PRACTICAL APPROACHES TO PAIN MANAGEMENT FOR NON-CANCER PATIENTS

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Objectives

- Focus on safe prescribing of opioids
- OVERVIEW—potential benefits and risks
- CASE—mitigating risk
- CASES—prescribing challenges

Chronic non-Cancer Pain—Scope of the Problem

- 100 mil Americans, 25 mil moderate-severe
  - 5-8 mil prescribed longterm opioids

- **1 in 4** patients in primary care settings report persistent pain that interferes w/function
  - In U.S., only **4** Board Certified pain specialists for every **100,000** patients with chronic pain

Trescot AM, Boswell MV et al. Pain Physician 2006. Breuer B et al. J Pain 2007. Reuben DB et al. Ann Intern Med 2015.

Approaches to Chronic Pain Management

- **Non-Pharmacologic Treatments**
- Non-controlled Drugs Used in Chronic Pain
- Role of Opioids in Chronic Pain

Non-Pharmacologic Treatments

- Physical therapy and conditioning
- Acupuncture (esp. osteoarthritis and fibromyalgia)
- Heat, Cold
- Massage therapy
- Cognitive-Behavioral Therapy
- Biofeedback/Relaxation training
- Operant-behavioral therapy
- Pain management groups, family therapy
- Complementary and Alternative Medicine supplements

Ostelo R et al. Cochrane Database 2005.

Cognitive-Behavioral Therapy

- Cognitions and behaviors affect pain experience
- Coping skills training
- 8-10 small group or individual sessions
- RCT evidence for LBP, OA and RA

Keefe FJ. Clin Psychol 1996.

Multidisciplinary Pain Rehabilitation

~50% reductions in

- pain
- opioid use
- surgeries
- hospitalizations
- patients on disability

Turk DC in Pain Treatment Centers at a Crossroads: A Practical and Conceptual Reappraisal, Progress in Pain Research and Management 1996.

Non-Controlled Drugs Used in Chronic Pain

Screen for depression

RCT of 12 months optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain

- 50% reduction in baseline depression severity
- Statistically significant improvements in pain severity, anxiety and quality of life

Kroenke K. JAMA 2009.

Non-Controlled Drugs Used in Chronic Pain

- Acetaminophen, NSAIDs
- Adjuvants

  have a primary indication other than analgesia, but have analgesic properties

  - TCAs
  - Other antidepressants
  - Anticonvulsants
- Muscle relaxants
- Sleep aids, anxiolytics
- Vitamin D
- Topical preparations (anesthetics, aromatics)

Adjuvant Analgesics

TCAs

- Amitriptyline best studied, >50mg increased side effects w/o added benefit
- Low dose, 10-12 hours before arising
- Nortriptyline less sedating

Other antidepressants

- SSRIs not as effective
- Bupropion, SNRIs (venlafaxine, duloxetine) may be effective

Anticonvulsants (gabapentin, pregabalin)

- For patients not tolerating TCAs

Role of Opioids in Chronic Pain

Potential Benefits

- Analgesia
- Improved function
- Improved QOL

Potential Risks

- Toxicity/side effects
- Functional impairment
- Physical dependence
- Hyperalgesia
- Addiction, other misuse

from Parran T. SAMHSA-CSAT: Clinical Challenges in Prescribing Controlled Drugs. 2012.

Evidence for Efficacy of Opioids—RCTs

- Opioids alleviate pain more effectively than other drugs
  - Weaker opioids (tramadol, codeine) ~ NSAIDs and TCAs
  - Trials report large variation, typically 2 to 3 points on a 0 to 10 scale
- Depression scores not improved
- Functional status, QOL generally improved

Noble M. Cochrane Database Syst Rev 2010. Furlan A. CMAJ 2006. Kalso E. Pain 2004.

Limitations of Opioid RCTs

- >50% Drop-out rate
  - though benefit was observed on Intention-to-Treat analysis
- Diagnoses of substance abuse or major depression excluded
- 90% funded by pharma
- Study length average only 5 weeks

Furlan A. CMAJ 2006. Kalso E. Pain 2004.

Evidence for Efficacy of Chronic Opioids

- Long term studies poorly controlled or observational
- Patients observed w/satisfactory analgesia on moderate non-escalating doses w/improved function and minimal addiction risk

Chou et al. Ann Intern Med 2015. Ballantyne JC. Southern Med J 2006.

Opioid Side Effects

- Constipation, nausea, vomiting, dizziness, drowsiness, dry skin/pruritus
- Tolerance to side effects develops (except for constipation)
- ?Impact on driving performance w/chronic stable dose

Furlan A. CMAJ 2006. Kalso E. Pain 2004. Chou et al. Ann Intern Med 2015.

Untoward Effects of Chronic Higher Dose Opioids

- Overdose
- Abuse
- Hyperalgesia
  - *Heightened pain response to noxious stimuli*
  - Demonstrated in animal studies
  - Some patients have ↑pain at higher opioid doses and improve w/tapering medication
- MI
- Fracture
- Suppression of both adrenal and gonadal axes
  - Especially testosterone deficiency
- Altered immune function

Chou et al. Ann Intern Med 2015.

Treatment Goals in Management of Chronic Pain—the Four A's[1]

Analgesia
- Pain reduction, not eradication

Activities of daily living
- Work, play, socialization

avoid **A**dverse events
- Side effects, hyperalgesia

avoid **A**berrant drug-related behaviors
- Addiction, diversion

Affect[2]
- Mood, sleep

[1]Passik. Clin Ther 2004. [2]Arnow BA et al. Psychosom Med 2006.

Monitoring Benefit

1. What number best describes your pain on average in the past week:

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

2. What number best describes how, during the past week, pain has interfered with your enjoyment of life?

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

3. What number best describes how, during the past week, pain has interfered with your general activity?

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

The PEG three-item scale. **Items from the Brief Pain Inventory reproduced with permission from Dr. Charles Cleeland. Krebs et al. JGIM 2009.*

Opioids are powerful drugs—should be reserved for serious pain

- Pain with a clear patho-anatomic or disease basis
- Underlying cause is disabling
- Cannot be improved by primary disease treatment or lifestyle changes
- Goal of pain treatment is comfort
- All other treatments (best efforts) have failed

NOTE:

At least 90% of pain complaints do not meet these criteria

Chou R et al. J Pain 2009. Sullivan MD, Ballantyne JC. Arch Int Med 2012.

