Cancer Pain Management: Strategies for Safe and Effective Opioid Prescribing

Judith Paice, PhD, RN, FAAN

Robert H. Lurie Comprehensive Cancer Center of Northwestern University

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Strategies for Safe and Effective Opioid Prescribing

- Gain knowledge on safety concerns and best practices for opioid prescribing

Northwestern Medicine | Robert H. Lurie Comprehensive Cancer Center of Northwestern University

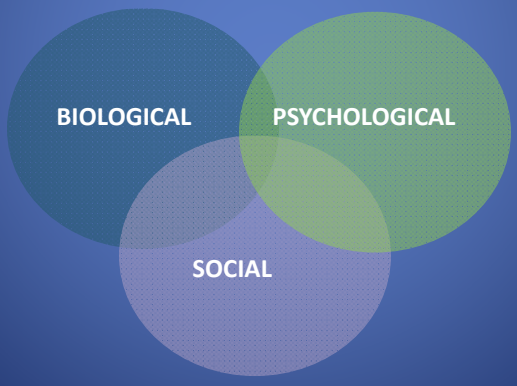
Pain Control

- Goal – balance
- Balance pain relief, function and safety
  - Pain relief – “No pain” is no longer the goal
  - Enhanced function
  - Safety
    - Safe patient
    - Safe prescriber
    - Safe community

Pain

- Pain is an unpleasant sensory and emotional experience, associated with actual or potential tissue damage

Merskey, 1979



Assessing Pain & Pain Relief

- Onset
- Location
  - "Total pain"
- Duration
- Quality
- Intensity
  - Use rating scale
- Type of pain or pain syndrome
- Aggravating/alleviating factors

Assessment *cont'd*

- Effects of pain on the person, level of function and quality of life
- Current medications and schedules
- Previous treatment and outcomes
- Co-morbid conditions – biopsychosocial, spiritual, financial
- Risk for adverse effects, misuse
- Patient goals for pain care
- Document assessment findings

Quality of Pain: Treatment

Type of pain	Pharmacologic interventions
Somatic (nociceptive)	Non opioids • Acetaminophen • NSAIDs Opioids
Neuropathic	Opioids (may require higher doses) Adjuvant analgesics • Antiepileptics • Antidepressants • Corticosteroids • Local anesthetics • NMDA antagonists
Visceral	Opioids Corticosteroids Adjuvant analgesics?

Adverse Effects of **Opioids**

- Respiratory depression
- Nausea and vomiting
- Constipation
- Cognitive/sedation
- Pruritus
- Urinary retention
- Hormonal changes
- Rigidity
- Seizures (meperidine)
- Miosis
- Diuresis
- Diaphoresis
- Edema
- Myoclonus
- Hyperalgesia

Those at Risk for Undertreatment

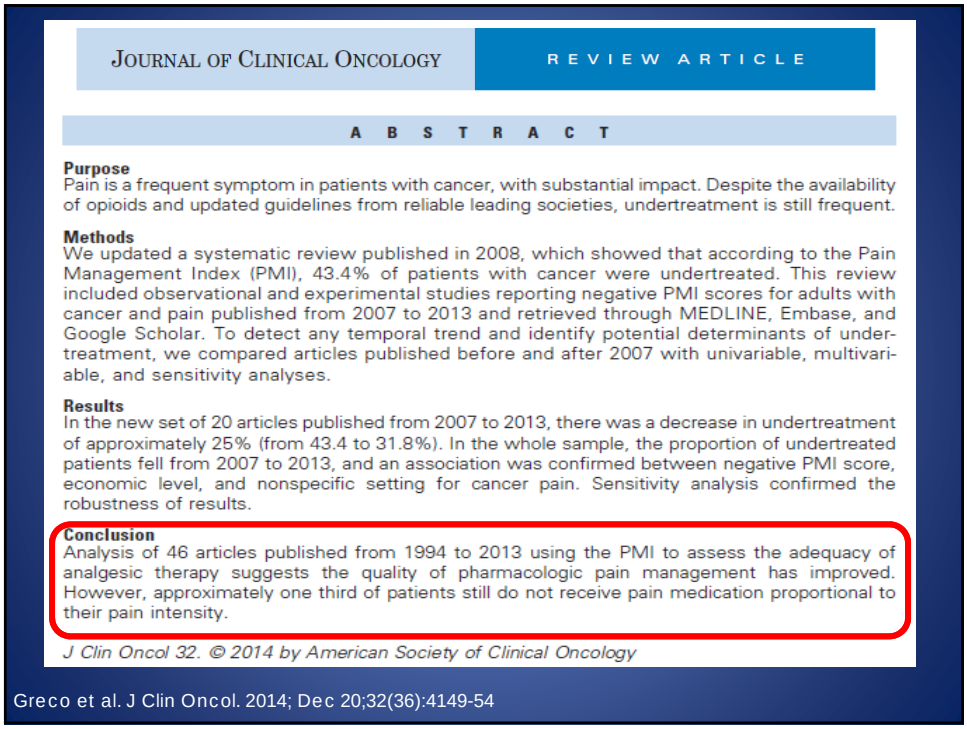
Infants and children	Elderly - > 65 years of age	Cognitively impaired	Nonverbal individuals
People with mental health disorders	Minorities	Female gender	Good performance status
Non-English speaking	Long-term survivors	Socio-economically disadvantaged	Uninsured

