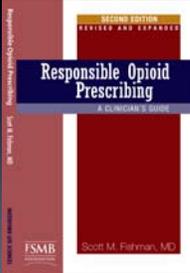


Pain, Law, Drug Abuse and Responsible Prescribing



Scott M. Fishman, MD
 Professor
 Chief, Div. of Pain Medicine
 Dept. of Anesthesia & Pain Medicine
**Univ. of California, Davis
 School of Medicine**



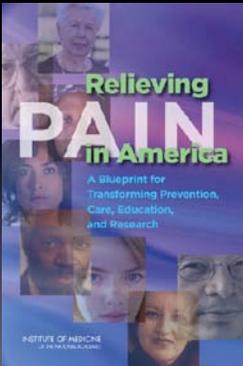
Disclosure

- I am not a lawyer and do not offer legal advice
- Information presented here is from the perspective of a concerned physician
- No Direct Financial Relationships with Drug Companies
- *Engage in official CME speaking*
- *No Pharma / industry speakers or consultation programs*
- *Past President and Chair, American Pain Foundation*



The Problem of Undertreated Pain

- World Health Organization has said that undertreated pain is the number one health problem in America
- # of patients with chronic pain in the U.S. exceeds diabetes, heart disease and cancer combined
- National Center for Health Statistics. Health, United States, 2006 with Chartbook on Trends in the Health of Americans. Hyattsville, MD: US Department of Health and Human Services; 2006:68-71



**Institute of Medicine
 2011 Report:
 Relieving Pain in America**

IOM
 Relieving Pain in America 2011

- At the request of Congress and HHS
 - IOM assessed the state of the science regarding pain research, care, and education
- Chronic Pain
 - Affects an estimated 116 million American adults
 - Costs the nation up to \$635 billion each year in medical treatment and lost productivity

IOM

Relieving Pain in America 2011

- Recommendations
 - HHS develop population-level strategies to increase awareness about pain and its treatments
 - Offers a blueprint for action in transforming prevention, care, education, and research, with the goal of providing relief for people with pain in America

Generalized View of Opioid Therapy for Chronic Pain



- Opioid are not for everyone
 - Opioids seem to work for some
 - Opioids seem to be ineffective for some
 - Opioids seem to be problematic for some
- Although it may be difficult to know who is in which group
 - Opioids can be used chronically with efficacy and safety
 - Particularly when there is little else to offer
 - High dose Tx is questionable

“Prescriptions for opiates (hydrocodone and oxycodone products) have escalated from around 40 million in 1991 to nearly 180 million in 2007, with the U.S. their biggest consumer. The U.S. is supplied 99 percent of the world total for hydrocodone (e.g., Vicodin) and 71 percent of oxycodone (e.g., OxyContin).”

Statement of Nora D. Volkow, M.D., Director, NIDA/NIH:
To US Senate Committee on Judiciary March 12, 2008
http://judiciary.senate.gov/hearings/testimony.cfm?renderforprint=1&id=3199&wit_id=70381

“Opioid overdose is now the second leading cause of accidental death in the United States”

Thomas McLellan, MD: Director of the Center for Substance Abuse Solutions at the University of Pennsylvania School of Medicine & Former Deputy Director: ONDCP

- CDC: National Centre for Injury Prevention and Control
 - MVA's are #1
 - Leading cause of accidental death in the U.S. for 45-54 age group

THE BALTIMORE SUN

Cracking down on prescription drug abuse

April 07, 2010

Prescription drug abuse has grabbed recent headlines with the high profile deaths of celebrities like Corey Haim, Heath Ledger, Anna Nicole Smith and Michael Jackson. But the epidemic of prescription drug abuse is not limited to Hollywood.

Prescription drugs are the now the No. 1 cause of overdose death in the U.S. abused drug behind mariju

The Boston Globe

Haim shopped for doctors

Associated Press / April 7, 2010

Actor **Corey Haim** employed "doctor shopping" to obtain 553 prescription pills in the two months before his death last month, California Attorney General **Jerry Brown** said yesterday. Haim obtained the meds, which included Valium, Vicodin, Xanax, and Soma, through seven doctors and seven pharmacies, Brown said. He called Haim — the star of 1980s films such as "The Lost Boys" and "License to Drive" — a "poster child" for prescription drug abuse.

The Oxycontin Express

“South Florida: the Columbia of prescription drugs”

THE OXYCONTIN EXPRESS

November 18, 2009

In the season premiere of Vanguard, correspondent Mariana van Zeller travels to South Florida, the "Columbia of prescription drugs", to expose a bustling pill pipeline that stretches from the beaches of Ft. Lauderdale to the rolling hills of Appalachia. "The OxyContin Express" features intimate access with pill addicts, prisoners and law enforcement as each struggles with a growing national epidemic.