The 90% of chronic pain for which opioids have not proven helpful

Axial low back pain without a pathoanatomic diagnosis

Fibromyalgia

Headache

Opioid Trial

We lack accurate predictors of

- Who will experience lasting benefit from chronic opioid analgesia

90 days may be a key decision time if you do prescribe

- often used in definitions of chronic pain
- after 90 days of continuous use, opioid treatment is more likely to become life-long
- patients who continue opioids >90 days tend to be high-risk patients

Opioids are rarely sufficient

- Non-pharmacologic treatments
- Adjunctive medications

Korff MV et al. Clin J Pain 2008. Martin FB et al. J Gen Intern Med 2012.

CASE—Mitigating Risk when Prescribing Long-Term Opioids

62 year old man, new to your practice, working only part time as an electrician for a number of years due to incapacitating low back pain which is worse w/standing and walking

- Pain meds "not working as well anymore"
  - Naproxen 1500mg/day
  - Gabapentin 2400mg/day
  - Percocet 10/325, 1-2 tabs every 6 hrs PRN, #240/month
- Outside records document
  - MRI last year: severe spinal stenosis
  - Physical therapy X 2 w/o improvement
  - Ortho: epidural injections X 2 w/o response; pt declined laminectomy
- **If I prescribe, what can I do to prescribe safely?**

Opioids—Dependence, Tolerance, Addiction

Physical dependence

- A drug class-specific withdrawal syndrome
- Can be produced by abrupt cessation, rapid dose reduction, decreasing blood level, administration of an antagonist
- *Develops in most patients*

Ballantyne JC. Southern Med J 2006.

Opioids—Dependence, Tolerance, Addiction

Tolerance

- Exposure to a drug results in a diminution of the drug's effects over time
- *May/may not develop*

Ballantyne JC. Southern Med J 2006.

Opioids—Dependence, Tolerance, Addiction

Addiction

- Behaviors: impaired control over drug use, compulsive use, continued use despite harm, craving
  - Historic view: negligible risk in never-addicted medical patients[1,2]
  - More recent concerns: addictive behaviors exhibited by "stable" patients undergoing taper[3]

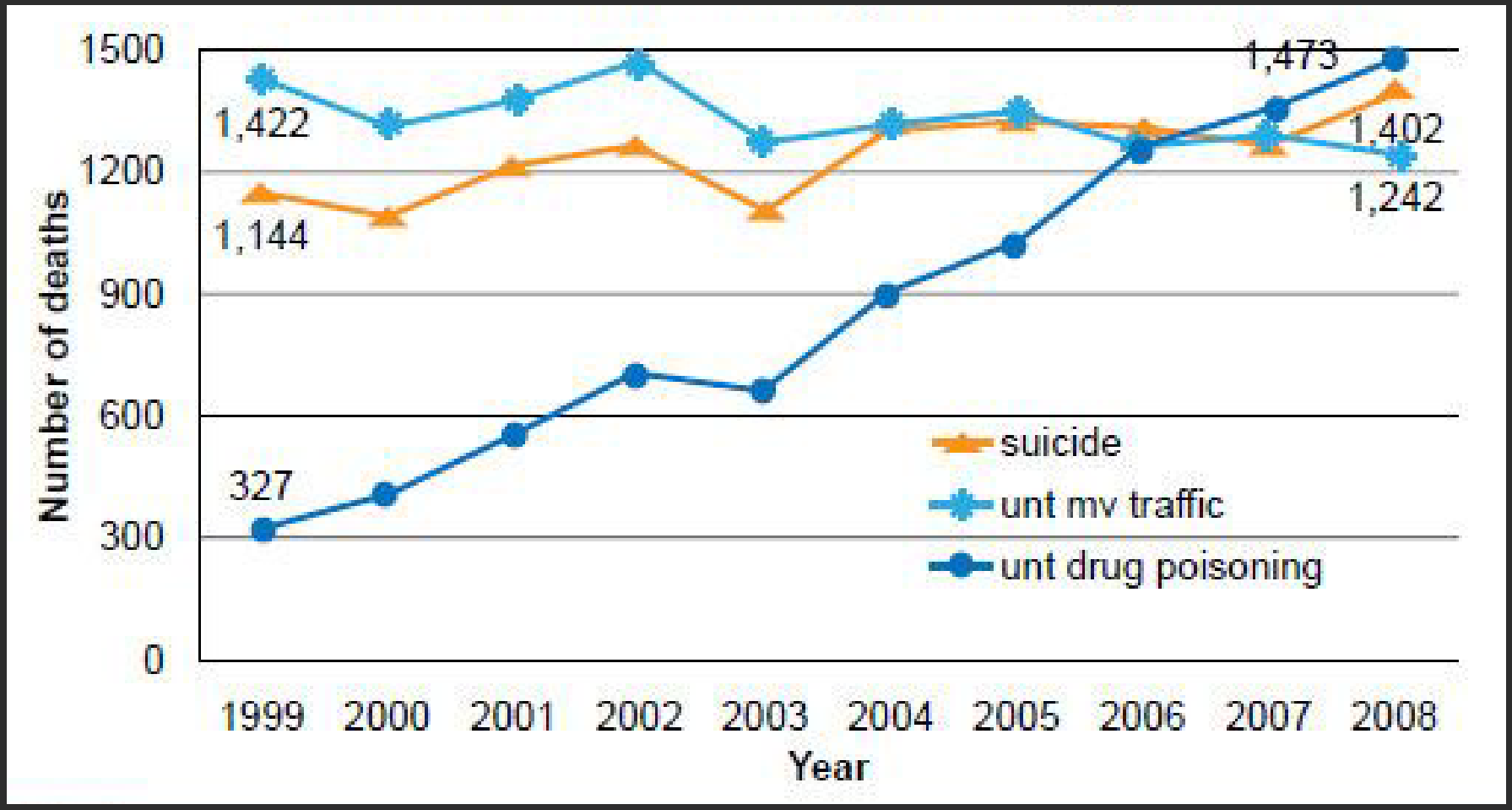
[1]Noble M. Cochrane Database Syst Rev 2010. [2]Ballantyne JC. Southern Med J 2006. [3]Ballantyne et al. Arch Intern Med 2012.