Those with current or past substance use disorders

We do not want to lose sight of the need for pain control.

Paice and Von Roenn. J Clin Oncol 2011;32: 1721-1726
Paice and Ferrell. CA Cancer J Clin 2011;61(3):157-182
Fisch, et al. J Clin Oncol 2012;30(16):1980-1988
Kwon JH. J Clin Oncol 2014;32(16):1727-1733

Greco et al. J Clin Oncol. 2014; Dec 20;32(36):4149-54



JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

A B S T R A C T

Purpose
Pain is a frequent symptom in patients with cancer, with substantial impact. Despite the availability of opioids and updated guidelines from reliable leading societies, undertreatment is still frequent.

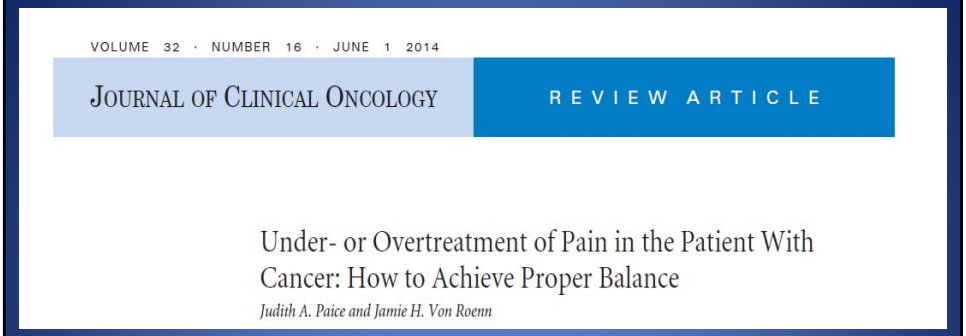
Methods
We updated a systematic review published in 2008, which showed that according to the Pain Management Index (PMI), 43.4% of patients with cancer were undertreated. This review included observational and experimental studies reporting negative PMI scores for adults with cancer and pain published from 2007 to 2013 and retrieved through MEDLINE, Embase, and Google Scholar. To detect any temporal trend and identify potential determinants of undertreatment, we compared articles published before and after 2007 with univariable, multivariable, and sensitivity analyses.

Results
In the new set of 20 articles published from 2007 to 2013, there was a decrease in undertreatment of approximately 25% (from 43.4 to 31.8%). In the whole sample, the proportion of undertreated patients fell from 2007 to 2013, and an association was confirmed between negative PMI score, economic level, and nonspecific setting for cancer pain. Sensitivity analysis confirmed the robustness of results.

Conclusion
Analysis of 46 articles published from 1994 to 2013 using the PMI to assess the adequacy of analgesic therapy suggests the quality of pharmacologic pain management has improved. However, approximately one third of patients still do not receive pain medication proportional to their pain intensity.

J Clin Oncol 32. © 2014 by American Society of Clinical Oncology

Greco et al. J Clin Oncol. 2014; Dec 20;32(36):4149-54



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JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

Under- or Overtreatment of Pain in the Patient With Cancer: How to Achieve Proper Balance

Judith A. Paice and Jamie H. Von Roenn

- Can pain relief be provided while reducing negative consequences of treatment?
- Which patients should be prescribed what medications, in what situations, for what kind of pain, and who should be managing the pain?

