, et al. *J Pain*. 2006;7:200-210.

Pain Patients

- Depressed
- Poor function
- On polypharmacy with frequent AEs and drug-drug interactions
- Opioids
  - Constipation, nausea/vomiting, pruritus, sweating
  - Somnolence, dizziness, euphoria, dysphoria
  - Opioid-induced hyperalgesia
  - Opioid-induced hypogonadism
    - Endocrine dysfunction

Ray

- Tested for total and free serum testosterone
- Started on replacement
- Pain, mood, energy, and some libido improvement
- ALL = QoL improvement!

RECOGNIZING AND OVERCOMING OPIOID-ASSOCIATED ADVERSE EVENTS

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Englewood, NJ

The Opioid Receptors

- Shortly after the discovery and observance of endogenous opioid peptides, multiple classes of unique opioid receptors were found.
- There are four main opioid receptors, the mu receptor, the delta receptor, the kappa receptor, and the ORL-1 receptor.
- The sigma receptors were once thought to be opioid receptors, however, pharmacological testing indicated that the sigma receptors were activated by drugs completely unrelated to the opioids.

Endogenous Opioid Peptides

- The receptors are found on cell membranes in both the nervous system and periphery and have different effects.
- When an opioid binds to the mu receptor, it induces a change in shape which in turn induces a change in the ion channels of the associated cell membrane.
- Opioid peptides work by modulating the release and uptake of specific neurotransmitters.

Complexities of Opioid Therapy

- Variable response, partial efficacy
- Drug-drug interactions
- AE profile
- OIH (opioid-induced hyperalgesia)
- Endocrine dysfunction (hypogonadism)
- Abuse, misuse and diversion
- Regulatory concerns, fears (rational?)
  - Extensive documentation

Variable Response, Partial Efficacy

- Response to a drug may depend on a number of factors including drug absorption, distribution, metabolism and elimination.
- Drug concentration at the target site, the number and morphology of target receptors, together with variation in multiple downstream events will also influence response.
- Individual differences in pharmacokinetics and pharmacodynamics, the type of pain, and the method of drug administration can account for the response variability to analgesics.

Variable Response, Partial Efficacy

- 10–30% of patients do not respond to morphine, achieving poor analgesic response or intolerable adverse effects.*
- At present, we cannot predict which patients are likely to achieve good analgesia or develop adverse effects. In patients who do not tolerate morphine, it is becoming increasingly common to prescribe other strong opioids. Even with the use of alternative opioids, outcomes are often variable and unpredictable.

*Cherny N, et al. *J Clin Oncol.* 2001;19:2542−2554.

Drug-Drug Interactions

- Cytochrome P450 enzymes are essential for the metabolism of many medications.
- Although this class has more than 50 enzymes, six of them metabolize 90% of drugs.
- The two most significant enzymes are CYP3A4 and CYP2D6.
- Genetic variability (polymorphism) in these enzymes may influence a patient's response to commonly prescribed drug classes, including beta blockers and antidepressants.

Lynch T, Price A. *Am Fam Physician.* 2007;76:391-396.

Opioids and Other Drugs Metabolized by CYP 3A4 and CYP 2D6

Enzymes	Opioids	Popular Medications/ Substrates
CYP2D6	Codeine	Carvedilol
	Dextromethorphan	Propafenone
	Dihydrocodeine	Amitriptyline
	Oxycodone	Paroxetine
	Tramadol	Risperidone
		Thioridazine
		Fluoxetine
		Lidocaine
		Nortriptyline
		Propranolol
		Tamoxifen
		Venlafaxine
CYP3A4	Buprenorphine	Clarithromycin
	Fentanyl	Erythromycin
	Methadone	Alprazolam
	Oxycodone	Cyclosporine
		Chlorpheniramine
		Diltiazem
		Lovastatin
		Hydrocortisone
		Buspirone
		Caffeine
		Nifedipine
		Verapamil
		Diazepam

Sinatra R. *J Am Board Fam Med.* 2006;19:165-177.

Side Effects / Adverse Reactions

- **GI dysfunction**
  - Constipation, nausea, vomiting, anorexia
- **CNS dysfunction**
  - Light-headedness, dizziness, sedation, euphoria, dysphoria
  - Increased intracranial pressure, miosis, myoclonus
- **Respiratory dysfunction**
  - Depression, arrest
- **Cutaneous: pruritus**
- **Circulatory depression: hypotension**

Opioid-Induced Nausea

- Opiates activate receptors in the chemoreceptor trigger zone located outside of the blood brain barrier.
- This transmits a signal to the emesis center, located in the medulla of the brain.
- Tolerance to the nauseating effects may occur.
- Slow titration to a therapeutic dose may decrease likelihood of developing nausea.