Prescription Opioid Misuse

- Prescription painkiller overdoses killed nearly 15,000 people in the US in 2008. This is nearly 4 times the 4,000 people killed by these drugs in 1999.
- In 2010, about 12 million Americans (age 12 or older) reported nonmedical use of prescription painkillers in the preceding year.

http://www.cdc.gov/vitalsigns/PainkillerOverdoses/index.html *Accessed 8/10/15.*

Unintentional drug poisoning exceeds MVA and suicide as leading cause of injury death



Ohio Department of Health Violence and Injury Prevention Program. August 2009.

Heroin overdose deaths surge across the state

Police and drug counselors struggle to explain reasons for recent activity

PAT GREENHOUSE/GLOBE STAFF

By Sarah Schweitzer and Trisha Thadani | GLOBE STAFF AND GLOBE CORRESPONDENT DECEMBER 17, 2014

Heroin and other opiate overdoses are spiking across Massachusetts, with an alarming 58 suspected deaths so far this month, the

From: **The Changing Face of Heroin Use in the United States: A Retrospective Analysis of the Past 50 Years**

JAMA Psychiatry. 2014;71(7):821-826. doi:10.1001/jamapsychiatry.2014.366

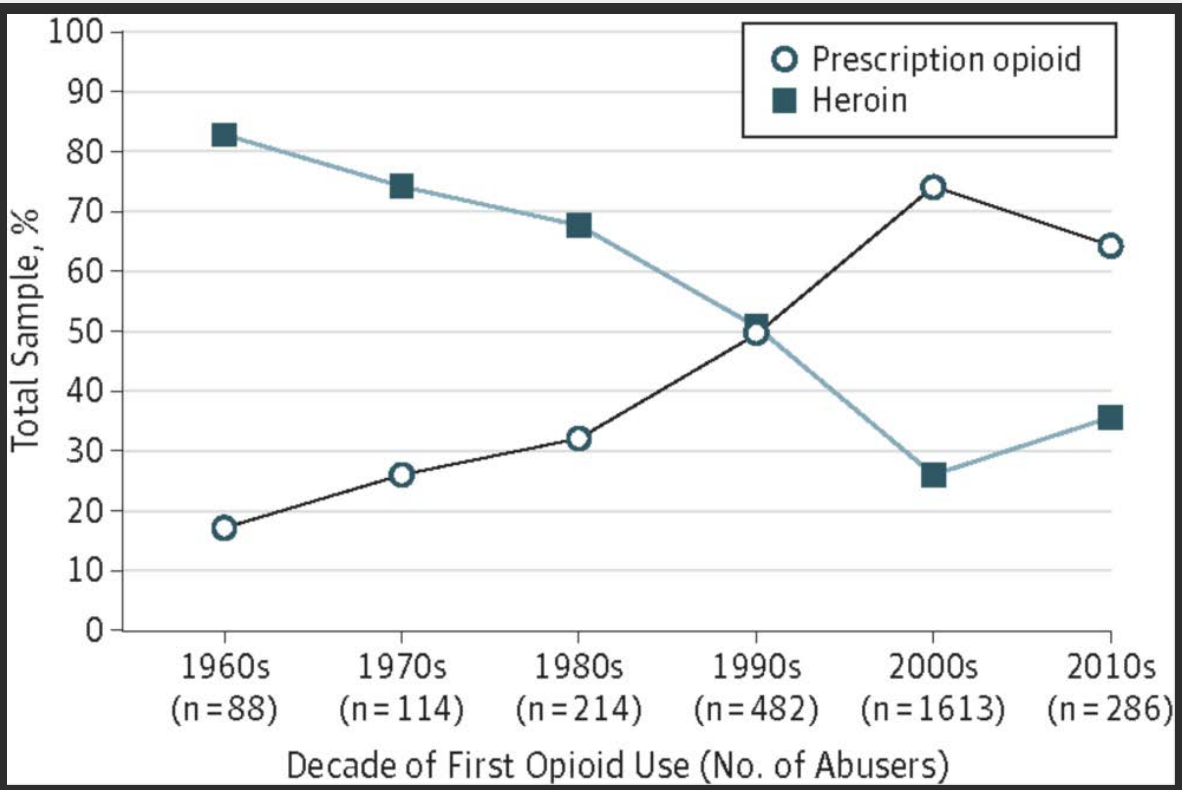
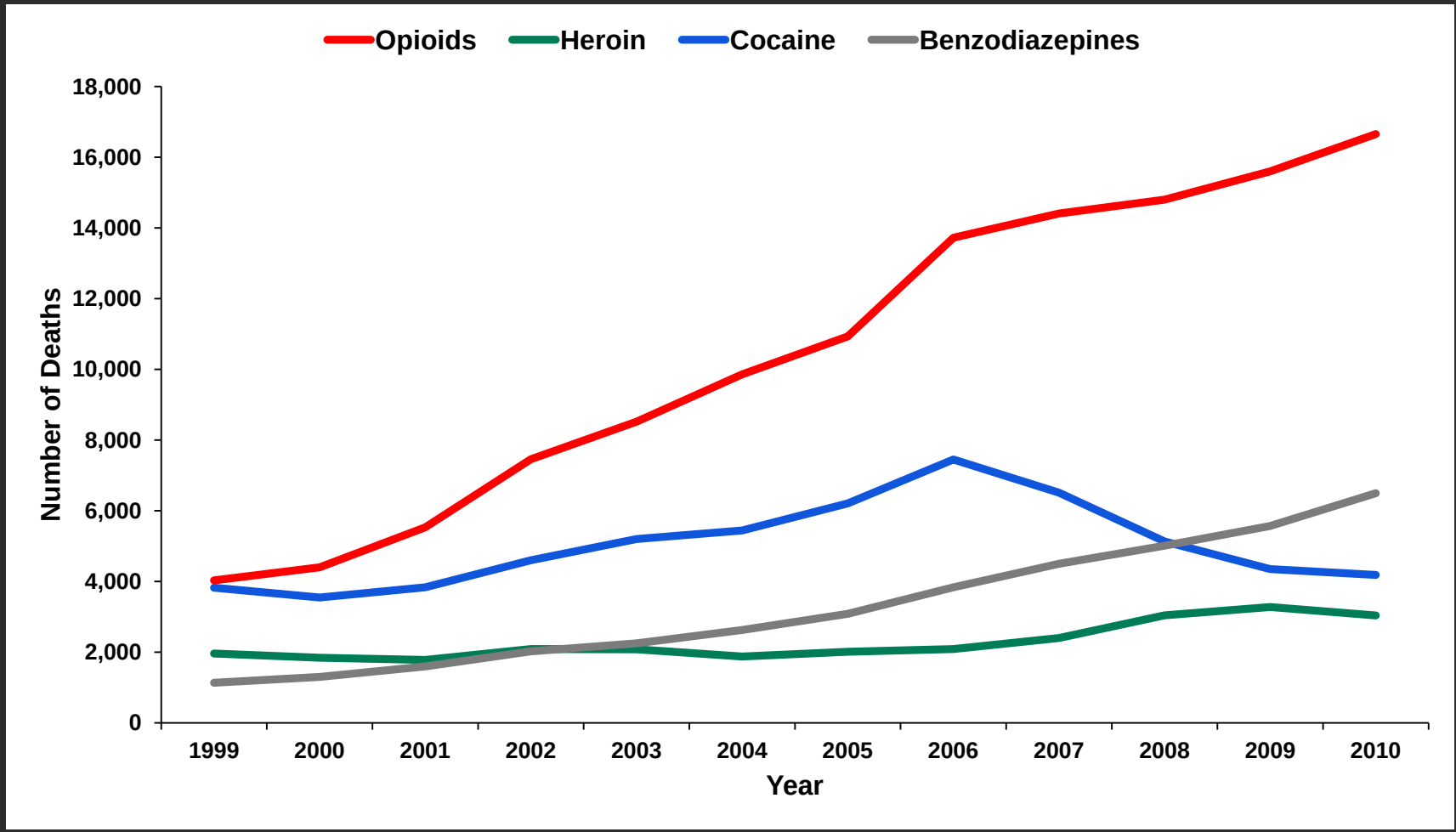


