PAIN MANAGEMENT AND THE OPIOID EPIDEMIC

MNASCA EDUCATION

CONFERENCE

APRIL 8TH, 2016

PETER STILES, MD

MEDICAL DIRECTOR

TRIA PAIN PROGRAM



259 million

In 2012, health care providers wrote 259 million prescriptions for opioid pain relievers – enough for every American adult to have a bottle of pills ¹



300% increase

Prescription opioid sales in the United States have increased by 300% since 1999², but there has not been an overall change in the amount of pain Americans report^{3,4}.



2 million

Almost 2 million Americans, age 12 or older, either abused or were dependent on opioid pain relievers in 2013.⁵



16 thousand

In 2013, more than 16,000 people died in the United States from overdose related to opioid pain relievers, four times the number in 1999.⁶

Paulozzi, Mack, & Hockenberry, 2014

CDC. Vital Signs: Overdoses of Prescription Opioid Pain Relievers – United States, 1999 – 2008. Morbidity and Mortality Weekly Report 2011: 60(43); 1487-1492. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mmo04344_wffirg2_cid=mmo04344_wffirg2. August 17, 2015.

²Chang H, Daubresse M, Kruszewski S, et al. Prevalence and treatment of pain in emergency departments in the United States, 2000 – 2010. Amer J of Emergency Med 2014; 32(4): 421-31.

Daubresse M, Chang H, Yu Y, Viswanathan S, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000 – 2010. Medical Care 2013; 51(10): 870-878

CDC. National Vital Statistics System mortality data. Available at http://www.cdc.gov/nchs/deaths.htm. Accessed August 17, 2015

DISCLOSURES

- Scientific Advisor to Chrono Therapeutics (http://www.chronothera.com/)
- Unpaid board member of the Steve Rummler Hope Foundation, an organization dedicated to response opioid prescribing and opioid overdose rescue







OBJECTIVES

UPON COMPLETION OF THIS SESSION, PARTICIPANTS SHOULD BE BETTER ABLE TO:

- Describe the scope of the opioid epidemic, how this impacts expectations in patients and management by medical providers
- Discuss current options and emerging trends in responsible,
 interdisciplinary pain management

PAIN IS RELEVANT TO EVERY PRACTICE

- > 100 million people
- •#1 presenting complaint to health professionals
- Est. \$560 \$635 Billion
 - Roughly the cost of cancer, heart disease, and diabetes.....combined!







SUBSCRIBE NO 3 MONTHS for th

Monday, December 17, 2012 As of 11:36 AM EST

TOP STORIES IN WSJ

Pain Physician. 2012 Jul;15(3 Suppl):ES9-38.

Seib & Wessel Politics & Policy

Opioid epidemic in the United States.

Manchikanti L, Helm S 2nd, Fellows B, Janata JW, Pampati V, Grider JS, E Pain Management Center of Paducah, Paducah, KY, USA. drlm@thepainmd.com

Consensus

'Infidelity Phones'

The New Hork Times

U.S. NEWS | Updated December 17, 2012, 11:36 a.m. ET

A Pain-Drug Champion Has Second Thoughts

A call to stop the "epidemic" of opioid pain medicine overdoses

N.Y. / Region

Congress Blog

By Bob Twillman is the 2011-2012 Mayday Pain and Society Fellow, and also the Director of Policy and Advocacy at the American Academy of Pain Management - 11/08/11 11:27 AM ET



Article

Stock Quotes

Comments (129)

















By THOMAS CATAN and EVAN PEREZ



More than 16,000 people die from opioid overdoses every year. Now, Dr. Russell Portenoy, who campaigned for wider prescription of pain medications like Vicodin, Oxycontin and Percocet, is having second thoughts. WSJ's Thomas Catan reports. Photo: Bryan Thomas

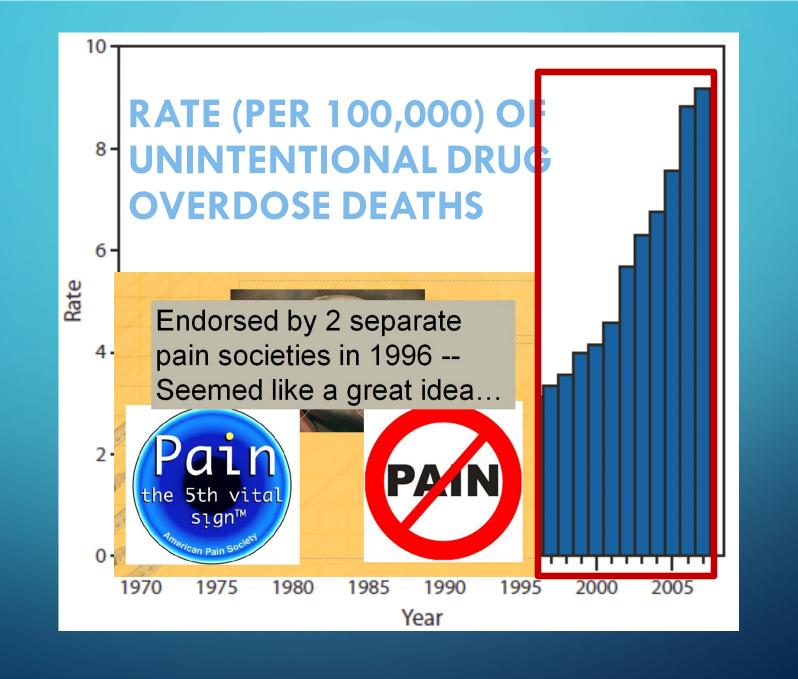
WORLD U.S. N.Y. / REGION BUSINESS TECHNOLOGY SCIENCE HEALTH SPORTS OPINION New York City to Restrict Prescription Painkillers in