The OxyContin Express
by MarianaVanZeller

Current TV (AI Gore): Vanguard Program: Peabody Award-winning television documentary series (Laura Ling and Euna Lee)

DEA Facts on Prescription Drug Abuse

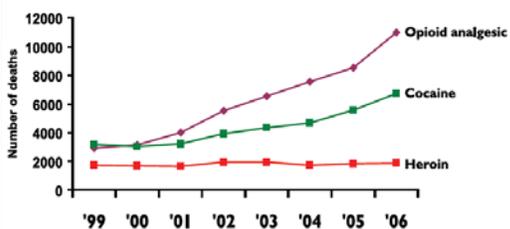
- Nearly 7 million Americans are abusing prescription drugs
 - More than the number who are abusing cocaine, heroin, hallucinogens, Ecstasy, and inhalants, combined
 - 80 percent increase in just 6 years

DEA Facts on Prescription Drug Abuse

- Prescription pain relievers are new drug users' drug of choice, vs. marijuana or cocaine
 - In 2009, 6,027 persons /day abused prescription pain relievers for the first time
 - Every day 2,500 teens use prescription drugs to get high for 1st time
 - 1 in 7 teens admit to abusing prescription drugs to get high in the past year
 - 60% of teens who abused prescription pain relievers did so before the age of 15
 - 56% of teens believe that prescription drugs are easier to get than illicit drugs

CDC: Poisoning Deaths Involving Unintentional Opioids in US 1999-2006

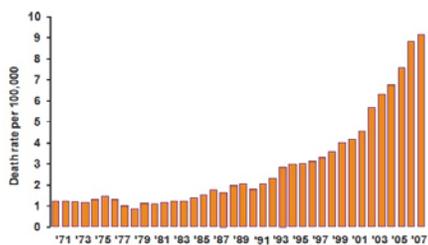
Figure 2: Unintentional drug overdose deaths by major type of drug, United States, 1999-2006



Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. CDC's Issue Brief: Unintentional Drug Poisoning in the United States. <http://www.cdc.gov/HomeandRecreationalSafety/Poisoning/brief.htm>. 2010

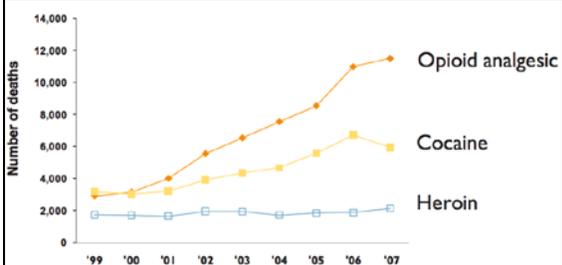
CDC: Poisoning Deaths in US 1971-2007

Figure 1: Rate of unintentional drug overdose death in the United States, 1970-2007



Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. CDC's Issue Brief: Unintentional Drug Poisoning in the United States. <http://www.cdc.gov/HomeandRecreationalSafety/Poisoning/brief.htm>. 2010

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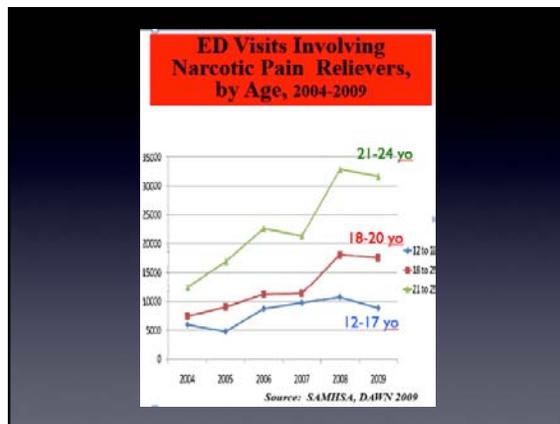
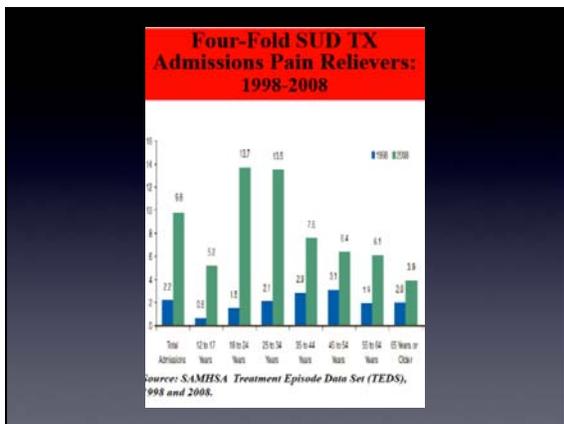
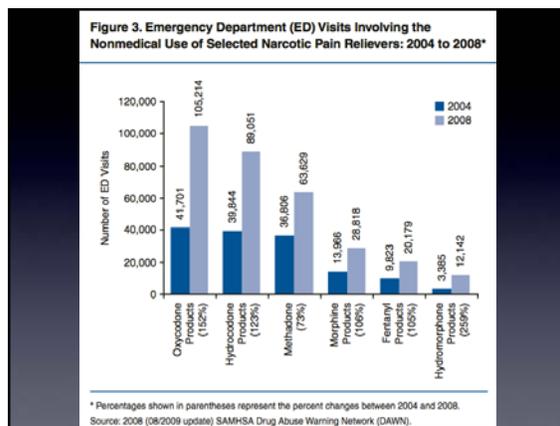
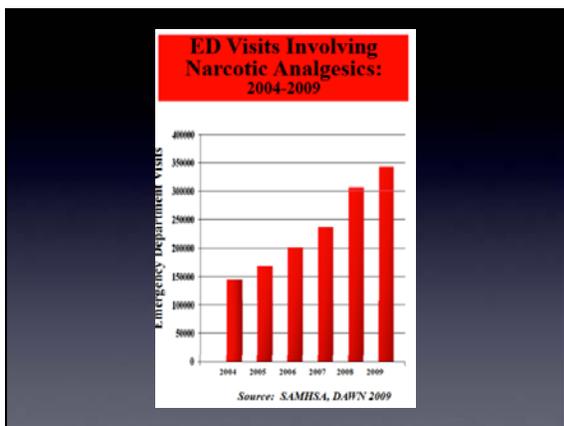
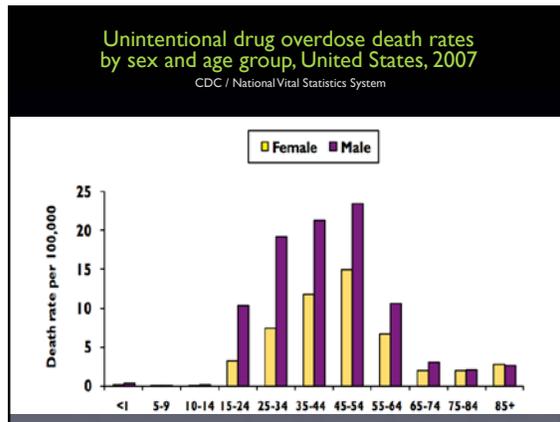
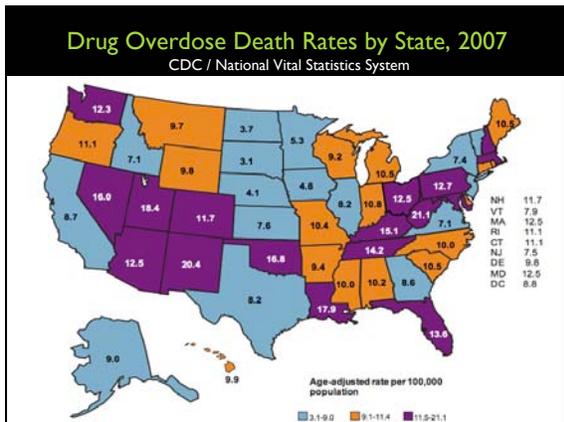


Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. CDC's Issue Brief: Unintentional Drug Poisoning in the United States. <http://www.cdc.gov/HomeandRecreationalSafety/Poisoning/brief.htm>. 2010

CDC: Poisoning Deaths in US

- Poisoning deaths
 - Rates have increased ~ 5X since 1990
 - "The increase in drug overdose death rates is largely because of prescription opioid painkillers" ...CDC
 - Cases involving methadone increased ~7X
- In 2007, opioids were involved in more overdose deaths than heroin and cocaine combined
 - ~ 2X the number involving cocaine
 - > 5 X the number involving heroin

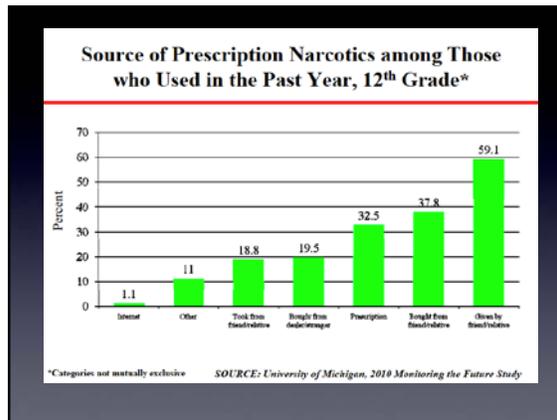
Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. CDC's Issue Brief: Unintentional Drug Poisoning in the United States. <http://www.cdc.gov/HomeandRecreationalSafety/Poisoning/brief.htm>. 2010



Alarming #of Teens have False Sense of Security About Safety of Abusing Prescription Medications

2005 Partnership and Attitude Study from: Partnership for a Drug-Free America

- 19% of teens report abusing prescription medications to get high
- 40% believe that prescription medicines are "much safer" to use than illegal drugs
- 31% believe there's "nothing wrong" with using prescription medicines without a prescription "once in a while"
- 29% believe prescription pain relievers are not addictive

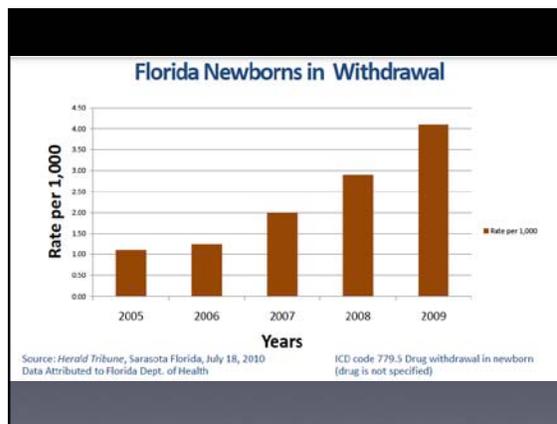


The New York Times U.S.
 WORLD | U.S. | NY / REGION | BUSINESS | TECHNOLOGY | SCIENCE | HEALTH | SPORTS | OPINION

Newly Born, and Withdrawing From Painkillers

BANGOR, Me. — The mother got the call in the middle of the night: her 3-day-old baby was going through opioid withdrawal in a hospital here and had to start taking methadone, a drug best known

New York Times Sunday April 10, 2011



WV Data on Opioid Poisoning

Hall et al: **Patterns of Abuse Among Unintentional Pharmaceutical Overdose Fatalities.** JAMA, 2008; 300(22):2613-2620

- WV experienced largest increase in drug overdose mortality rates from 1999-2004
- Study looked at OD deaths in year 2006
 - 295 decedents ages 18 – 54
 - 63 % involved diversion
 - ~ Largely Male: 2/3= males
 - ~ Largely Younger: > in ages 18 -24 years
 - ~ Decreased across each successive age group
 - ~ >> association with illicit contributory drugs