Paice and Von Roenn. J Clin Oncol. 2014 Jun 1;32(16):1721-6.

Those at Risk for Overtreatment

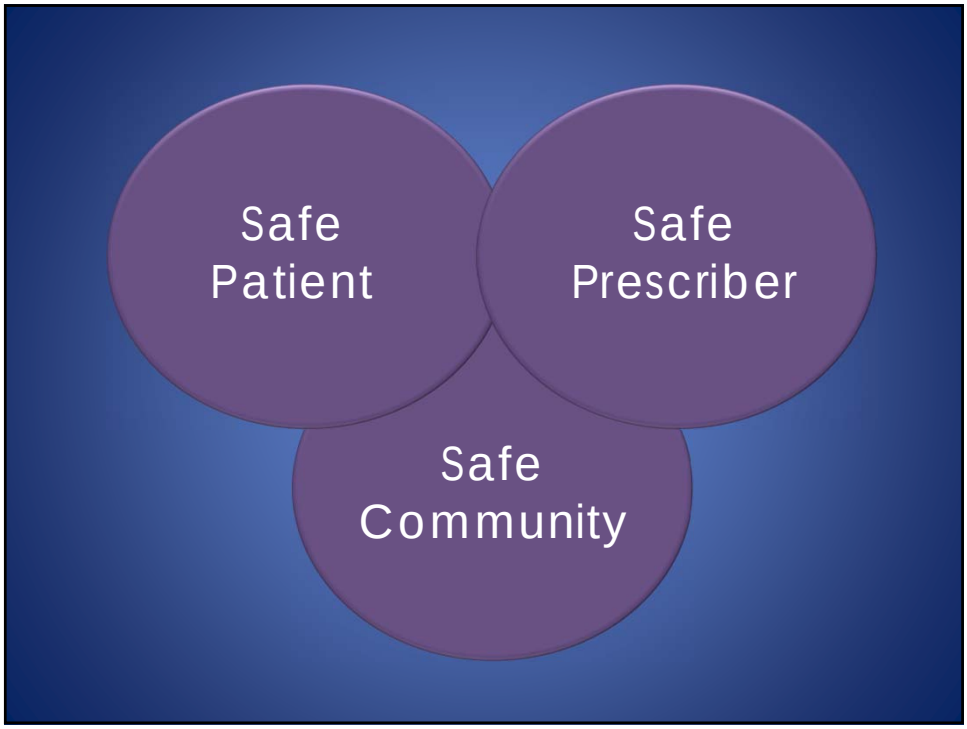
- Long term survivors
- Co-morbid mental health conditions
  - Anxiety
  - Depression
  - Sleep disorders
  - “Chemical copers”/limited coping strategies
- Lack of financial resources
  - Limited or no reimbursement for PT/OT, counseling, integrative therapies
- Pre-existing substance use disorders

Paice and Von Roenn. J Clin Oncol. 2014 Jun 1;32(16):1721-6.

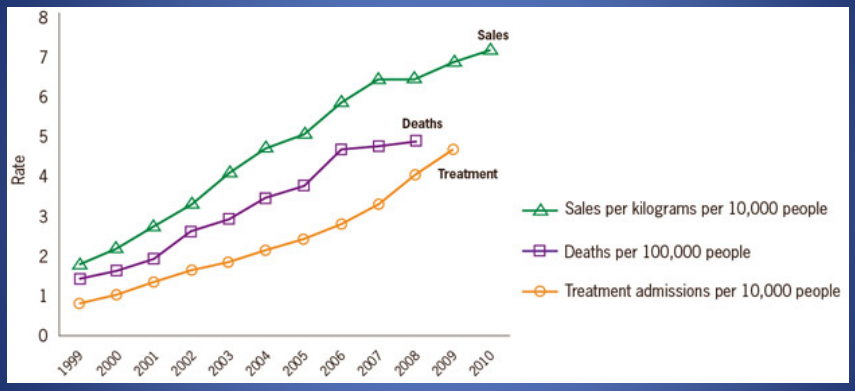
What are the Risks of Overtreatment?