Figure Legend:

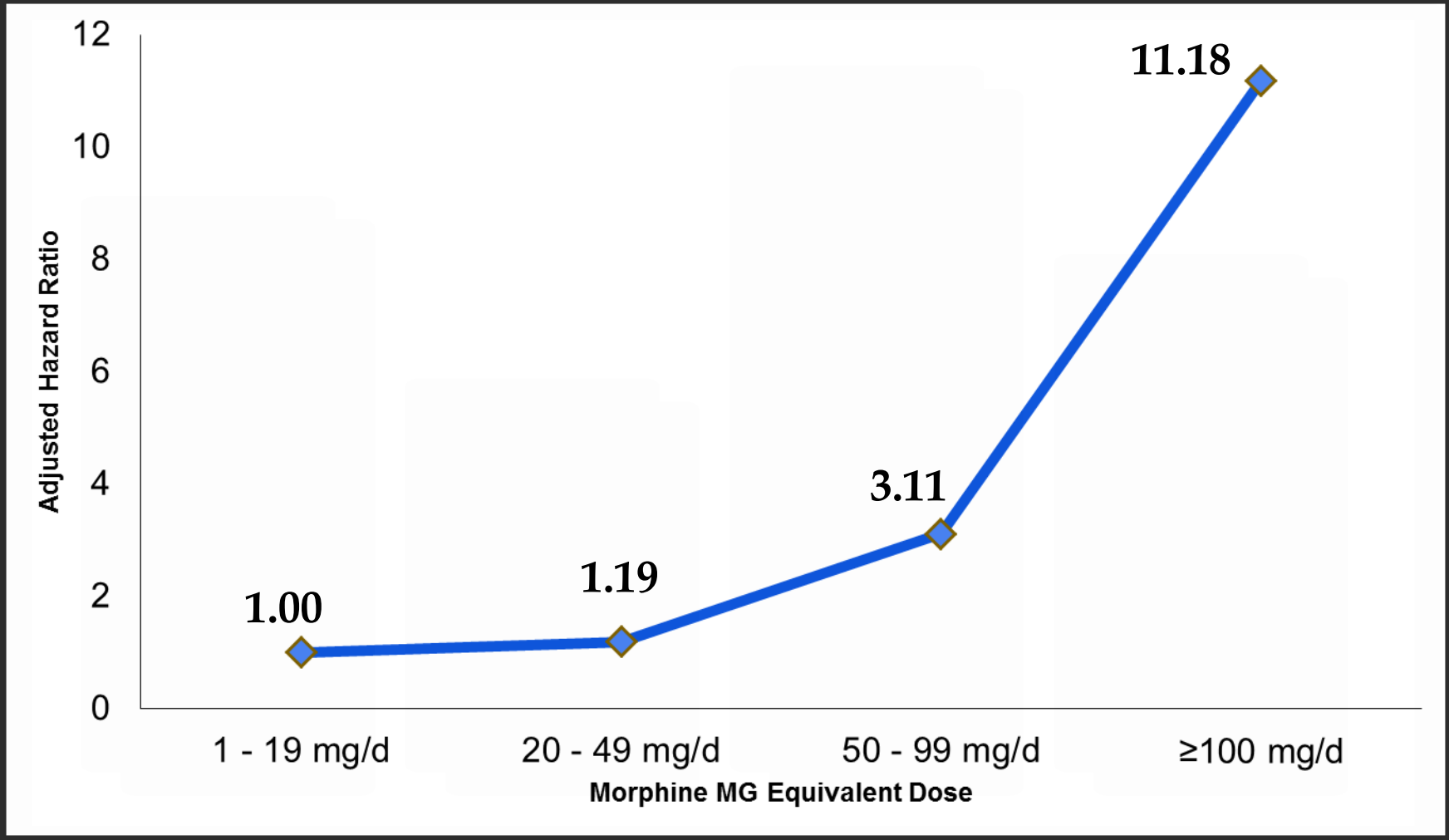
Percentage of the Total Heroin-Dependent Sample That Used Heroin or a Prescription Opioid as Their First Opioid of AbuseData are plotted as a function of the decade in which respondents initiated their opioid abuse.

In 2010, opioids were involved in more overdose deaths than heroin and cocaine combined.



CDC, National Center for Health Statistics, National Vital Statistics System, CDC Wonder. Updated with 2010 mortality data.

High Opioid Dose and Overdose Risk



* Overdose defined as death, hospitalization, unconsciousness, or respiratory failure.

Dunn et al. Ann Int Med. 2010.