WV Data on Opioid Poisoning

Hall et al: **Patterns of Abuse Among Unintentional Pharmaceutical Overdose Fatalities.** JAMA, 2008; 300(22):2613-2620

- OD deaths in year 2006
 - Evidence of doctor shopping in 21% (1 in 5)
 - ~ Prescriptions for CS from ≥5 clinicians in the year prior to death
 - Largely Female: F > M (~2:1 , 31% to 17%)
 - Largely Older: 71% age > 35
 - Negative association between drug diversion + doctor shopping
 - ~ Only 8% met criteria for both

WV Data on Opioid Poisoning

Hall et al: **Patterns of Abuse Among Unintentional Pharmaceutical Overdose Fatalities.** JAMA, 2008; 300(22):2613-2620

- OD deaths in year 2006
 - › Methadone
 - ~ Most attributed opioid in single-drug deaths
 - ~ Involved in more deaths than any other drug (40% all deaths)
 - › 95% w/ indicators of substance abuse
 - › 79% of all cases associated with multiple contributory substances
 - › 93% of all cases involved opioid analgesics
 - ~ **66% did not have a prescription**
 - 34% had prescription

WA State Data on Opioid Poisoning

Dunn KM et al: **Opioid Prescriptions for Chronic Pain and Overdose: A Cohort Study.** Ann Intern Med, 2010. 152 (2):85-92

- 9940 people w/3 or more opioid prescriptions within 90 days for chronic non-cancer pain between 1997 and 2005 (8 yrs)
- Measures
 - Avg daily opioid dose over the previous 90 days from automated pharmacy data
 - Nonfatal and fatal overdoses identified through diagnostic codes from inpatient and outpatient care and death certificates (confirmed by medical record review)
- 51/9940 opioid-related overdoses and 6 deaths
- Patients receiving ≥ 100 mg/d = ~ 9X increase in OD risk compared with Patients receiving 1-20 mg/d
 - Patients receiving 50-99 mg/d had a ~4X increase in OD risk

Alterations in brain structure and functional connectivity in prescription opioid-dependent patients

Jaymin Upadhyay,^{1,2} Nasim Maleki,^{1,3} Jennifer Potter,^{2,3,4,5} Igor Elman,⁶ David Rudrauf,⁵ Jaime Knudsen,¹ Diana Wallin,¹ Gautam Pendse,¹ Leah McDonald,^{2,3} Margaret Griffin,^{2,3} Julie Anderson,¹ Lauren Nuttle,¹ Perry Renshaw,⁶ Roger Weiss,^{2,3} Lino Becerra,^{1,7} and David Borsook^{1,2}

PAIN Journal of the International Association for the Study of Pain

Articles & Issues - For Authors - Journal Information - Press Releases - Subscribe - IASP

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Previous PAIN Volume 152, Issue 8, Pages 1803-1810, August 2011 Next

Prescription opioid analgesics rapidly change the human brain

James W. Younger, Larry F. Chu, Nicole T. D'Arcy, Kiley E. Todd, Laura E. Jastrab, Sean G. Mackey

Received 28 April 2010; received in revised form 21 March 2011; accepted 23 March 2011; published online 02 May 2011.

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- Compared w/controls, Opioid dependent individuals displayed
 - Decreased functional connectivity in seed regions that included the anterior insula, nucleus accumbens and amygdala subdivisions.
 - Longer duration of prescription opioid exposure associated with greater changes in functional connectivity

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Paradigm Shift in Opioid Prescribing

- Competing Public Health Crises
 - › Under Treated Pain
 - › Prescription Drug Abuse
- Increasing Need for Safe & Effective Pain Management
 - › Decreased barriers to appropriate opioid use
 - › Increased safety in opioid use

CONSUMERAFFAIRS.COM

White House Declares 'Epidemic' of Prescription Drug Abuse
Multi-agency effort aims to reduce misuse of opioids

The White House on Tuesday unveiled a multi-agency plan aimed at reducing the widespread prescription drug abuse in the U.S. industry an "Opioid Education Program" that partners with leading the misuse and misprescribing of opioids.

The bill for national prescription drug abuse awareness, the latter of comprehensive education in cooperation with the Department of Justice, Office of Inspector General, Drug Control Policy, and other agencies to prevent further participation in the opioid abuse in prescription drug abuse.

The plan is a collaborative effort involving agencies of the departments of Justice, Health and Human Services, Veterans Affairs, California, and others and is intended to provide a national framework for reducing prescription drug abuse and the number of prescription drugs for recreational use.

CBS NEWS

POLITICAL HOT SHEET

America's fastest-growing drug problem: Prescription drug abuse

Prescription drug abuse is the nation's fastest-growing drug problem, according to the latest of national drug control policy.

It is now the second most abused category of drugs after marijuana, and the second leading cause of accidental death in the U.S. after car accidents.

In a joint press conference today, representatives from the Food and Drug Administration (FDA), Drug Enforcement Administration (DEA), Center for Disease Control and Prevention (CDC) and Health and Human Services (HHS) announced the Obama administration's

FDA:
Risk Evaluation Mitigation Strategies

U.S. Department of Health & Human Services
FDA U.S. Food and Drug Administration
FDA Acts to Reduce Harm from Opioid Drugs

The White House on Tuesday unveiled a multi-agency plan aimed at reducing the "epidemic" of prescription drug abuse in the U.S.—including an FDA-backed education program that zeroes in on reducing the misuse and misprescribing of opioids.