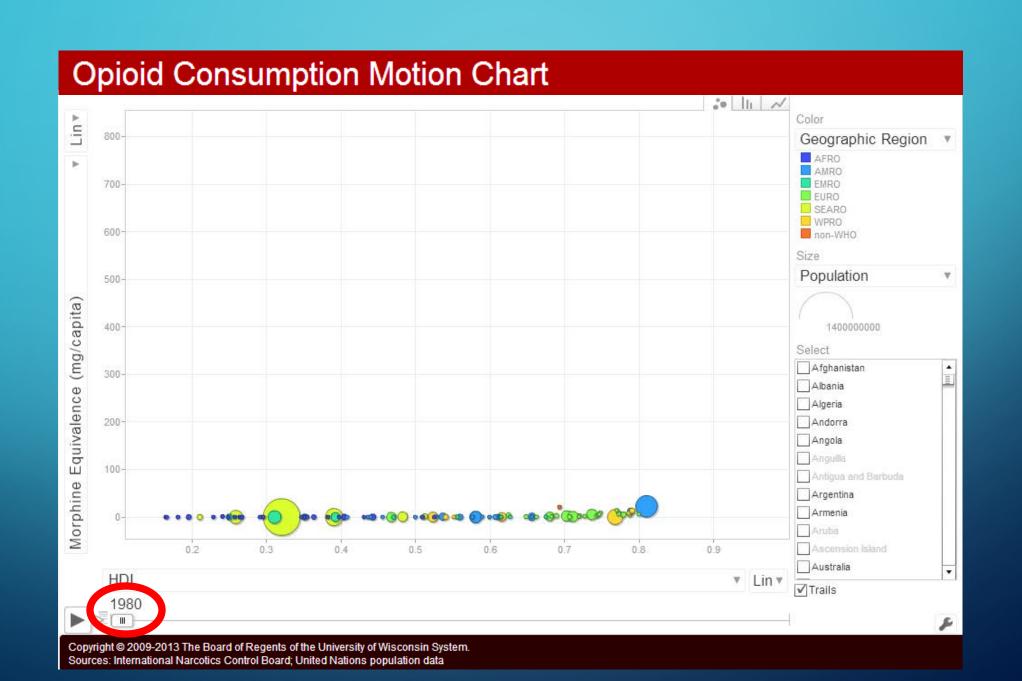
Public Hospitals' Emergency Rooms

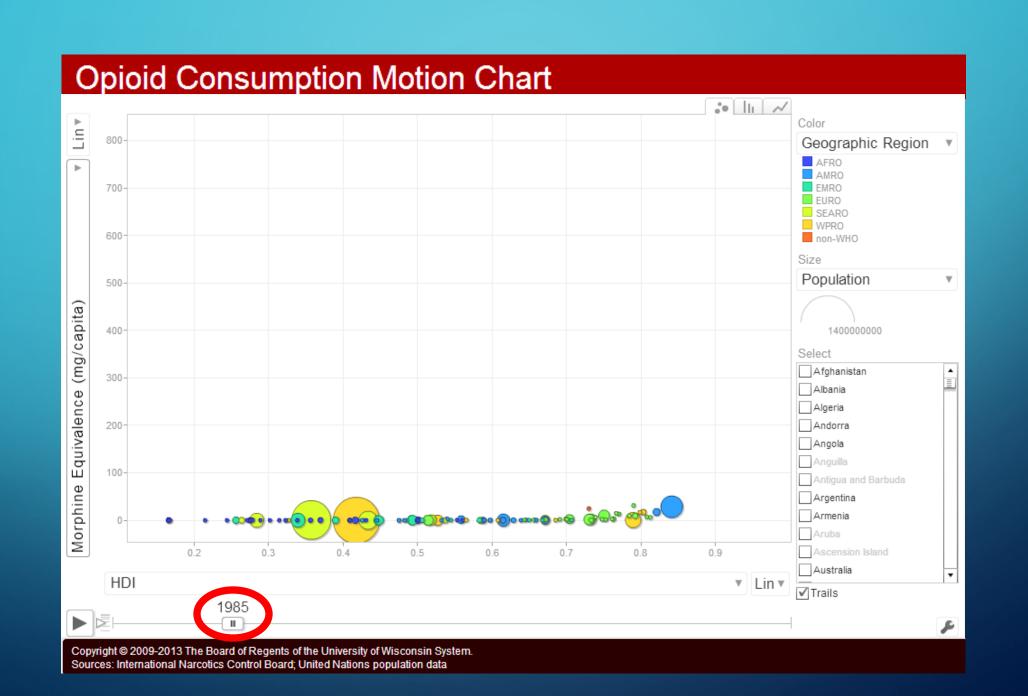
Where lawmakers come to blog

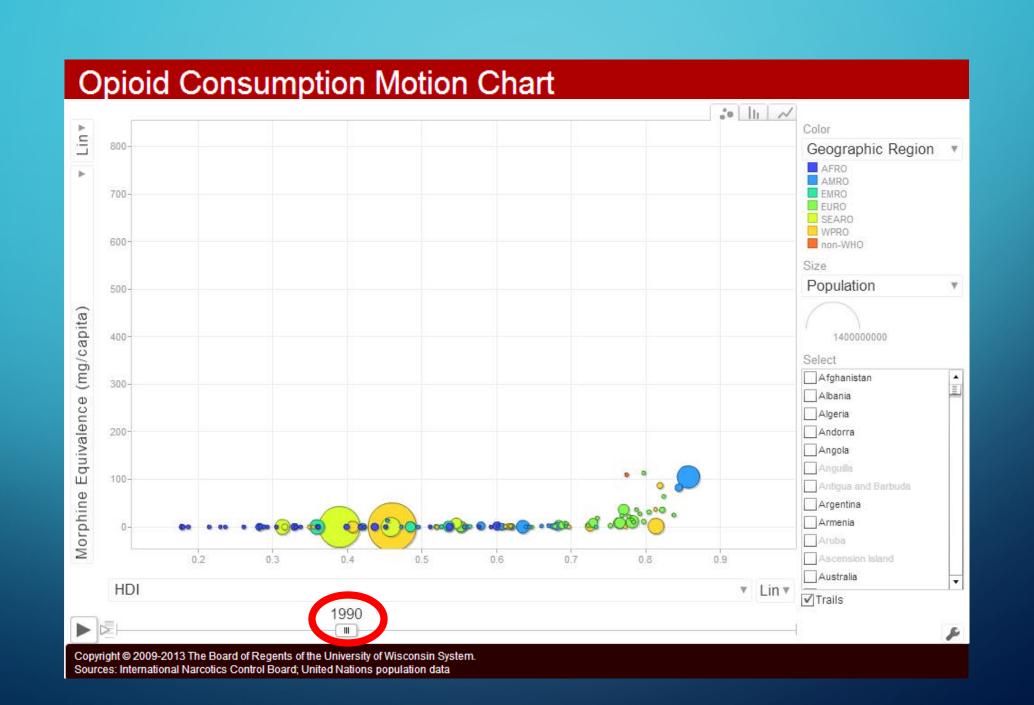


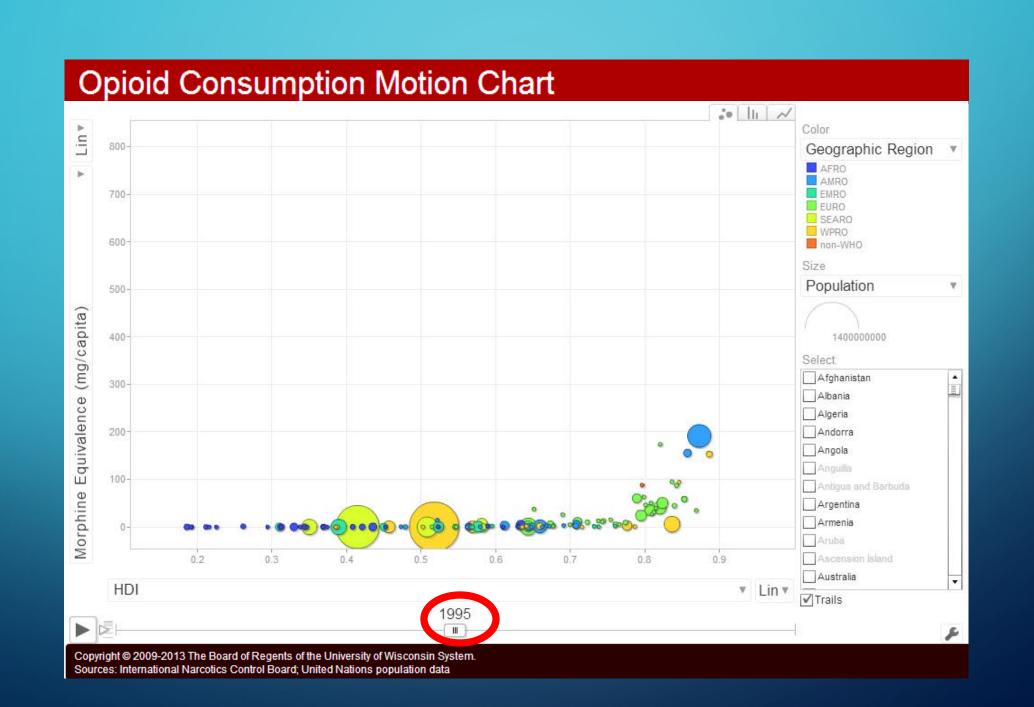
Mayor Michael R. Bloomberg, with the health commissioner, Dr. Thomas A. Farley, at the lectern, and other health officials and doctors, announced new measures to stop the abuse of some pain drugs