- Long term benefit – limited data
- Cognitive difficulties
- Depression
- Hypogonadism
  - Fertility/sexual dysfunction, fatigue, osteoporosis, altered wound healing
- Safety
  - Respiratory depression (OSA)
  - Overdose

Paice and Von Roenn. J Clin Oncol. 2014 Jun 1;32(16):1721-6.



Safe Patient – Safe Community



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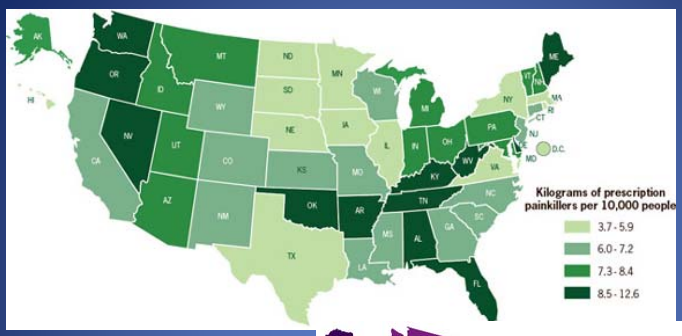
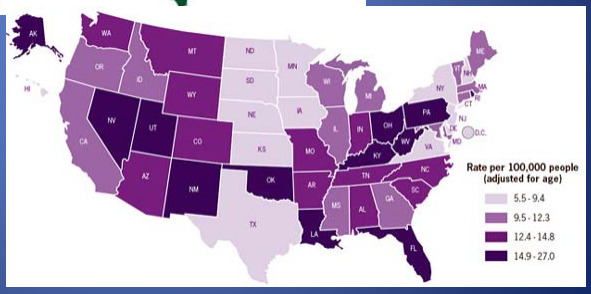
Okie. *N Engl J Med* 2010;363(21):1981-1985.



Amount of prescription painkillers sold by state per 10,000 people (2010)

Drug overdose death rates by state per 100,000 people (2008)



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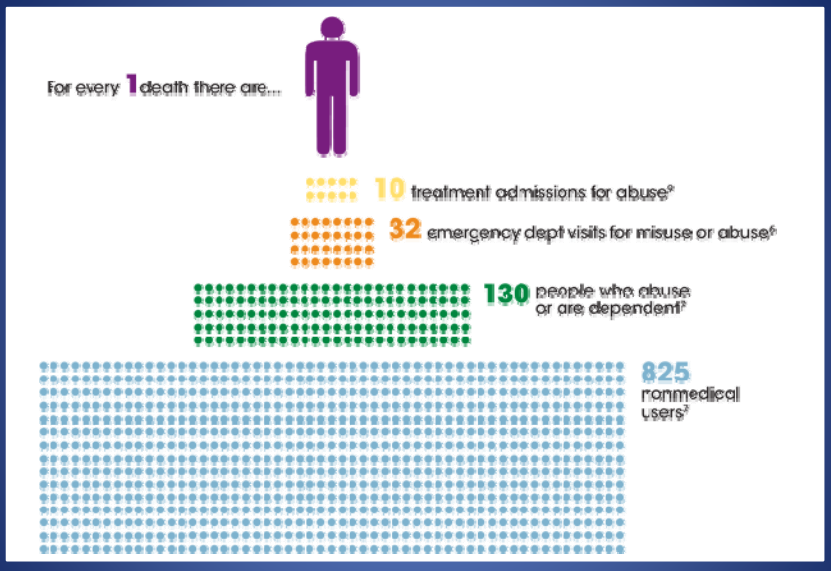
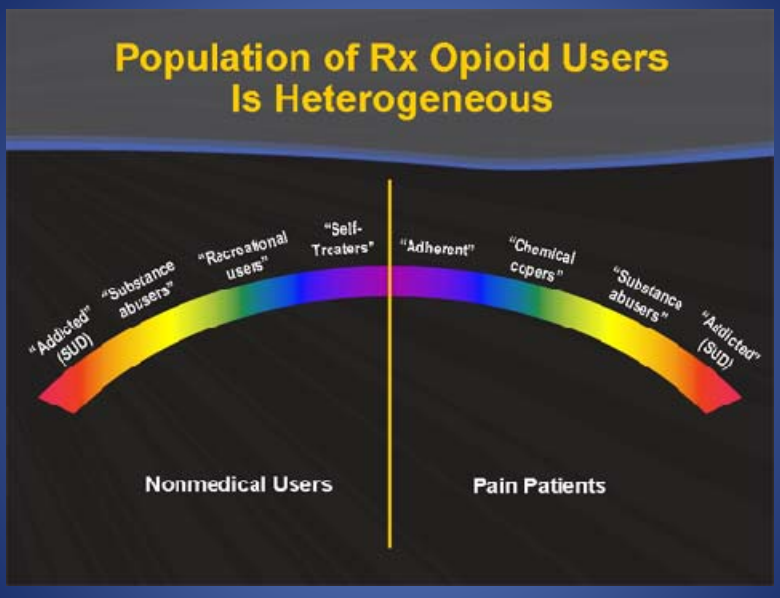
http://www.cdc.gov/vitalsigns/PainkillerOverdoses/index.html