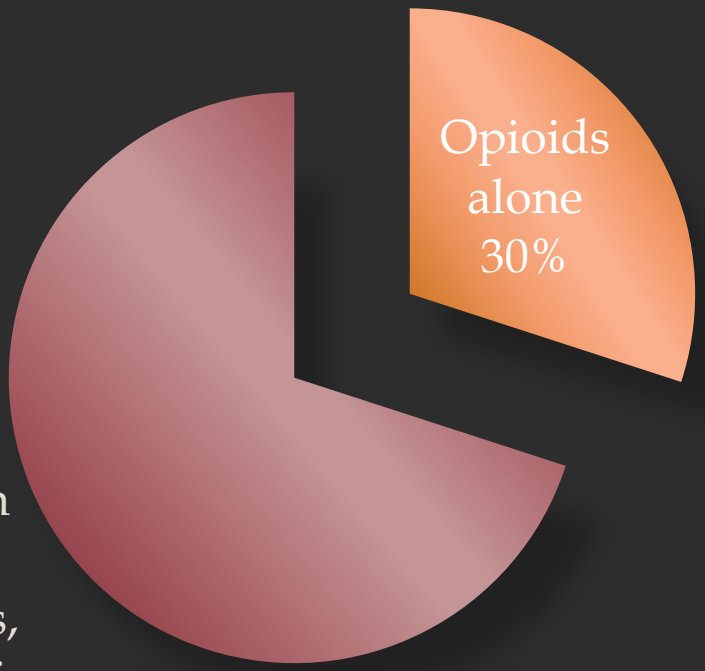
CDC Recommendation

If a patient's dosage has increased to ≥120 morphine milligram equivalents per day without substantial improvement in pain and function, seek a consult from a pain specialist.

http://www.cdc.gov/HomeandRecreationalSafety/pdf/poison-issue-brief.pdf *Accessed 8/10/15.*

Non-Opioids frequently contribute to fatal opioid overdoses

Opioid-Related Overdose Deaths 2010



Jones et al. JAMA 2013.

Diversion also implicated in these deaths

Less than half of patients w/opioid overdose had ever been prescribed these medications[1]

34%	Gift; friend/relative got from physician(s)
31%	Bought/took from a friend/relative
13%	Bought from drug dealer or other stranger
11%	Gift; friend/relative got from elsewhere
7%	Got from physician(s)
4%	Stole from pharmacy/wrote fake prescription/ Internet pharmacy[2]

[1]Hall AJ et al. JAMA 2008. [2]2008 National Survey on Drug Use and Health.

Known Risk Factors for Addiction are Good Predictors for Prescription Drug Misuse

- **Positive CAGE, f-CAGE**
- **Lifetime history of substance use disorder**
- **Family history of substance use disorder**
- Heavy tobacco use
- History of severe depression or anxiety
- History of legal problems

Adapted from Alford DP. SAMHSA-CSAT: Clinical Challenges in Prescribing Controlled Drugs. 2012.

Stratifying Risk: Triage Guide

Low Risk—*Primary Care*

- No history of substance abuse; minimal risk factors

Medium Risk—*Primary Care w/Specialist Support*

- Past history of substance (but not prescription opioid) abuse

High Risk—*Specialty Pain Management*

- Active substance abuse problem; history of prescription opioid abuse
- [Opioids may not be appropriate]

Adapted from Gourlay et al. Pain Med 2005.

Urine Drug Testing

Typical assays

- Immunoassay drug testing, laboratory based
- POC (e.g., "dip-stick" testing)

- most useful if positive for non-prescribed medications/illicit drugs
- were designed to detect toxic level, not prescribed doses
- may detect semi-synthetic (oxycodone) or synthetic (fentanyl) opioids only at very high doses

Confirming therapeutic adherence often requires more sensitive test

- Laboratory-based specific drug identification (e.g., high-performance liquid chromatography) immunoassay

UDT Strategies

- Most useful if positive for cocaine
- Random monitoring specified in agreement
- Base frequency of screening on assessment of patient's risk for misuse
- Combine with pill (patch) counts
- Combine with utilization of Prescription Monitoring Program
- Keep it open-ended…*"Your urine was positive for drugs, what happened??"*

Contracts, Agreements

- Recommended,[1,2] efficacy not well established[3]
- Shifts paradigm from seemingly arbitrary decisions of individual provider to office/clinic "policy"
- Articulates
  - rationale, intended benefits, potential risks of treatment
  - monitoring and action for aberrant medication-taking behavior

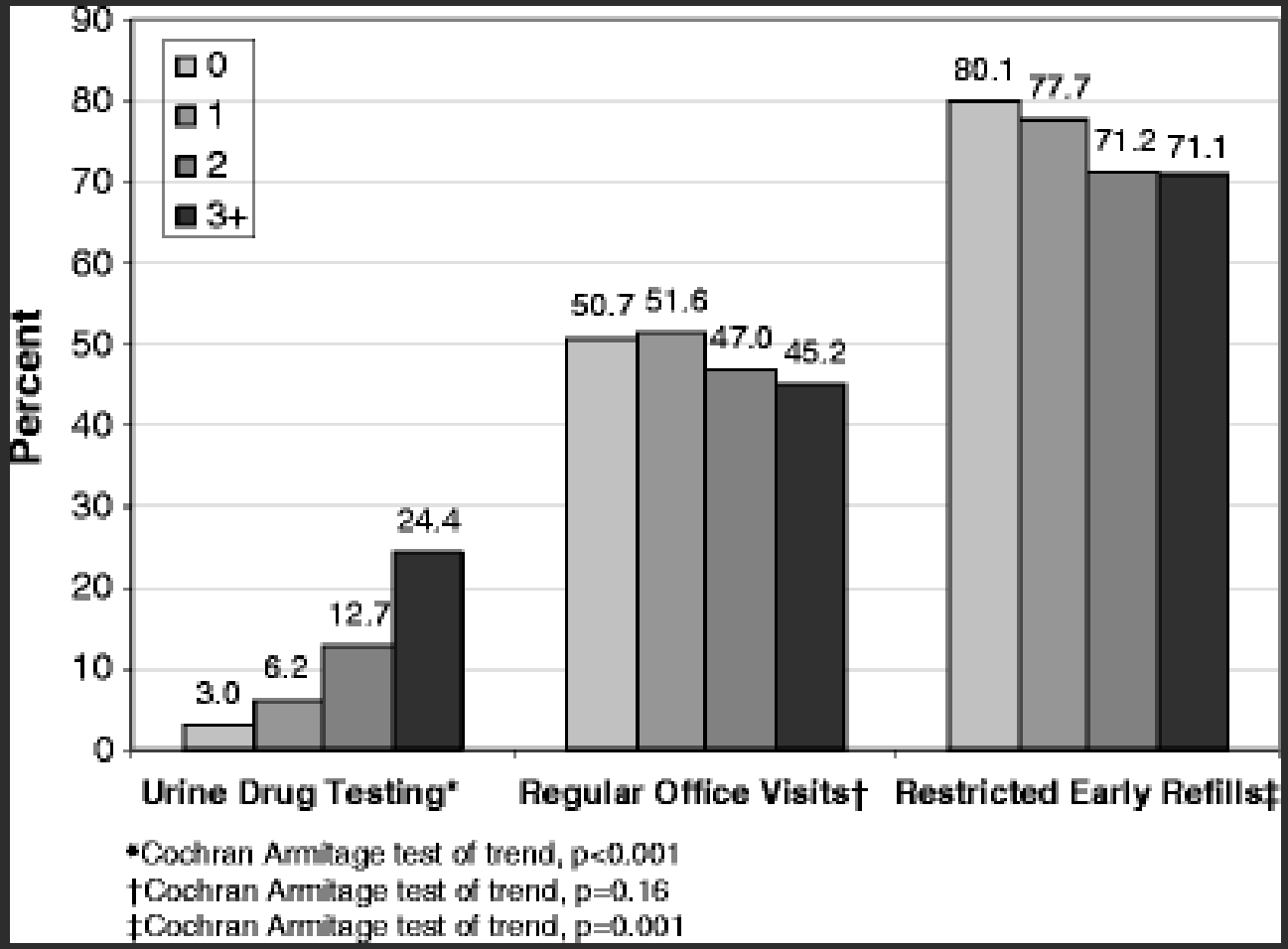
[1]Fishman SM. J Pain Symp Manag 2002. [2]Arnold RM et al. Am J Med 2006.
[3]Starrels JL et al. Ann Intern Med 2010.