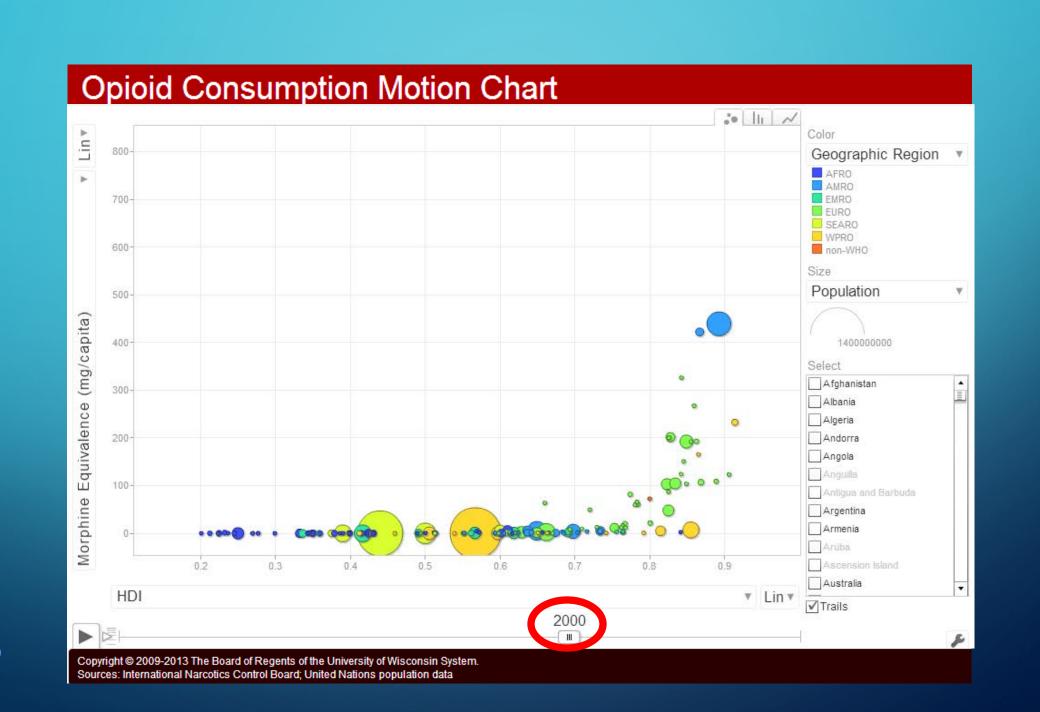


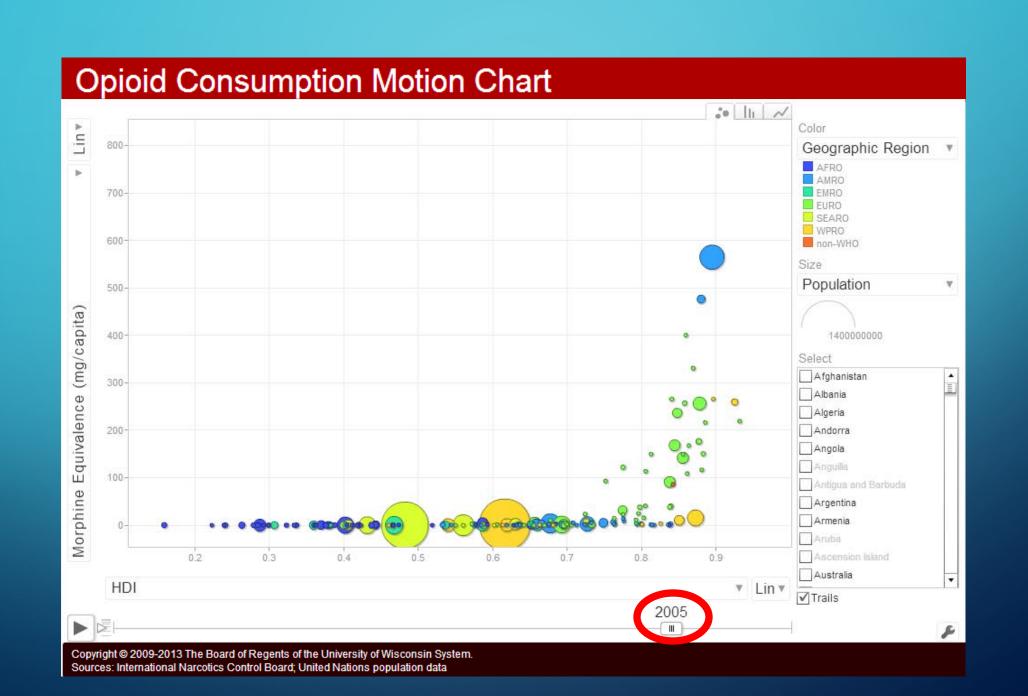


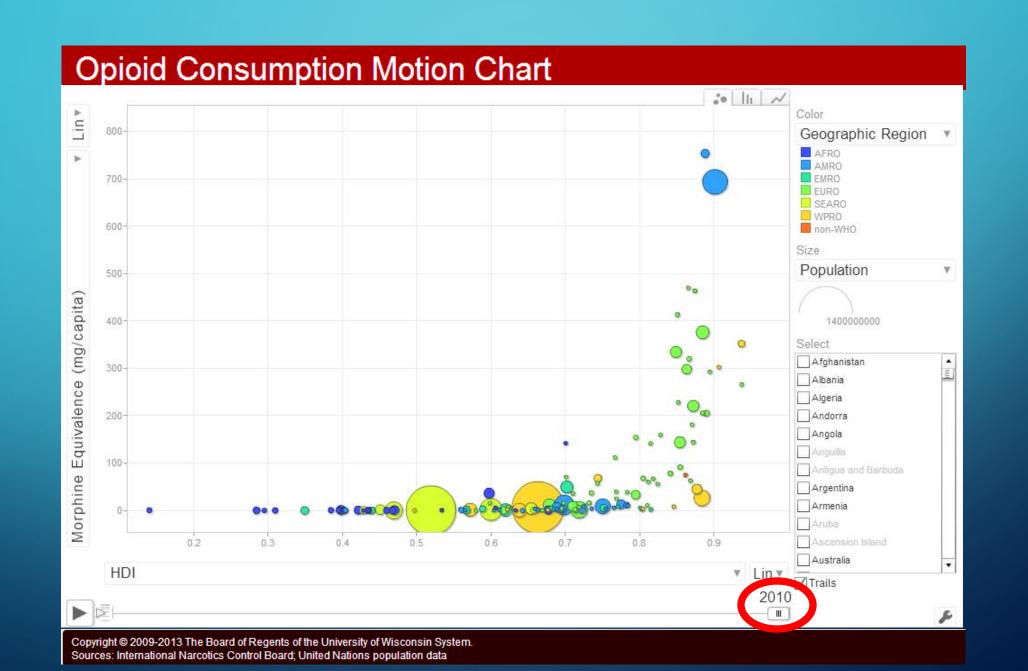


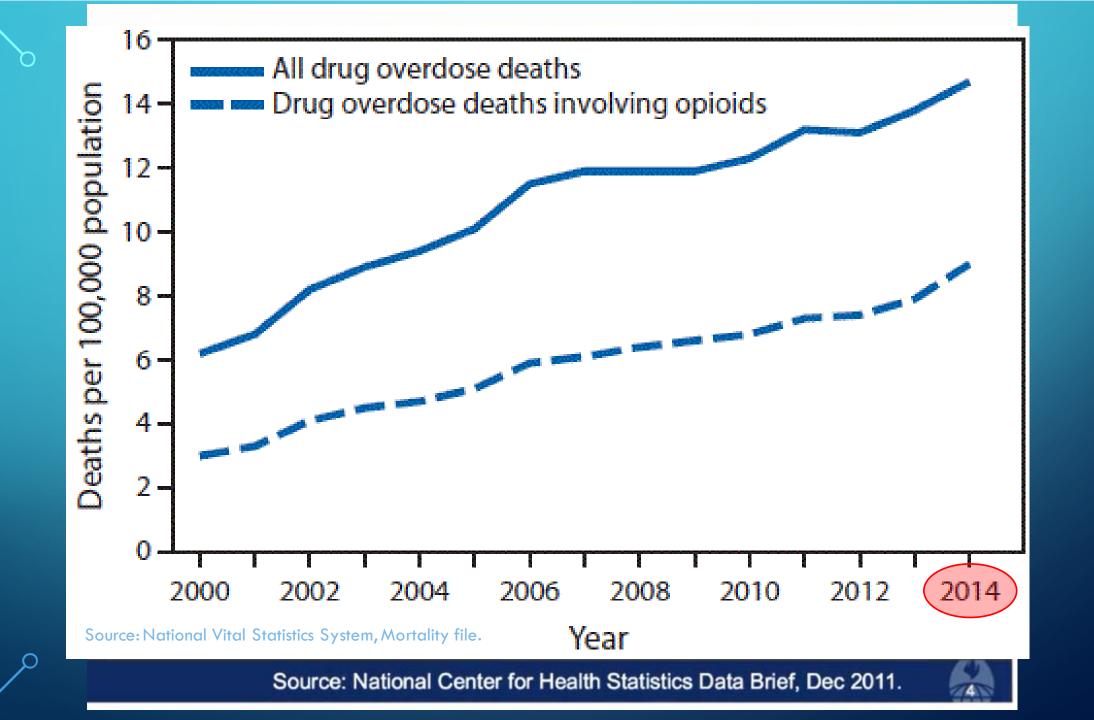














NEW OPIOID IS 5x's STRONGER!