Gil Kerlikowske, director of the White House Office of National Drug Control Policy, says the plan—a collaborative effort involving agencies of the departments of Justice, Health and Human Services, Veterans Affairs,



YOU MUST PICK ONE

OBSCURE SCHOOL OR BATH

SIT! SELL! OVER!

Dog's Hell




Jerry Brown
...SERIOUS STUFF

MICHAEL JACKSON

Anna Nicole's boyfriend, doctor charged

CNN.com

PLAY ▶

DAILY NEWS Health

Internet tied to growth in Percocet and Oxycodone prescription drug abuse in U.S.

Growing Internet Use May Help Explain The Rise In Prescription Drug Abuse In The United States

ABSTRACT The rising availability through the Internet of commonly abused prescription drugs has raised public health concerns. We examined whether the growth of US prescription drug abuse may be explained by the parallel growth in high-speed Internet use. We find that for every 10 percent increase in high-speed Internet use at the state level, associated treatment facility admissions for prescription drug abuse rose by 1 percent. Admissions for abuse of alcohol, cocaine, and heroin, which are not easily purchased online, had sustained or negative growth during the same period. The results suggest that better surveillance of online prescription drug sales is warranted, and aggressive efforts to curb illegitimate online pharmacies may be necessary.



Complicating Global Market
Internet Pharmacies

- "...anyone of any age can obtain dangerous and addictive prescription drugs with the click of a mouse"
- Joseph Califano, Director of the National Center on Addiction and Substance Abuse at Columbia University & Former Secretary HHS
- 85 % of all internet prescription sales involved controlled drugs (per DEA)
- Only 11 percent for regular pharmacies

Internet Pharmacies

- **Columbia University Study**
- Search of pharmacies advertising on Internet
 - » Using popular search engines
 - ~ ie. Google, Yahoo and MSN
- Found 206 sites selling controlled drugs
 - » **159 sites directly sold controlled drugs**
 - ~ 135 (85%) did not require a prescription or provided them on the basis of online questionnaires

Ryan Haight Online Pharmacy Consumer Protection Act

- Named for Ryan Haight
 - Died in 2001 at 18 after prescription narcotic OD purchased online
- Responds to concerns about rising availability of controlled prescription drugs on the Internet
- Took effect in April 2009 -- Amended CSA of 1970
 - Prohibited delivery, distribution, and dispensing of controlled prescription drugs over the Internet without a prescription from a physician who interviewed and examined the patient in person

Opioids & Driving

Fishbain, Cutler, Rosomoff, Rosomoff: Are Opioid-Dependent/Tolerant Patients Impaired in Driving-Related Skills? A Structured Evidence-Based Review. *Journal of Pain and Symptom Management* Vol. 25 No. 6 June 2003

"...potential instructions to stop driving to a patient utilizing opioids essentially dooms the patient to a life of disability"

"...the answer to this controversy has widespread implications both for the patient and the medical practitioner."

Doctors, Drugs, and Driving Tort Liability for Patient-Caused Accidents

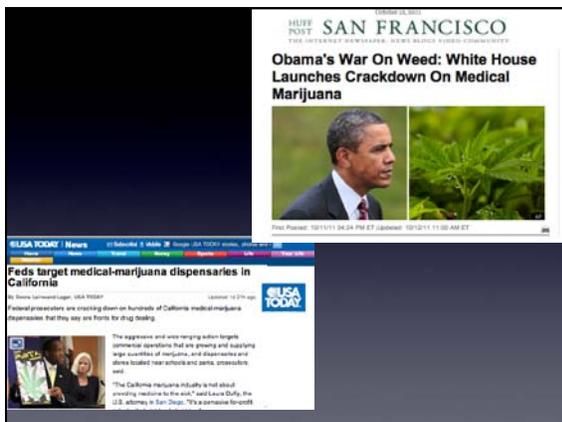
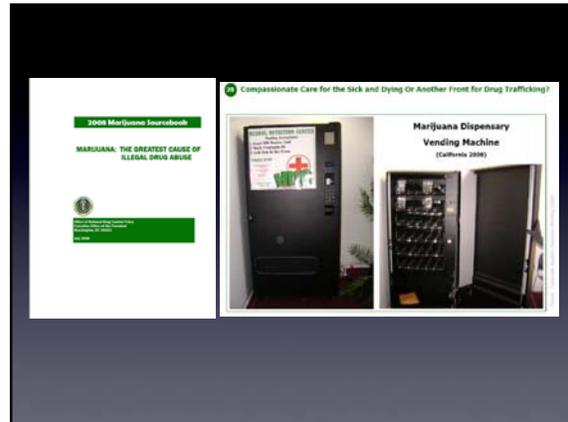
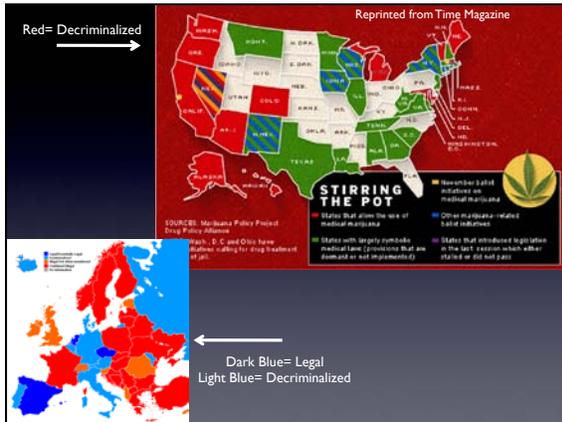
George J. Annas, J.D., M.P.H.
NEJM vol 359(5) July 31, 2008

Do physicians have any duty to patients who are taking drugs the physician has prescribed when those drugs are likely to have an adverse effect on the patient's ability to drive safely?