Opioid-Induced Sedation

- Usually resolves in <1 week
- Initiate opioids at lowest possible doses
  - Tailor to patient opioid history and clinical status
  - If dose needs to be increased, titrate slowly
- Consider CNS stimulants
  - Caffeine, methylphenidate, dextroamphetamine, modafinil
- Evaluate for other causes of sedation if it persists >1 week after initiation of opioids
  - CNS pathology, other sedating medications, hypercalcemia, dehydration, sepsis, hypoxia

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Adult Cancer Pain. v.1.2007. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

Opioid-Induced Sedation

- **Persistent sedation >1 wk after start**
  - Consider change of opioid or ↓ dose to lowest possible
  - Consider adjuvant analgesics
  - Consider lower dose more frequently to ↓ peaks
- **Refractory sedation**
  - Reassess cause and severity & consider neuroaxial analgesia or neuroablative techniques

Opioid-Induced Delirium

- Assess for other causes of delirium
  - Hypercalcemia, CNS pathology, brain metastasis, other psychoactive medications
- Consider change of opiate or adjuvant analgesic to decrease dose
- Consider neuroleptic agent
  - Antipsychotics: haloperidol, risperidone, etc.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Adult Cancer Pain. v.1.2007. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

Opioid-Induced Motor and Cognitive Dysfunction

Stable dose of opioids >2 weeks are not likely to interfere with psychomotor and cognitive function

- Monitor closely during analgesic administration and titration
- Patients should not drive during initial titration and should be counseled not to drive for 48 hours after dose increase

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Adult Cancer Pain. v.1.2007. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

Opioid Toxicity Syndrome

- Use of extremely high doses of opioids (>100 mg/hr morphine or equivalent)
- Hyperalgesia, myoclonic jerks
  - – ↑ dose of opioid ↑ pain not analgesia
  - – Associated with dehydration, renal impairment, and debilitated patients with advanced disease
- Treatment: opioid rotation and NMDA antagonists (methadone or ketamine)

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Adult Cancer Pain. v.1.2007. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
Davis MP, et al. *J Clin Oncol.* 2007;25:4497-4498.

Opioid-Induced Hyperalgesia

- Opioids elicit paradoxical “pain” in both animals and humans
- In humans, hyperalgesia is noted in areas of the body different from the site of the original pain complaint
- Methadone maintenance patients are hyperalgesic
- Hyperalgesia may normally be masked by concurrent analgesic actions…different mechanisms, different time courses
- Hyperalgesia is evoked; both low and high threshold stimuli elicit allodynia/hyperalgesia
- The mechanisms of opioid-induced hyperalgesia are unknown

Opioid-Induced Respiratory Depression

- Use reversal agents sparingly
- If respiratory problems or acute MS Δ
  - Naloxone intravenous administration
  - 0.4 mg diluted in 10 mL NS: give 1 mL (0.04 mg) Q 2-3 minutes until improvement in symptoms is noted
  - Note: half-life of opioid >>> half-life of naloxone
- If no response, consider alternative causes of respiratory depression

NS, normal saline; MS, mental status
National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Adult Cancer Pain. v.1.2007. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

Opioid-Induced Constipation

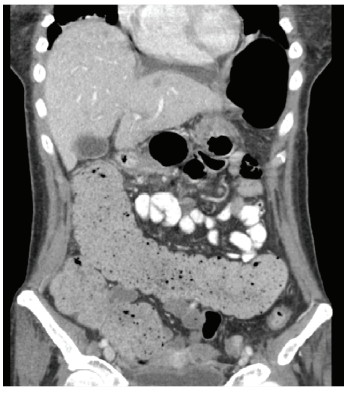
Cause

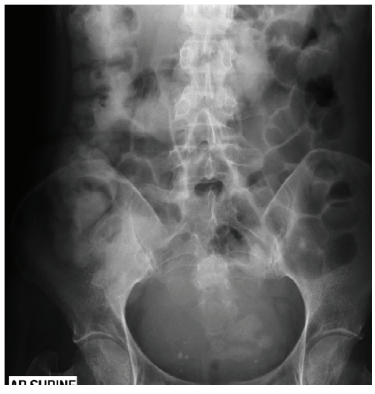
- Opioid analgesics – directly acting on opioid receptors in the gut
- Dehydration, electrolyte abnormalities
- Other Rx
- Chemotherapy agents known to affect nerve conduction in the gut

Prevention

- Hydration/fluids, exercise
- **Stool softener**
  - Sorbitol, lactulose, docusate, miralax, SMOG enemas
- **Stimulant laxatives**
  - Bisacodyl, senna
- Saline laxatives
  - MOM, fleets, magnesium citrate
- Opioid Antagonists: Methylnaltrexone
- Prokinetic agents: Metoclopramide