Available in March



EVIDENCE





From: Association Between C		Overdose Deaths, No.	Person- Months	Rate per 1000 Person-Months (95% CI)	Related	Deaths
	Patients With Chronic N Maximum prescribed daily opioid dose, mg/d	oncancer Pai	n Diagnoses			
	0	243	2729022.7	0.09 (0.08-0.10)		
JAMA. 2011;305(13):1315-1321.	1-<20	44	395 205.0	0.11 (0.08-0.15)		
• •	20-<50	108	458 296.2	0.24 (0.19-0.28)		
	50-<100	86	129491.6	0.66 (0.53-0.82)		
	≥100	125	100 479.3	1.24 (1.04-1.48)		

Patients With Chronic Noncancer Pain Diagnoses Maximum prescribed daily opioid dose, mg/d						
0	243	2729022.7	0.09 (0.08-0.10)			
1-<20	44	395 205.0	0.11 (0.08-0.15)			
20-<50	108	458 296.2	0.24 (0.19-0.28)			
50-<100	86	129491.6	0.66 (0.53-0.82)			
≥100	125	100 479.3	1.24 (1.04-1.48)			
Fill types			0.00 (0.00 0.40)			
Regularly scheduled only	115	323 304.7	0.36 (0.29-0.43)			
As needed only	152	672 276.0	0.23 (0.19-0.27)			
Simultaneous as needed and regularly scheduled	96	87891.5	1.09 (0.88-1.33)			
			·			

Fill types						
Regularly scheduled only	42	65 163.2	0.64 (0.46-0.87)			
As needed only	52	142311.5	0.37 (0.27-0.48)			
Simultaneous as needed and regularly scheduled	31	20 259.8	1.53 (1.04-2.17)			
Patients With Substance Use Disorder Diagnoses						
Maximum prescribed daily opioid dose, mg/d		•				
0	159	378 244.9	0.42 (0.36-0.49)			
1-<20	24	44630.0	0.54 (0.34-0.80)			
20-<50	42	53 584.0	0.78 (0.56-1.06)			
50-<100	27	17019.2	1.59 (1.05-2.31)			
≥100	44	14809.2	2.97 (2.16-3.99)			
Fill types						
Regularly scheduled only	44	38722.0	1.14 (0.83-1.53)			
As needed only	59	78314.2	0.75 (0.57-0.97)			
Simultaneous as needed and regularly scheduled	34	13006.3	2.61 (1.81-3.65)			
Alabara dations CL confidence interval						

WHO IS AT RISK?

The most significant risk factors substance abuse are:

- Personal or family history of aberrant alcohol and drug-related behaviors
- History of physical or sexual abuse
- Co-occurring psychiatric conditions



34% opioid addiction among chronic pain patients on opioids

J Addict Dis. 2011 Jul-Sep;30(3):185-94. doi: 10.1080/10550887.2011.581961

Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria.

Boscarino JA, Rukstalis MR, Hoffman SN, Han JJ, Erlich PM, Ross S, Gerhard GS, Stewart WF. Center for Health Research, Geisinger Clinic, Danville, PA 17822-4400, USA. jaboscarino@geisinger.edu

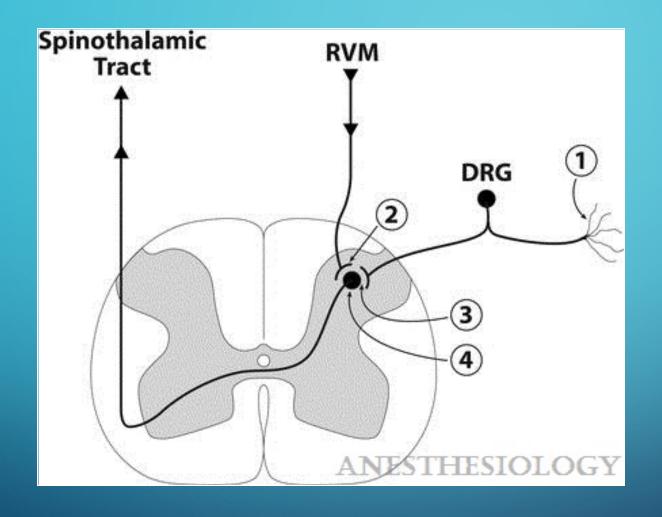
Abstract

The authors estimated the prevalence of lifetime prescription opioid-use disorder among outpatients on opioid therapy usin criteria from both versions 4 and 5 of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Using electronic records from a large health care system, a random sample of outpatients undergoing long-term opioid therapy for non-cand pain was identified and 705 participants completed diagnostic interviews. The prevalence of lifetime DSM-5 opioid-use disorder among these patients was 34.9% (95% confidence interval [CI] = 30.5739.5), similar to the prevalence of DSM-4 opioid dependence (35.5%, 95% CI = 31.1740.2). The Kappa value between DSM-5 and DSM-4 criteria was high (Kappa =

As a pain physican, I respect the dangers of abuse, addiction and overdose...



...but it turns out that opioids aren't even very good to manage pain!



Opioid-induced Hyperalgesia: A Qualitative Systematic Review

Angst, Martin S.; Clark, J David Anesthesiology. 104(3):570-587, March 2006.

Fig. 2. Neuroanatomical sites and mechanisms implicated in the development of opioid-induced hyperalgesia during maintenance therapy and withdrawal. (1) Sensitization of peripheral nerve endings. (2) Enhanced descending facilitation of nociceptive signal transmission. (3) Enhanced production and release as well as diminished reuptake of nociceptive neurotransmitters. (4) Sensitization of second-order neurons to nociceptive neurotransmitters. Figure 2 does not illustrate all potential mechanisms underlying opioid-induced hyperalgesia, but rather depicts those that have been more commonly studied. DRG = dorsal root ganglion; RVM = rostral ventral medulla.



HOW HAVE WE RESPONDED?

• In response to recent CDC findings the government issued a plan which calls for a multiagency, multispecialty approach with the goal of decreasing opioid use in the United States

"Research and medicine have provided a vast array of medications to cure disease, ease suffering and pain, improve the quality of life, and save lives. This is no more evident than in the field of pain management. However, as with many new scientific discoveries and new uses for existing compounds, the potential for diversion, abuse, morbidity, and mortality are significant. Prescription drug misuse and abuse is a major public health and public safety crisis. As a Nation, we must take urgent action to ensure the appropriate balance between the benefits these medications offer in improving lives and the risks they pose."

- The CDC has also offered new opioid prescribing guidelines...
 - This is presently quite controversial
 - 12 guidelines

NEW CDC OPIOID PRESCRIBING GUIDELINE

"This guideline provides recommendations for primary care providers who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses:

- 1) when to initiate or continue opioids for chronic pain;
- 2) opioid selection, dosage, duration, follow-up, and discontinuation;
- 3) assessing risk and addressing harms of opioid use."