Opioids and the Internet
Opioids and Driving





Dr. Ali Shaygan

- 36 yo Miami Physician
- Accused & acquitted
 - 141-count indictment
 - Writing illegal prescriptions
 - Reportedly met with patients at Starbucks
 - Prescribed to undercover DEA agents
 - One case involved patient's death from a methadone overdose
- Faced minimum 20 years prison because patient death

The Quest to Understand Addiction



Addiction, Abuse, & Aberrant Behavior in Pain Patients



Webster LR, Webster RM. Pain Med. 2005;6:432.

Terms Associated with Opioid Use

Addiction

- Psychological component
- Drug-seeking behaviors
- Nonmedical use of drug despite potential harm

Pseudo-addiction

- Iatrogenic problem - inadequate analgesia

Tolerance

- Not relevant to efficacy if agents and dosage are adjusted

Physical Dependence

- Natural process; weaning from drug is a simple medical process

Dependence vs. Addiction vs. Abuse

Clonidine

Cocaine, Gambling, Food, Sex

Entrepreneurs

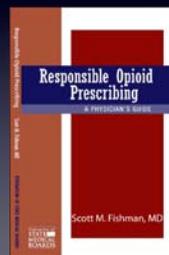
Addiction vs. Analgesia

- Patients with addiction take increasing amounts of abusable drugs
 - » Function does not improve
 - Usually worsens
- Patients usually find a stable dose
 - » Pain doesn't completely abate
 - balance of least pain/most function
 - » Function improves
 - DOES NOT DECREASE
 - If decrease → does NOT = Addiction

Risk Management with Opioids

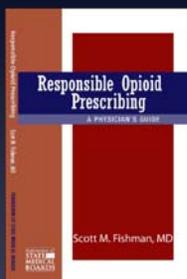
- Requires understanding of functional outcomes
 - Side effect management
 - ~ Improved function → Efficacy
 - ~ Static or decreased function →
 - ~? Efficacy ? Toxicity
- Universal Precautions
 - Standardized programs that apply to all
 - ~ Consistent risk management practices
 - ~ Persistent vigilance
 - ~ Minimized bias

Federation of State Medical Boards of the United States, Inc. Model Policy for the Use of Controlled Substances for the Treatment of Pain



FSMB House of Delegates May 2004
Available www.fsmb.org

FSMB Model Policy Basic Tenants



- Pain management is **important** and **integral** to the practice of medicine
- Use of opioids may be **necessary** for pain relief
- Use of opioids for other than a legitimate medical purpose poses a threat to the individual and society

FSMB Model Policy

- **Physicians have a responsibility to minimize the potential for abuse and diversion**
- Physicians may deviate from the recommended treatment steps based on good cause
- Not meant to constrain or dictate medical decision-making

FSMB Model Policy

- Complete patient evaluation
- Written treatment plan
- Informed patient consent and agreement for treatment
- Periodic review of the course of treatment
- Willingness to refer
- Maintenance of complete and current medical record

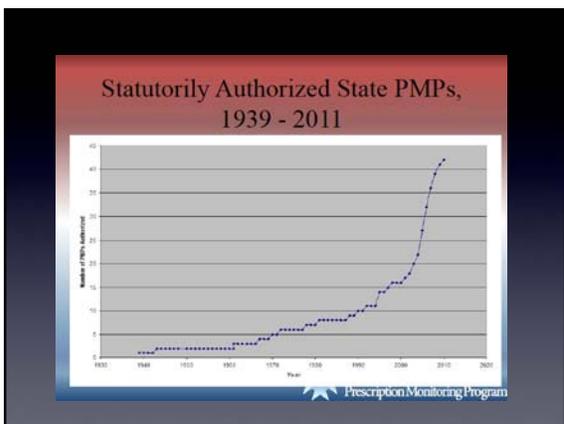
Goals of Treatment

- Improved level of independent function
- Decreased Pain



ADHERENCE

- History, Presentation, Side Effects
 - » YELLOW & RED LIGHTS
- Diaries
- Questionnaire based screens
- Drug Screening
 - » Urine, Serum, Hair, Markers (e.g. Phenobarbital, Digitalis)
- Opioid Agreements / Contracts
- PMPs



THE NATIONAL ALL SCHEDULES PRESCRIPTION ELECTRONIC REPORTING ACT OF 2005 (NASPER H.R.3015)

National Prescription Monitoring Program

- Promise of improving pain care
- Greater oversight of abusive drugs
- Clinical utility at point of care
- Risks associated w/ chilling effects on pain control
 - Clear message to prescribers
 - Confidentiality concerns
 - Variable PMP plans

TIME
States to Link Prescription Databases
By AP / EMERY P. DALESIO Friday, Oct. 18, 2010

OPIOID ANALGESICS

- The Gold Standard
 - » Severe Pain
 - » Unremitting Pain

King Pharmaceuticals + Pain Therapeutics

Remoxy

- **SR oxycodone formula in a viscous gel base**
 - **Deters dose dumping**
 - ~ Accessing entire 12-h dose of CR medication at 1 time
 - **Difficult to crush, break, freeze, heat, dissolve**
 - ~ The viscous gel-cap base of PTI-821 cannot be injected
 - ~ Resists crushing and dissolution in alcohol or water

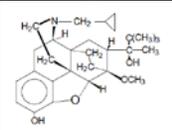


Remaining Questions About Abuse Resistant Compounds

- How much does the barrier approach deter the determined
- How much do Agonist/Antagonist compounds retain efficacy
- How much do Agonist/Antagonist compounds pose serious adversity
- How to deter over use without manipulation

Buprenorphine

An Abuse-Resistant Opioid?