Agreements/Contracts should be individualized & goal-directed

- Prescriptions cannot be refilled early
- Refills require a clinic visit by appointment, w/regular provider
- No urgent requests for refills
- Lost or stolen meds or scripts cannot be refilled
- They must be safeguarded
- Bring pill bottles to clinic appointments
- Periodic random urine drug screens
- Follow through on referrals to pain program, psychologist
- Failure to follow these policies may result in discontinuation of pain meds
- Lack of clear benefit on review at 3 months also may result in discontinuation of pain meds.

Fishman SM et al. J Pain Sympt Manag 2002. Chou R et al. J Pain 2009.

Primary Care Provider Management of Higher Risk Patients



Starrels et al. JGIM 2011.

FDA Risk Evaluation & Mitigation Strategy

Prescribers of ER/LA opioid analgesics are strongly encouraged to do all of the following:

- **Train (Educate Yourself)** - a REMS-compliant education program offered by an accredited CME provider
- **Counsel Your Patients** – regarding the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics every time you prescribe these medicines
- **Emphasize Patient and Caregiver Understanding of the Medication Guide** - stress the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid is dispensed to them
- **Consider Using Other Tools** - including Patient-Prescriber Agreement (PPA) and risk assessment instruments

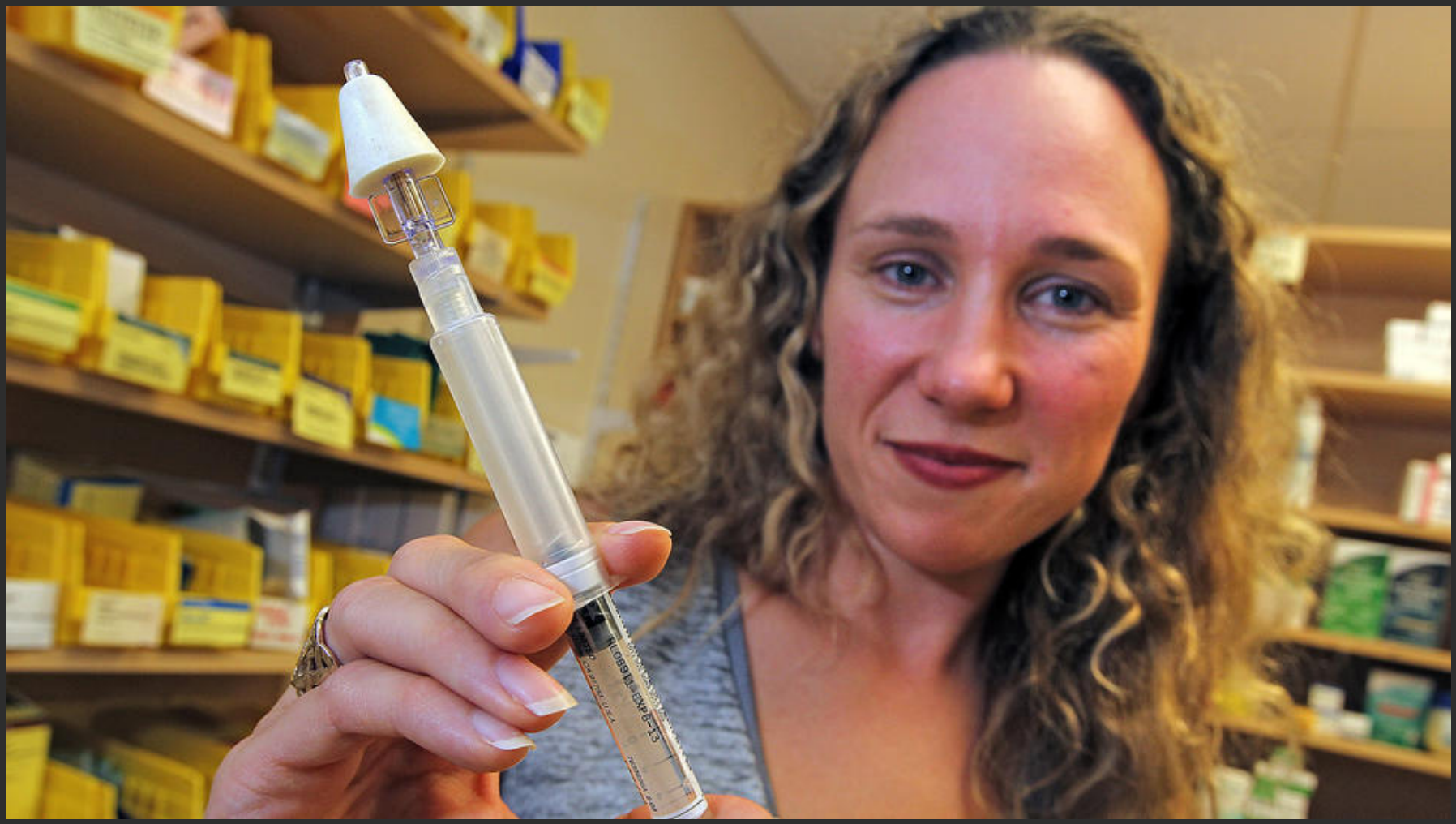
Systems Strategies

- Insurer Restrictions (e.g., BCBS of MA)
- DEA reclassified hydrocodone to Schedule II, narcotic, required abuse-deterrent extended-release oxycodone
- State Medical Boards/State Laws
  - pain education for licensure