NEW CDC OPIOID PRESCRIBING GUIDELINE

- Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate. (Recommendation category: A; evidence type: 3)
- Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety. (Recommendation category: A; evidence type: 4)
- Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy. (Recommendation category: A; evidence type: 3)
- When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids. (Recommendation category: A; evidence type: 4)
- When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to 50 morphine milligram equivalents (MME) or more per day, and should avoid increasing dosage to 90 MME or more per day or carefully justify a decision to titrate dosage to 90 MME or more per day. (Recommendation category: A; evidence type: 3)
- Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed. (Recommendation category: A; evidence type: 4)
- Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids. (Recommendation category: A; evidence type: 4)
- Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/d), or concurrent benzodiazepine use, are present. (Recommendation category: A; evidence type: 4)
- Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months. (Recommendation category: A; evidence type: 4)
- When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs. (Recommendation category: B; evidence type: 4)
- Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible. (Recommendation category: A; evidence type: 3)
- Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder. (Recommendation category: A; evidence type: 2)

DIEW CDC GUIDELINES - SUMMARY

- Establish functional goals and employ non-pharmacologic treatment when possible
- Review risks with patients frequently, monitor for side effects check urine drug screens and evaluate within 1 month of starting any opioids.
- Provide the lowest possible dose, stick to short acting medications; try to provide less than 50 MEDs, definitely not more than 90 MEDs.
- Prescribe Naloxone and act quickly if you suspect opioid use disorder. Always check a prescription monitoring report.
- Don't mix opioids and benzodiazapines.
- Three day max prescription for injury or 'flares'

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DR. STILES' PRINCIPLES WHEN USING OPIOIDS

- SET EXPECTATIONS from the outset
- Avoid long acting opioids for acute conditions
- Explain that opioid pain medications are to facilitate physical therapy, function, and will not be continued for more than 3 months under any circumstance
- Don't mix sedatives, or use concurrent 'uppers and downers'
- Check prescription monitoring reports, urine drug screens and document like crazy



Opioid Epidemic

Pain Management



THE BODY'S ALARM SYSTEM

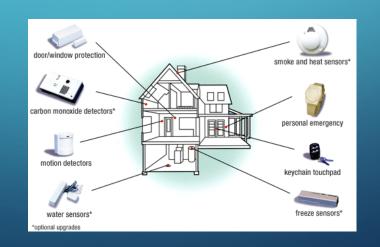
INTRUDER BREAKING IN



NORMAL ALARM ACTIVATION

ACUTE PAIN



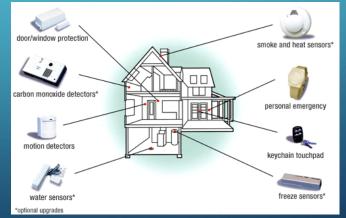




THE BODY'S ALARM SYSTEM



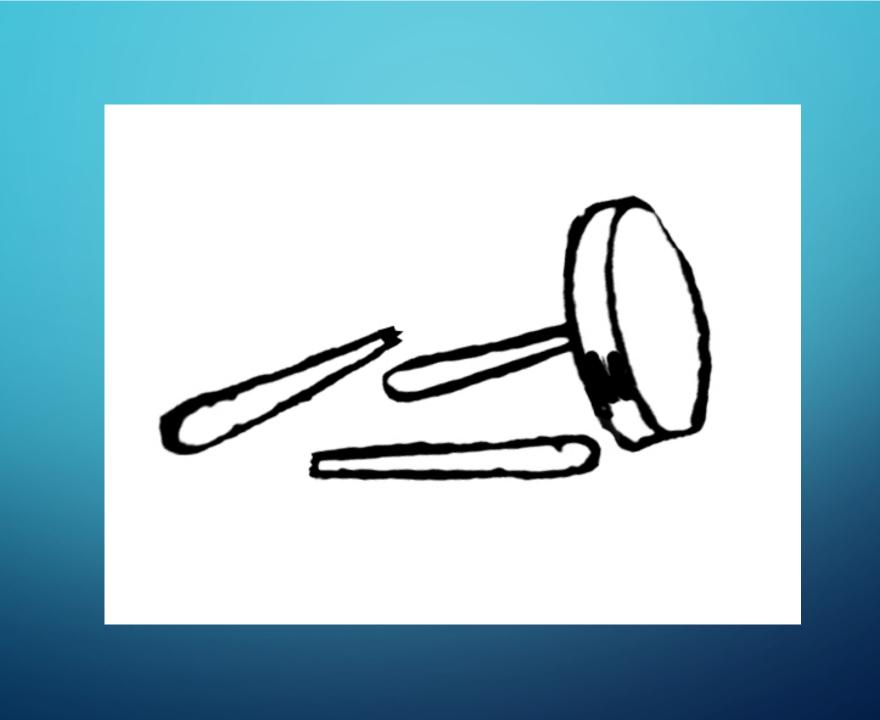




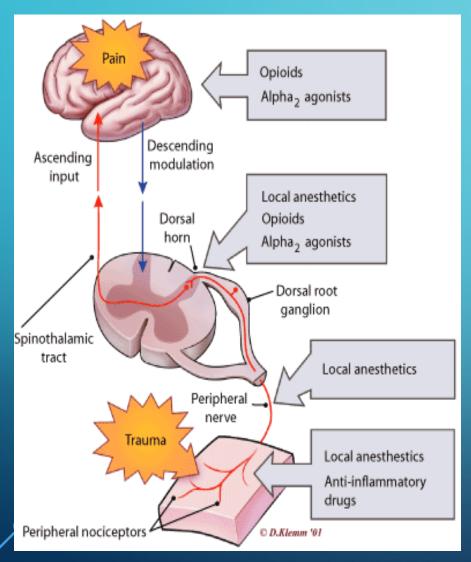


PAIN MANAGEMENT IS A TEAM SPORT



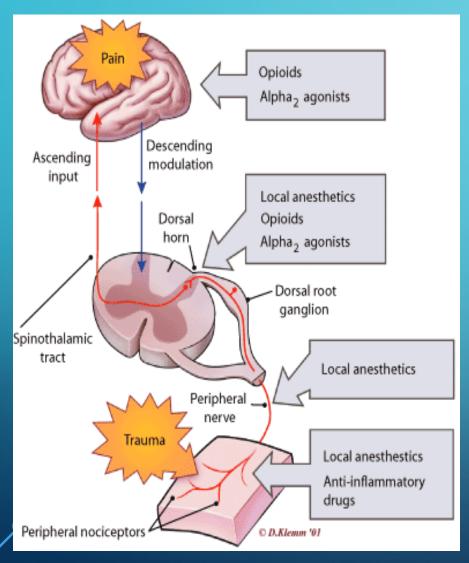


MULTIMODAL PHARMACOLOGY



- Treat pain at multiple sites on pain pathway
- Improved pain control
- Opioid-sparing
- Decreased side effects

MULTIMODAL PHARMACOLOGY



- Opioids
- Cyclooxygenase inhibitors
- NSAIDs
- Norepi modulators
- Alpha-2 agonists
- Membrane stabilizers
- Magnesium
- Topicals
- And more...