Opioid-Induced Constipation





Neuroendocrine Effects

Hypothalamic-pituitary-adrenal axis
↓ plasma cortisol

Hypothalmic-pituitary-gonadal axis
↑ prolactin
↓ LH, FSH, testosterone, estrogen

LH, luteinizing hormone; FSH, follicle-stimulating hormone

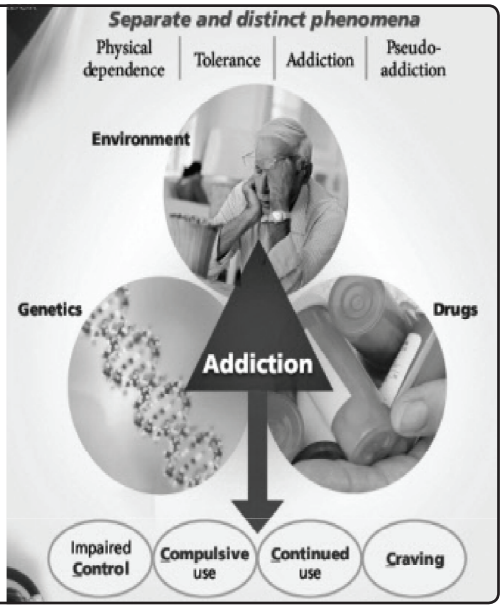
Addressing Concerns About Abuse, Addiction, and Diversion

- **Prevalence of addiction**[1]
  - Approximately 10% of the population
    - Reports range from 3% to 16%
- **Prevalence of abuse and diversion is more difficult to quantify**
  - Lack of standard definitions[2]
  - Differing sources of diversion[2]
    - Theft from pharmacies and other sources
    - Internet
    - Cross-border traffic
    - Counterfeiting
    - Prescription writers
      - Probably small percentage of diverted controlled substances

Key is to determine the underlying motivation of the patient's aberrant behavior

1. Savage SR. *J Pain Symptom Manage.* 1996;11:274-286.
2. Joransen DE, et al. *J Pain Symptom Manage.* 2005;30:299-301.

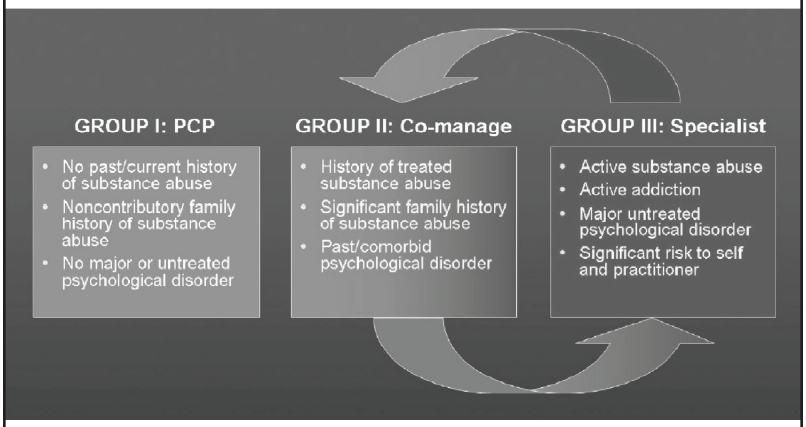
Understanding the Terminology



Drug Abuse

- Difficult
- Time consuming
- Frustrating
- Resource consuming
- Vigilance a must
- Screening helps
- Technology should revolutionize

Patient Triage



Gourlay DL, Heit HA, et al. *Pain Med.* 2005;6:107-112.

Opioid Withdrawal

- Symptoms may be severe, cause significant distress, and often impair functioning
- Many opioid dependent individuals continue to use opiates only to avoid withdrawal
- Opioid withdrawal is generally managed in the outpatient setting
  - Methadone, buprenorphine
  - Rapid, slow detoxification

Diagnostic Criteria for Opioid Withdrawal

Three or more symptoms that include

▪ Dysphoric (negative) mood	▪ Goosebumps or sweating
▪ Nausea or vomiting	▪ Diarrhea
▪ Muscle aches	▪ Yawning
▪ Runny nose or watery eyes	▪ Fever
▪ Dilated pupils	▪ Insomnia

Many Complexities of Opioid Therapy

- Variable response, partial efficacy
- Drug-drug interactions
- AE profile
- OIH (hyperalgesia)
- Endocrine dysfunction (hypogonadism)
- Abuse, misuse and diversion
- Regulatory concerns, fears (rational?)
  - Extensive documentation