  - referral of patients on high doses of opioids to pain specialists
  - prohibiting Schedule II/III office-based dispensing
  - enforcement actions against clinicians prescribing outside accepted practice
  - use of PDMP for narcotic/benzo prescribing
- Naloxone distribution

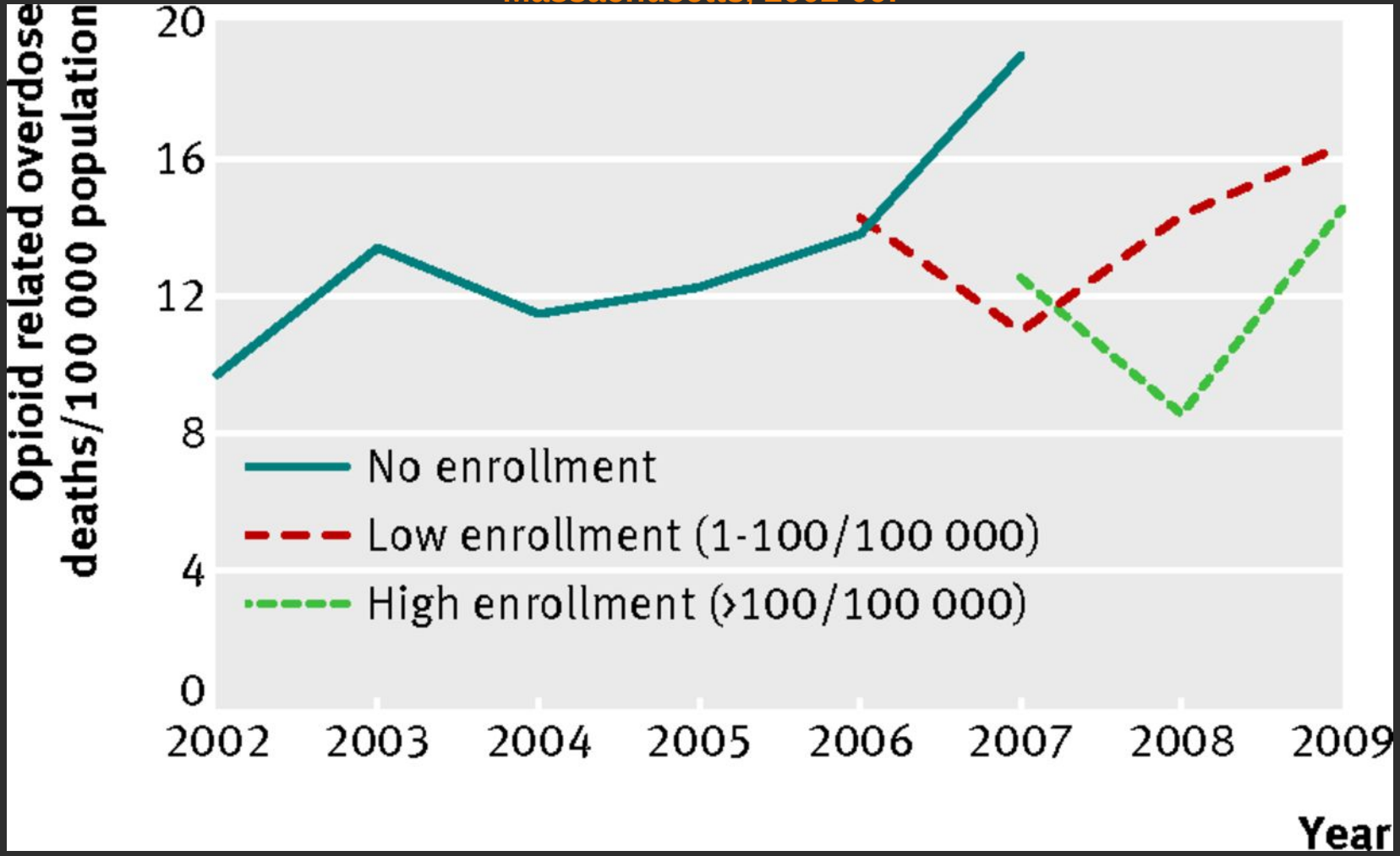
Prescription Drug Monitoring Programs (PDMPs)

- Opioid-related overdose deaths
  - 6 times more likely in patients using 4 or more prescribers or 4 or more pharmacies
  - 11 times more likely in patients prescribed more than 100 morphine mg equivalent dose
- Patients with 1 or more of these risk factors accounted for over ½ of all overdose deaths[1]
- PDMPs associated with decrease in "doctor-shopping"[2]

[1]Gira Baumblatt JAMA 2014. [2]www.pdmpexcellence.org *Accessed 8/9/15.*



Unadjusted unintentional opioid related overdose death rates in 19 communities with no, low, and high enrolment in overdose education and nasal naloxone distribution program in Massachusetts, 2002-09.



Alexander Y Walley et al. BMJ 2013;346:bmj.f174

thebmj

Systems Strategies—Evidence

- 8% of Oregon clinicians prescribed 80%of Sched II-IV medications[1]
- Top 20% of Ontario FP opioid prescribers wrote final opioid prescription 63% of opioid-related deaths[2]
- 27% (FL), 50% (WA) decline in opioid overdose deaths[3,4]
- Over past decade, 20% decrease opioids dispensed, 20% decrease opioid OD rates…but 20% increase heroin OD rates[5]

[1]Authority OH. Oregon PDMP: 2012. Accessed 8/9/15. [2]Dhalla IA et al. Can Fam Physician 2011. [3]Johnson H. MMWR Morb Mortal Wkly Rep 2014. [4]Franklin GM. Am J Ind Med 2010. [5]Larochelle MR et al. JAMA Intern Med 2015.