DELIBERATE OTC DOSING

- If ibuprofen and acetaminophen are alternated, the patient can be taking an OTC analgesic every 4 hours.
- 1g of acetaminophen q8
- 600-800 of ibuprofen q8



TIP: Remember that acetaminophen is included in other medications

PHARMACOLOGIC ALTERNATIVES TO CONSIDER

- Magnesium Supplementation
 - Mag Glycinate is the most bioavailable form; 400-600mg daily
 - Mechanism is somewhat unclear, but...
- Norepinephrine Modulators
 - Duloxetine (20-60mg daily) or TCAs seem to be most effective
- Gabapentin or Lyrica
 - Extrapolated from perioperative data
 - Side effects might be limiting
- Topical Compounded Creams
 - Very low risk and limited side effects
 - Can administer otherwise unavailable medications

Lee, Cheol et al. The Effects of Magnesium Sulfate Infiltration on Perioperative Opioid Consumption and Opioid-Induced Hyperalgesia in Patients Undergoing Robot-Assisted Laparoscopic Prostatectomy with Remifentanil-Based Anesthesia." Korean Journal of Anesthesiology 61.3 (2011): 244–250

Sun, Yong-Hai et al. "Synergistic Analgesia of Duloxetine and Celecoxib in the Mouse Formalin Test: A Combination Analysis." Ed. Claudia Sommer. PLoS ONE 8.10 (2013): e76603. Schmidt PC, et al. "Perioperative gabapentinoids: choice of agent, dose, timing, and effects on chronic postsurgical pain." Anesthesiology. 2013 Nov;119(5):1215-21

INTERVENTIONS

- Must recognize pain procedures are only to facilitate functional improvement
- Balance risk vs benefit



INTERVENTIONS

Decrease Bad Stuff

- Steroid Injections
- Radiofrequency Neurotomy

Increase Good Stuff

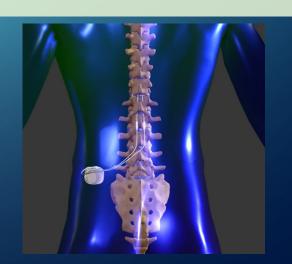
- "Prolotherapy"
- Stem Cell Therapy

Other

- Neurostimulation
- Intrathecal Drug Delivery





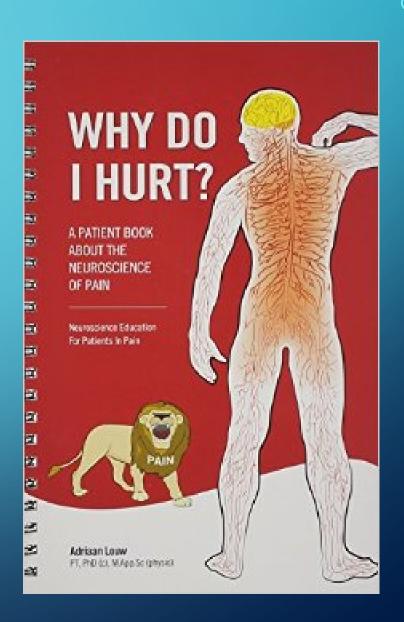


FUNCTIONAL THERAPY

- Rare promises:
 - Lack of activity and exercise will make pain worse
 - It will get worse before it gets better
 - Physical therapy is not a place you go, or even a thing you do, it is a lifestyle

FUNCTIONAL THERAPY

- Therapeutic Neuroscience Education
 - Focus first on education
 - Then on activity
 - Then on re-engagement



BEHAVIORAL HEALTH

Pain is a multi-system, multi-faceted experience

Mood

Sleep

Suffering

Employment

Context

Anxiety

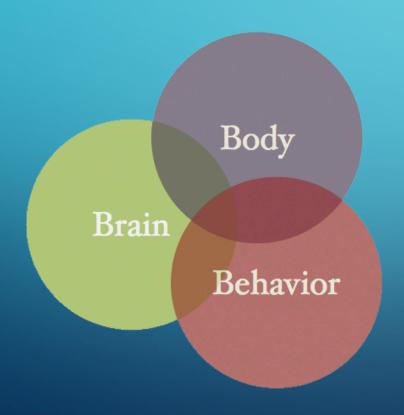
Experience

Abuse

Relationships

BEHAVIORAL HEALTH

- At the very least, this must be recognized
- Sometimes, it must be addressed professionally



- Coping strategy development
- Cognitive behavioral therapy
- Education about pain
- Pacing activity
- Biofeedback
- Group therapy
- Anxiety management
- Addressing abuse/trauma

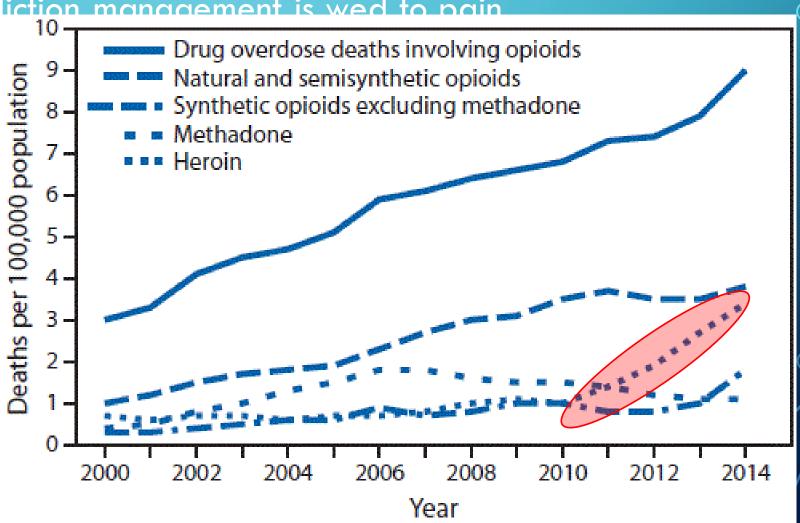
ADDICTION MEDICINE

• At least for now, addiction management is wed to pain

management

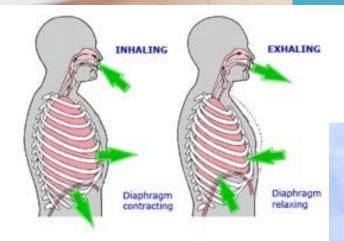
Addiction specialists

Important to ensure



INTEGRATIVE MEDICINE









PRINCIPLES TO GUIDE A TOUGH CONVERSATION

- Set expectations from the outset
 - There will be bad days, and it will get worse before it gets better
 - Set clear relationship guidelines
 - Pain is a normal part of life
 - The goal of pain management is to restore function
 - If there were any 'quick fix,' our country wouldn't spend \$600 billion on pain

PRINCIPLES TO GUIDE A TOUGH CONVERSATION

- Do not ever hint pain is in their head
 - By they time they get to you, they've heard this before and it hurt
 - Have a plan for when they ask, "why does it still hurt?" or "where is the pain coming from?"