- Antagonist of Kappa opioid receptor
- Agonist of Mu opioid receptor
 - ▶ Tightly binds to mu receptor with less respiratory depression and withdrawal



Butrans

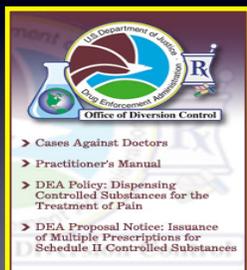
Buprenorphine TD Formulation

- Sublingual/Transdermal delivery bypasses first pass hepatic metabolism
- Oxidation via P450 isoenzyme 3A4
- Recent FDA approval of transdermal compound June 2010
 - Q-T prolongation at 40mcg/hr dose
 - Low dose formulation

Regulatory Agencies and Pain



“Final” Policy Statement September 6, 2006



“Final” Policy Statement September 6, 2006

- As a condition of being a DEA registrant
 - A physician prescribing controlled substances has an obligation to take reasonable measures to prevent diversion
 - Interim Report described physicians responsibility to minimize abuse and diversion
 - Why the change from MINIMIZE to PREVENT?

Multiple Prescriptions for Schedule II Controlled Substances

Fed Register: November 19, 2007

- “Issuance of Multiple Prescriptions for Schedule II Controlled Substances.”
 - Effective December 19, 2007
 - Final Rule amends DEA’s regulations
 - Allows practitioners to provide individual patients with multiple prescriptions for a specific schedule II controlled substance
 - Written on the same date.
 - To be filled sequentially
 - Combined effect sequential multiple prescriptions allows a patient to receive over time up to a 90-day supply of that controlled substance
 - CSA does not permit refilling Schedule II controlled substances, requiring that a new prescription be issued for each quantity of the substance

Fed Register, November 19, 2007

NEW REGULATORY INITIATIVES

- Federal Medicaid requirements
 - Effective April 2008
 - Tamper-resistant prescription pads for all reimbursable prescriptions
 - Irrespective of schedule or non-scheduled drugs
 - Iraq Appropriations Act of 2007 [Section 7002(b)]
 - Savings measure in the Social Security Act [Section 1903(i)(23)]
 - White House Office of Management and Budget estimated cost savings of \$142 million over 5 years
- FDA: REMS

Food and Drug Administration Amendments Act of 2007 FDAAA

- Signed into law September 27, 2007
 - Primary goal to enhance medical product safety
 - Represents many significant additions to FDA authority -- 200 specific provisions
- Risk Evaluation and Mitigation Strategies (REMS)
 - FDAAA authorizes FDA to require a “REMS” for new drug applications and drugs already approved if the Agency determines it’s necessary to ensure that the benefits of the drug outweigh the risks

FDA: Risk Evaluation Mitigation Strategies





Risk Evaluation & Mitigation Systems

25 Drugs & Biologics

FDA U.S. Food and Drug Administration

FDA News

FOR IMMEDIATE RELEASE
March 27, 2008

FDA Identifies First Steps in Requirements for Safety Plans for Certain Drugs and Biologics
New FDAAA requirements being implemented

The U.S. Food and Drug Administration has identified 25 drugs and biologic products that will be required to submit safety plans called Risk Evaluation and Mitigation Strategy (REMS), the FDA said in a Federal Register notice published today.

Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA can require manufacturers to submit a REMS when a drug first comes on the market, or later if FDA becomes aware of new safety data about the drug. The manufacturers of the 25 drugs and biologic products identified in today's notice must submit to the agency a proposed REMS by May 23, 2008.

Certain drugs present a dilemma: They can provide an important benefit to patients, but they can be especially dangerous if not used properly. For example, certain drugs may be safe and effective for patients, but if taken while pregnant can harm the fetus or cause miscarriage. Rather than deny FDA approval of such drugs, the agency has granted approval and required that the manufacturers develop a safety plan, or REMS, to help ensure that health care professionals prescribe the drug correctly and that patients use it safely. While FDA has previously approved some drugs and biologics with these safety plans, the new law makes explicit FDA's authority to require them and certain specific enforcement authority, when conditions or non-compliance with the plans requirements occur.

"These safety plans allow patients to have continued access to certain medicines for which there are safety concerns that can be managed through appropriate use," said Jose Alvarez, associate director for policy, Center for Drug Evaluation and Research, FDA. "The FDA approved the drugs identified today, before the new law was passed, and they will now be brought within the new safety plan requirements and enforce FDAAA."