©Centers for Disease Control and Prevention
http://www.cdc.gov/homeandrecreationalsafety/rxbrief/

Pain and Substance Use Disorders

Ballantyne, JC. *Pain* 156 (4): 567-568, 2015



Passik SD. *Mayo Clinic Proceedings*. 2009;84(7):593-601.

How Do We Know?

Differential Diagnosis of Aberrant Drug Taking Behavior

- Pseudo-addiction
  - Amount of drug ordered too low – dose, number of tablets
  - Insurance limits, prior authorizations, pharmacy partial fills due to supply limits
- Psychiatric disorders
  - Chemical coping
  - Mood disorders (anxiety, depression)
  - Encephalopathy

Differential Diagnosis of Aberrant Drug Taking Behavior

- Inability to follow a treatment plan
  - Low literacy
  - Use of pain medication to treat other symptoms (sleep, anxiety, depression)
  - Misunderstanding regarding “prn”
  - Fear of pain returning
- Addiction
- Criminal intent

Optimal Management in Medically Ill

Assess

Pain

Function

For addiction/diversion

- Abuse of other drugs
  - Current/past misuse of prescription or street drugs
  - Alcohol/smoking
- Environmental/genetic exposure
  - Family or friends with substance abuse disorder
- Sexual abuse
  - Childhood, preteen

Blackhall et al. J Palliat Med 2013;16(3):237-242.
Dev et al. Cancer 2011;117(19):4551-4556

Optimal Management: Universal Precautions

Opioid management agreements or "contracts" – limited evidence in oncology/palliative care

Adherence monitoring
- Urine drug testing (UDT)
- Pill counts
- Prescription drug monitoring programs

Starrels et al. *Ann Intern Med* 2010;152(11):712-720.

Benefits of PDMPs

- Screen for aberrant behaviors
- Verify medication, dose, next refill date when patient uncertain/did not bring in pill bottles
  - "I take the blue pill"
- Safety

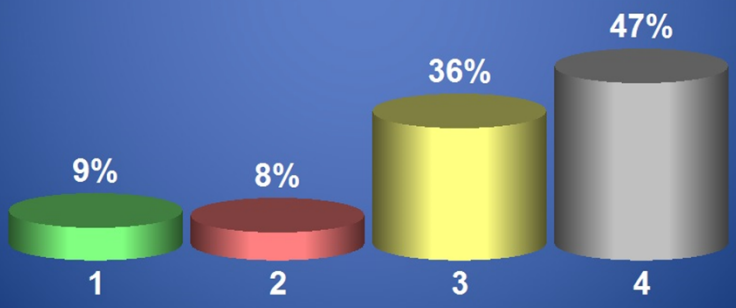
Case: Pain in the Clinic

- Patient to receive chemotherapy. Patient reports significant pain, did not bring pill bottles, requesting injection. Clinic nurse pages APN to request assistance.
  - Patient reports taking oxycodone extended release (ER) 80 mg q 8 and oxycodone immediate release (IR) 30 mg 3-4 per day.

Audience Polling Results

What is the most appropriate intervention for this patient?