SOME PEOPLE THINK THAT
TO BE STRONG IS TO NEVER FEEL PAIN.

IN REALITY

THE STRONGEST PEOPLE
ARE THE ONES WHO FEEL IT,
UNDERSTAND IT, AND ACCEPT IT.

PRINCIPLES TO GUIDE A TOUGH CONVERSATION

- Partner with the patient
 - This is a marathon, not a sprint
 - Do not abandon the patient, this is what they fear more than pain



OBJECTIVES

UPON COMPLETION OF THIS SESSION, PARTICIPANTS SHOULD BE BETTER ABLE TO:

- Describe the scope of the opioid epidemic, how this impacts expectations in patients and management by medical providers
- Discuss current options and emerging trends in responsible,
 interdisciplinary pain management

REFERENCES

- d'Hemecourt PA, Gerbino PG, Micheli LJ. Back injuries in the young athlete. Clin Sports Med.2000; 19:663-679
- Petering, Ryan C., and Charles Webb. "Treatment Options for Low Back Pain in Athletes." Sports Health 3.6 (2011): 550–555
- Lee, Cheol et al. "The Effects of Magnesium Sulfate Infiltration on Perioperative Opioid Consumption and Opioid-Induced Hyperalgesia in Patients Undergoing Robot-Assisted Laparoscopic Prostatectomy with Remifentanil-Based Anesthesia." Korean Journal of Anesthesiology 61.3 (2011): 244–250
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- Schmidt PC, et al. "Perioperative gabapentinoids: choice of agent, dose, timing, and effects on chronic postsurgical pain." Anesthesiology. 2013 Nov;119(5):1215-21
- Statistics from the International Narcotics Control Board United Nations population data
- Unreferenced images in presentation found via Google Image search, not copyrighted
- Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Anala. 2003 Aug;97(2):534-40.
- Bialosky, JE, Bishop, MD, Cleland JA. Individual Expectation: An Overlooked, but Pertinent, Factor in the Treatment of Individuals Experiencing Musculoskeletal Pain. Phys Ther. 2010 Sept; 90(9):1345–1355.
- Keltner JR, Furst A, Fan C, Redfern R, Inglis B, Fields HL. Isolating the modulatory effect of expectation on pain transmission: a functional magnetic resonance imaging study. J Neurosci. 2006 Apr 19;26(16):4437-43.
- Stomberg MW, Oman UB. Patients undergoing total hip arthroplasty: a perioperative pain experience. J Clin Nurs. 2006 Apr; 15(4):451-8.
- Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, Blow FC. Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths. JAMA. 2011;305(13):1315-1321
- Dasta JF, et al. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. Crit Care Med. 2005 Jun;33(6):1266-71.
- Overdyk FJ, et al. Improving outcomes in med-surg patients with opioid-induced respiratory depression. American Nurse Today. 2011 Nov;6(11)
- Weinborum AA, et al. Efficiency of the operating room suite. American Journal of Surgery. 2003;185:244–250
- Committee on Advancing Pain Research, Care, and Education, Institute of Medicine. "Summary." Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press, 2011.
- Sun D-C, Kim MS, Chow W, Jang E-J. Use of medications and resources for treatment of nausea, vomiting, or constipation in hospitalized patients treated with analgesics. Clin J Pain. 2011;27:508-17
- The White House. Epidemic: Responding to America's Prescription Drug Abuse Crisis. http:..www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan_0.pdf. Accessed October 21, 2012.
- Maund E, McDaid C, et al. Paracetamol and selective and non-selective and non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. Br J Anaesth. 2011 Mar;106(3):292-7.
- Brummet C. Management of Sublingual Buprenorphine (Suboxone and Subutex) in the Acute Perioperative Setting, http://anex.med.umich.edu/vault/1003149-Buprenorphine Suboxone Subutex Perioperative Management.pdf#pagemode=bookmarks
- Berkowitz, B.A., Finck, A.D., Hynes, M.D. & Ngai, S.H. (1979). "Tolerance to nitrous oxide analgesia in rats and mice". Anesthesiology 51 (4): 309–12
- Sawamura, S., Kingery, W.S., Davies, M.F., Agashe, G.S., Clark, J.D., Koblika, B.K., Hashimoto, T. & Maze, M. (2000). "Antinociceptive action of nitrous oxide is mediated by stimulation of noradrenergic neurons in the brainstem and activation of [alpha]₂₈ adrenoceptors". J. Neurosci. 20 (24): 9242–51.
- Angst, MS & Clark, DJ: Opioid-induced hyperalgesia: A qualitative systematic review. Anesthesiology 2006; 104:570–87
- Lee M, Silverman S, Hansen H, Patel V, Manchikanti L. A Comprehensive Review of Opioid-Induced Hyperalgesia. Pain Physician 2011;14:145-161.
- Song JW, Lee YW, Yoon KB, Park SJ, Shim YH. Anesth Analg. 2011 Aug;113(2):390-7. doi: 10.1213/ANE.0b013e31821d72bc. Epub 2011 May 19.
- Pesonen A, et al. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial. Br J Anaesth. 2011 Jun; 106(6):873-81. doi: 10.1093/bja/aer083. Epub 2011 Apr 6
- Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesth Analg. 2007 Jun; 104(6): 1545-56
- http://ppsg-production.heroku.com/chart
- http://www.cdc.gov/HomeandRecreationalSafety/pdf/poison-issue-brief.pdf
- http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a3.htm#fig1
- http://www.medpagetoday.com/Neurology/PainManagement/34650
- http://www.cdc.gov/nchs/data/databriefs/db81.pdf
- Weinger MB. Dangers of postoperative opioids. APSF Newsletter 2006-2007;21:61-7
- Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. JAMA. Published online March 15, 2016. doi:10.1001/jama.2016.1464.

Patient: Doctor, I don't feel well and I'm not sure why.



Doctor: I want you to meditate for 20 minutes, twice a day, exercise for at least 30 minutes a day, avoid processed foods, eat plenty of organic fruit and veg, spend more time in nature and less indoors, stop worrying about things you can't control and ditch your T.V. Come back in 3 weeks.