"Final" Policy Statement September 6, 2006

- "Final" Policy Statement – Sept 2006
 - Dispensing Controlled Substances for the Treatment of Pain
 - Registrant responsibility TO PREVENT diversion and abuse
 - Citing Gonzales v. Oregon
 - Properly determine a legitimate medical purpose for the prescription of a controlled substance
 - Act in the usual course of professional practice

FDA Release September 2009

Draft Guidance

NON-BINDING

90 day Comment Period

Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the Federal Register or the date announcing the availability of the draft guidance, whichever occurs later. Submit comments to the Division of Dockets Management (HFD-209), Food and Drug Administration, 1015 H Street, NE, Washington, DC 20202. All comments should be identified with the draft number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (DHF) Lillian Price, 301-794-2280, or (202)261-8100. The Office of Communications, Outreach, and Development (OCOD) at 301-827-3200 or 800-438-0270.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2009
Drug Safety

6 Elements of REMS

March 7, 2008

1. Health care providers who prescribe the drug have particular training, experience, certification
2. Pharmacies, practitioners or health care providers that dispense the drug are specially certified
3. Drug dispensed to patients only in certain health care settings
4. The drug is dispensed with documentation of safe use conditions, such as lab results
5. Each patient taking the drug subject to monitoring
6. Each patient using the drug enrolled in a registry

Pain and Legislation

The image shows a scale of justice, symbolizing the balance between the benefits and risks of a drug. On the left pan, there is a mortar and pestle, representing the pharmaceutical industry or the process of drug development. On the right pan, there is a pill bottle, representing the drug itself. The scale is balanced, suggesting that the benefits and risks are being weighed against each other.

Pain & legislation

- State Legislation
 - Most states are active
 - Most focused on prescription Rx Abuse
 - Washington State Guidelines and ESHB 2876

Pain & legislation

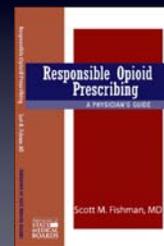
- National Legislation
 - VA Pain Care Act 2008
 - S 2162, HR 6122 (changed to HR 6445)
 - Military Pain Care Act 2008
 - Incorporated into The National Defense Authorization Act, H.R. 5658

Pain & legislation

- National Legislation: Health Reform
 - National Pain Care Policy Act of 2009
 - S 660 (Hatch/Dodd), HR 756 (Capps/Rogers)
 - As passed in Health Reform Bill of 2010
 - Patient Protection and Affordable Care Act 3/23/10
 - IOM Conference/Report on Pain
 - Required report to Congress
 - HHS grant program for Education and Training in Pain Care
 - Authorize training grants
 - Increased focus and investment on pain research at NIH

Conclusions

- Responsible opioid prescribing requires Risk Management
- Legal & Regulatory Forces
 - Pushing this outcome
 - Uncertain components



Conclusions

- Responsible opioid prescribing requires Risk Management
 - » Uncertain components
 - ~What it is
 - ~Who needs what parts
 - ~If universal approaches work
 - Equitable
 - Stigmatizing
 - ~Does it improve outcomes
 - For patients
 - For regulators
 - Why should these be different?

Pharmaco-Vigilant Prescribing

Risk Stratification and Management

- Screen for Risk Before Prescribing
 - Multifactorial aspects including physical, psychological & social domains
- Prepare for Risks after Tx Prior to Prescribing
- Prepare Clear Objective Tx Outcomes / End Points
 - Follow-up goals
- Obtain Real Informed Consent Based on Risks & Benefits
 - Include available evidence
 - Adjust Risk:Benefit determination relative to above considerations

Pharmaco-Vigilance with Opioids

- Risk Management
 - » Risk stratification and monitoring
 - » Functional outcomes
 - ~ Improved function
 - → Efficacy
 - ~ Static or decreased function
 - → ? Efficacy ?Toxicity
- Uniform Application
 - » Universal Precautions/Standardized programs
 - ~ Consistent risk management practices
 - ~ Persistent vigilance
 - ~ Minimized bias

CDC Recommendations to Health Care Providers

- Use opioid medications for acute or chronic pain only after determining that alternative therapies do not deliver adequate pain relief. The lowest effective dose of opioids should be used.
- In addition to behavioral screening and use of patient contracts, consider random, periodic, targeted urine testing for opioids and other drugs for any patient less than 65 years old with noncancer pain who is being treated with opioids for more than six weeks.
- 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.
- Do not prescribe long-acting or controlled-release opioids (e.g., OxyContin®, fentanyl patches, and μ methadone) for acute pain.
- Periodically request a report from your state prescription drug monitoring program on the prescribing of opioids to your patients by other providers.

Fishman's Basics of Chronic Opioid Prescribing

- Single prescriber - Single pharmacy
- Opioid agreement
- Lowest possible effective dose
- Caution using opioids with conditions potentiate AE's
 - COPD, CHF, sleep apnea, substance abuse, elderly, or renal or hepatic dysfunction, Mental Illness
- Caution in combining opioids with sedative-hypnotics, benzodiazepines or barbiturates
- Screen universally for substance abuse & mental illness
- Use functional outcomes
- Monitor for medication misuse and check random urine drug testing and PMP data

Conclusions

- Prescribers are largely Untrained
- Education solutions must begin at the beginning
 - Medical, dental, NP, PA students
 - Postgraduate residency training
- Principles of safe opioid prescribing consistent with safe use of all controlled substances

Conclusions

- Advice
 - » Err on the side of compassionate employment of best medical judgment
 - ~ Bounds of medicine defined by intent
 - » Get Trained
 - » Follow FSMB policy suggestions
 - » Manage Risk
 - ~ Transparent Documentation

THANK YOU : smfishman@ucdavis.edu