1. Send her to the ED for pain control
2. Administer iv oxycodone 5 mg
3. Administer oral oxycodone IR 15 mg
4. Administer liquid oxyocodone 30 mg for faster relief



Case: Pain in the Clinic (*cont.*)

- Patient reports taking oxycodone extended release (ER) 80 mg q 8 and oxycodone immediate release (IR) 30 mg 3-4 per day.
  - 24 hour dose oral oxycodone 330 mg
  - Morphine:oxycodone ratio 30:20
  - 24 hour OME approximately 500 mg morphine
  - 3:1 oral to iv ratio 24 hour iv morphine dose = 165
  - 165 iv morphine ÷ 24 = 6.9 mg/hour iv morphine
  - Breakthrough dose 50 – 100% of hourly rate
  - Would administer 3.5-7 mg iv morphine

Case: Pain in the Clinic (*cont.*)

- Review of IL PMP reveals patient last obtained oxycodone ER and oxycodone IR 3 months prior. On additional questioning patient admits she saves pain medications only for days when pain “bad”.
  - English as second language
  - Regimen was correct, but was not adherent
  - No insurance/Medicaid rarely pays for oxycodone ER
  - Cultural belief that injections best
  - Does not have to pay for medications given in clinic

Case: Pain in the Clinic (*cont.*)

- Discussed short action of parenteral opioids
  - Parenteral peak effect 15 minutes; duration 1-2 hours
  - Oral peak effect 1 hour; duration 3-4 hours
- Emphasized concerns regarding safety
- Administered morphine IR 15 mg tablets; repeated in 3 hours

Finding Balance: Aggressive Pain Management

Advanced Disease

- Escalation of opioids, adjuvant analgesics
- Referral for interventional therapies, PT/OT, CBT, integrative therapies

Long Term Survivors

- Minimal use of pharmacological therapies
- Referral for multidisciplinary care

Paice J, Von Roenn J. *J Clin Oncol* 32: 1721-1726, 2014

When Opioids are No Longer Beneficial: Weaning

- ✓ Slow downward titration – 10% reduction/week
- ✓ Offer psychosocial support
- ✓ Optimize nonopioids and adjuvant analgesics
- ✓ Use antidepressants rather than benzodiazepines to treat irritability and sleep disturbances
- ✓ Provide a clear verbal and written plan

The Management of Opioid Therapy for Chronic Pain Working Group. *VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain* Washington, DC; 2010.

Chou R, et al. *J Pain* 10:113-30, 2009

Pain and Substance Use Disorder

- Ongoing compassionate assessment
- Differentiate misuse/abuse behaviors from undertreatment
- Openly discuss concerns:
  - *"We have to balance pain control, function and safety; we do not want to jeopardize your health"*
  - *"I am worried about your relationship with the pain medications"*
  - *"Using these medicines to help you sleep is dangerous. Let's try other strategies."*

Whitcomb et al. Current Pain Headache Reports 2002;6:183-190

Risk Factors for Substance Abuse

- Past/current use
- Genetics/family history
- Sexual abuse
- Legal problems
- Cigarette smoking
- High opioid dose
- Mental health problems
- Multiple motor vehicle accidents
- Fewer side effects – no hangover

Risk assessment tools:
The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)
The Opioid Risk Tool (ORT)
Current Opioid Misuse Measure (COMM)

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Adult Cancer Pain (Version 1.2016). © 2016 National Comprehensive Cancer Network, Inc.

Risk Stratification

Low Risk	No past/current history of SUD No family history of SUD . No major untreated psychiatric disorder. Presence of social support system.	May be safely managed in primary care settings. Adherence monitoring at least annually.
Moderate Risk	History of treated SUD. Significant family history of SUD Younger than 25 years old. Current pharmacotherapy for addiction (methadone, buprenorphine).	May be in consultation with appropriate specialist support. Adherence monitoring at least every 6 months.
High Risk	Active SUD or aberrant behaviors. Major untreated psychiatric disorder.	Recommended management by pain management and addiction specialists as needed, because these patients pose significant risk to themselves and others. Frequent adherence monitoring: weekly or monthly

Adopted from Gourlay DL et al. Pain Med 2005;6:107-12.