Could the pendulum swing too far?

New rules on narcotic painkillers cause gried for veterans and VA. The DEA restrictions, adopted to curb opioid abuse, mean many vets have to make more appointments with an already overburdened VA

The Washington Post

DEA contributes to shortages of drugs with controlled substances.

THE WALL STREET JOURNAL

I have caught CVS and other pharmacies lying about not having oxycodone in stock.

MedsChat.com

Prescribing Challenges

Case 1—
Short vs Long-Acting Opioids

Case 2—
Aberrant Medication-taking Behavior

Prescribing Challenges Case 1—Short vs Long-Acting Opioids

62 year old man with severe incapacitating pain due to lumbar stenosis, presently taking

- Percocet 10/325, 1-2 tabs every 6 hours PRN, #240/month; naproxen and gabapentin

Since you are considering long-term prescribing you wonder about changing to a long-acting medication.

Opioids—Short vs Long Acting

Short-acting

- oxycodone
- hydrocodone
- hydromorphone
- morphine

Long-acting

Slow release delivery system

- transdermal fentanyl
- extended release morphine
- extended release oxycodone

Intrinsic pharmacokinetic property

- methadone

[1]Hariharan J et al. JGIM 2007. [2]Trescott AM et al. Pain Physician 2006.

Opioids—Short vs. Long Acting

- 38-60% of chronic pain patients treated with opioids are on short acting agents[1]
- Potential problems w/short acting opioids
  - Rate hypothesis and addiction risk
  - Early withdrawal syndrome
- But these proposed benefits for long acting opioids have not been systematically studied.[2,3]
- Patients initiated on long-acting opioids had 2x risk for opiate overdose[4]
- Recent evidence—Methadone associated with increased death rate compared with long-acting morphine, even at low doses[5]

[1]Hariharan J et al. JGIM 2007. [2]Trescott AM et al. Pain Physician 2006. [3]1Miller M et all. JAMA Intern Med 2015. [4]Chou R et al. Journal of Pain 2009. [5]Ray WA et al. JAMA Intern Med 2015.

Prescribing Opioids—General Principles

- Start low and go slow, using fixed-dose regimens
- Opiate PRNs <1/3 of the days each month
  - Increase fixed dose
  - Use non-opiates for breakthrough pain
- Consider switch to long-acting once stabilized
  - Calculate target (50-75% of equianalgesic dose) for new opioid
  - Reduce first opioid by 1/3 each day, while starting second opioid, titrating up over 3 days to target starting dose
  - When sedation occurs—problem of incomplete cross-tolerance due to inter-patient variability

Converting to Long Acting Opioid—an Example

- Average 8 Percocet 10/325 daily
- Each Percocet contains 10mg oxycodone
- 10mg po oxycodone = 15mg po morphine
- 80mg po oxycodone = 120mg po morphine
- 50% equianalgesic dose: 60 mg of po Morphine
- 70% equianalgesic dose: 84 mg of po Morphine

http://www.epocrates.com/marketing/products/medtools/opioidanalgesicconverter.html *Accessed 8/10/15.*

Cross-Taper to Long Acting Opioid—an Example

- Convert to MS Contin
  - initial target dose 30mg BID
- Day 1
  - MS Contin 15mg BID, Percocet 10/325 PRN (max 6)
- Day 2
  - MS Contin 15mg AM, 30mg PM
  - Percocet 10/325 PRN (max 4)
- Day 3
  - MS Contin 30mg BID
  - Percocet 5/325 PRN (max 4/day)

Prescribing Challenges Case 2—Aberrant Medication-taking Behavior

62 year old man with severe incapacitating pain due to lumbar stenosis, was taking

- Percocet 10/325, 1-2 tabs every 6 hours PRN, #240/month; naproxen and gabapentin

Opioid transitioned to MS Contin 30mg BID and Percocet 5/325 (max 2/day, required only 7 days per month)

Six months later, calls for early refill on Percocet, misses scheduled appointment

You ask your nurse to call him and schedule an appointment for later that week, and consider how you will approach the visit.

Aberrant Medication Taking Behavior—Differential Diagnosis

- Self-medication of psychiatric and physical symptoms other than pain
- Addiction
- Criminal intent—diversion
- Pseudo-addiction

Pseudo-addiction

- Intense focus on obtaining relief
- Mimics aspects of addiction, but behavior should resolve w/adequate pain relief[1]
- Causes
  - disease progression
  - opioid resistant pain
  - withdrawal mediated pain
  - opioid-induced hyperalgesia
- "Pain-relief seeking" or "Drug seeking"?…

  Pseudo-addiction as a concept promulgated by pharma, not evidence based[2]

[1]Weissman DE, Haddux JD. Pain 1989. [2]Dowel et al. JAMA 2013.

Individualizing Opioid Dosing Regimens

- Differences in absorption and metabolism
  - Long-acting opioids may need more frequent dosing
    - Long-acting morphine TID
    - Fentanyl patch q48 hours
  - Only adjust once present dose at steady state
- Differences in pain pattern
  - Asymmetric dosing
    - Example: Patient who has more pain before Noon

Response to Opioids may be quite variable

- Patients may respond differently to the same opioid
- Pain syndromes may respond differently to the same opioid
- Incomplete cross-tolerance between opioids

How to Stop Prescribing Opioids to a Patient—Legal Issues

Detoxing opioid addicts w/opioids requires licensing/certification

vs.

Tapering opioids when no longer appropriate in patients w/legitimate pain diagnosis

Heit HA et al. Pain Med 2004.

Examples of Tapering Schedules

Morphine SR/CR

- Decrease dose by 20-50 percent per day until you reach 45 mg/day
- Then decrease by 15 mg/day every two to five days

Oxycodone CR

- Decrease dose by 20-50 percent per day until you reach 30 mg/day
- Then decrease by 10 mg/day every two to five days

Consider supplementing with clonidine 0.1mg BID-TID

Keys to Safe Prescribing

1. Prescribe opioids for appropriate conditions, as last resort, at minimal dose, combined with other Pharm/non-Pharm therapies
2. Risk assessment and patient selection
3. Agreements, pill counts, drug screens, PMP
4. Safer maximal daily dosing, minimize combining with other sedating medications
5. Laws/regulations should focus on high volume clinicians who prescribe outside accepted practice