Pain and Substance Use Disorder

- Set realistic goals
- Treat concomitant psychiatric disorders
- Consider tolerance - patients with opioid misuse history usually require higher doses
- Multidisciplinary approach – one prescriber

Whitcomb et al. Current Pain Headache Reports 2002;6:183-190

Pain and Substance Use Disorder

- Limit the amount of medication given at any one time
  - Weekly prescriptions (“may fill xx/xx/xx”)
- Utilize pill counts
  - Assess for independent dose escalation and shortages
- Maximize nonopioid, nonpharmacological and interventional pain control methods
- Do not substitute benzodiazepines, antihistamines or other sedating medications for analgesics

Whitcomb et al. Current Pain Headache Reports 2002;6:183-190

Pain and Substance Use Disorder

- More frequent outpatient visits
- Solicit family/significant other for assistance
- Consider formulations less likely to be abused *
- Consider inpatient treatment for addiction

* Little agreement

Whitcomb et al. Current Pain Headache Reports 2002;6:183-190

Pain and Substance Use Disorder

For patients in recovery:

- Assess length and stability of recovery
- Encourage ongoing participation in recovery efforts
- Identify stressors for relapse
- Encourage open communication
- If in methadone maintenance or buprenorphine program, review drug – drug interactions, consult with addiction specialist

Kircher, et al. *J Pain* 2011;12(10):1025-1031.

Measures that Enhance Recovery

- Active in recovery-related support systems (aftercare, 12 step programs)
- Active sponsor
- Stability in workplace, home
- Medical and psychiatric support
- Avoid sleep deprivation
- Exercise program

Prater CD, et al. Successful pain management for the recovering addicted patient. Primary Care Companion J Clin Psychiatry 2002;4:125-131.

Issues in Methadone Use

- P450 interactions
- QT prolongation
- Long and variable half life
  - 3-5 hours duration of analgesia when started
  - 8-12 hours after repeated dosing
  - Repeated dosing may take 5-7 days to stabilize

Kornick, et al. Pain 2003;105; 499
Krantz, et al. Ann Intern Med 2002:137;501
Reddy S, et al. J Pall Med 2010:13; 638-9
http://www.atforum.com/addiction-resources/index.php

Drug-Drug Interactions: Methadone

Potential to ↑ Methadone Levels

- Gefitinib (Moderate)
- Imatinib (Moderate)
- Pazopanib (Major)
- Sorafenib (Moderate)

Potential for QTc Prolongation

- Abarelix (Severe)
- Dasatinib (Severe)
- Degarelix (Major)
- Doxorubicin (Major)
- Epirubicin (Major)
- Lapatinib (Severe)
- Pazopanib (Major)
- Sunitinib (Severe)
- Toremifene (Severe)

NCCN Adult Cancer Pain Guidelines and
www.clinicalpharmacology-ip.com

Risk Factors for QTc Prolongation

- Electrolyte abnormalities
  - Hypokalemia or hypomagnesemia
- Impaired liver function
- Structural heart disease
  - Congenital heart defects
  - History of endocarditis
  - Heart failure
- Genetic predisposition
- Use of drugs with QTc prolonging properties

Chou R, et al. J Pain 2014;15(4):321-337.

Medications Common in Oncology that Prolong QT Intervals

- Antibiotics/antifungals
  - Azithromycin, ciprofloxin, clarithromycin, erythromycin, fluconazole, levoflaxacin
- Antiemetics
  - Chlorpromazine, dolasetron, droperidol, granisetron, haloperidol, ondansetron
- Antineoplastics
  - Arsenic, crizotinib, dasatinib, erbulin, lapatinib, nilotinib, sorafenib, sunitinib, tamoxifen, vandetanib, vemurafenib
- Opioids
  - Methadone
- Misc
  - Amitriptyline, cocaine diphenydramine, octreotide, quetiapine, tacrolimus

Methadone

- Start low and titrate slowly
- If patient is on low doses of opioid (< 40- 60 mg OME/day)
  - 2.5 mg q 8
  - Increase no more than 5 mg every 5-7 days
- If patient is on higher doses of opioid (>60 mg OME)
  - 30-40 mg per day in divided doses
  - Increase no more than 10 mg every 5-7 days
- Methadone should not be used as breakthrough medication
- Hold if there is evidence of sedation
- Caution when combining with benzodiazepines especially at night
- Caution in patients with sleep apnea, respiratory infection

Chou R, et al. J Pain 2014;15(4):321-337

Buprenorphine

- Partial agonist
- Used for pain control and substitution therapy
- Available in sublingual tablets and strips (alone or with naloxone to deter abuse*), injection, transdermal patch
- Has ceiling dose
- May be difficult to achieve pain control with pure agonist opioids if patient is on chronic buprenorphine therapy

Cannabinoids

- CB_1 and CB_2 receptors
- Dronabinol
- Nabilone
  - Approved for CINV
- Nabiximols
  - THC and cannabidiol (CBD) – CBD may moderate euphoric effects of THC
  - Oral spray approved in Canada for MS spasticity, neuropathic pain and cancer pain
  - In US approved only for clinical trials
  - May inhibit metastatic growth

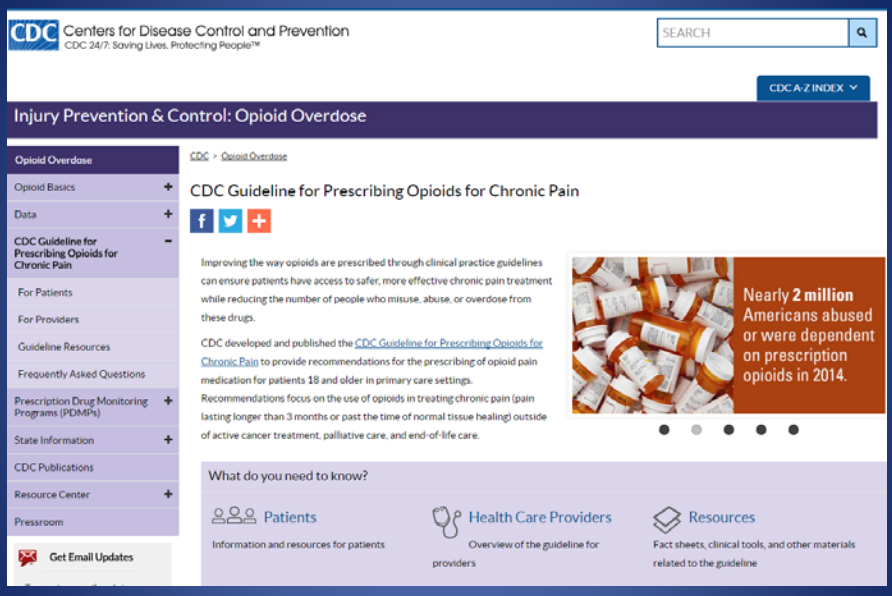
Safe Community

- Educate patients/families regarding safe medication practices
  - Don’t leave medications out
  - Lock boxes
- Primary sources of diversion
  - Thefts from pharmacies, drug distribution centers
  - Thefts from medicine cabinets
  - Internet
  - Smuggling
  - “Pill mills”

Safe Community

- Safe disposal
  - Take back programs – pharmacies, police depts
  - Mix drug in wet coffee grounds or kitty litter until dissolved, then dispose in garbage – do not flush down toilet (except opioids)

www.deadiversion.usdoj.gov

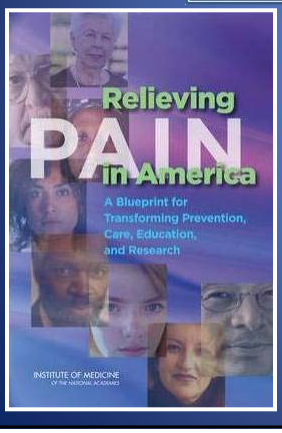


http://www.cdc.gov/drugoverdose/prescribing/guideline.html

National Pain Strategy

The Office of the Assistant Secretary for Health at the U.S. Department of Health and Human Services today released a National Pain Strategy.

Now available...
FINAL REPORT



National Pain Strategy outlines actions for improving pain care in America

Plan seeks to reduce the burden and prevalence of pain and to improve the treatment of pain

http://iprcc.nih.gov/National_Pain_Strategy/NPS_Main.htm

Summary

- Achieving balance in the appropriate use of opioids in the treatment of pain requires skill and compassion.
- How “aggressive” pain management is defined and implemented may vary.
- Universal precautions protect the patient, the prescriber and the community.
- Care of the patient with substance use disorder requires a multimodal, multidisciplinary approach.

"Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it is the only thing that ever has".

Margaret Mead

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